CHAPTER 7. POLYCYCLIC AROMATIC HYDROCARBONS IN AMBIENT AIR AND CANCER

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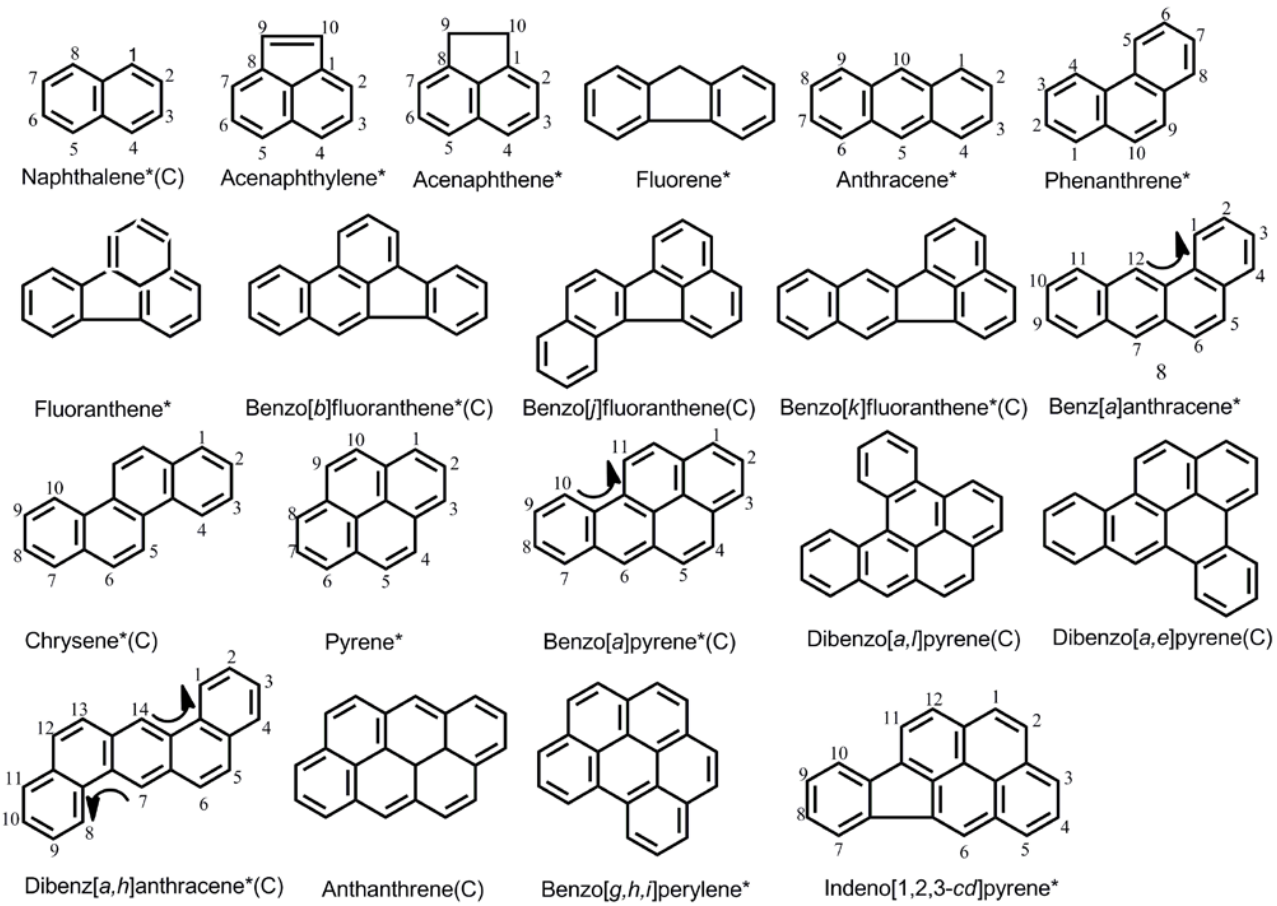
Polycyclic aromatic hydrocarbons (PAHs), which are generated from the incomplete combustion of organic (carbonaceous) material, are ubiquitous contaminants in ambient air (IARC, 1983, 1984a, 1984b, 1985, 2010; WHO, 1998). Their occurrence in the air we breathe has been substantial during the past centuries due to emissions from industrial processes and energy production, motor vehicular traffic, incineration of refuse, and residential heating.

PAHs consist of two or more fused aromatic rings made up of carbon and hydrogen atoms. The ring systems can be present in multiple configurations and may be unsubstituted or substituted. PAHs range from semivolatile molecules to molecules with high boiling points. Thus, they may be found both in the gas and the particulate phase of ambient air or in mixtures of both phases. About 500 different PAHs have been detected in air, but often the measurements focus on benzo[*a*]pyrene (B[*a*]P) as a representative of the whole PAH family (WHO, 1998; Boström *et al.*, 2002). Many of the PAHs in ambient air are carcinogenic (IARC, 1983, 1984a, 1984b, 1985, 2010) (Figure 7.1), and a recent reassessment of their carcinogenic potential led to B[*a*]P being upgraded to a Group 1 *known human carcinogen* (IARC, 2010). Thus there is considerable concern about the relationship between PAH exposure in the ambient air and the potential to contribute to human cancer incidence. The United States Environmental Protection Agency (EPA) monitors 16 priority PAHs in air due to health concerns: naphthalene, acenaphthylene, acenaphthene, fluorene, anthracene, phenanthrene, fluoranthene, pyrene, chrysene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, B[*a*]P, indeno[1,2,3-*cd*]pyrene, benzo[*g,h,i*]-perylene, and dibenz[*a,h*]anthracene (in order of number of aromatic rings per structure) (Figure 7.1). Of particular note is that several PAHs (naphthalene, chrysene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, B[*a*]P, dibenz[*a,h*]anthracene, dibenzo[*a,e*]pyrene and dibenzo[*a,l*]pyrene, and anthanthrene) have been found to be carcinogenic in experimental animals after inhalation or intratracheal ingestion, increasing concern about the levels of these carcinogens in ambient air (Figure 7.1).

Fig 7.1 PAHs in ambient air.



An asterisk denotes a United States Environmental Protection Agency priority pollutant. (C) indicates that the compound is carcinogenic by inhalation or intratracheal administration in experimental animals. Source: Park and Penning (2008); reproduced with permission from John Wiley & Sons.

PAH emissions in ambient air

A recent global atmospheric emission inventory of PAHs (Zhang and Tao, 2009) showed that the emission from the 16 priority PAHs listed by the EPA was 520 000 tonnes per year. Anthropogenic sources of total PAHs in ambient air emissions are greater than those that come from natural events such as forest fires and volcanic eruptions.

Apart from localized risk at or near the source of emission, PAHs can be dispersed regionally and intercontinentally through atmospheric long-range transport. For example, PAHs emitted from East Asia are transported to the west coast of the USA, and PAHs emitted in the Russian Federation influence atmospheric PAH concentrations in the Arctic (Zhang and Tao, 2009). The annual PAH emission from Asian countries is 290 000 tonnes (55% of the total); the amounts from China (114 000 tonnes per year) and India (90 000 tonnes per year) are the major contributors. The USA is the third largest emitter of PAHs, at 32 000 tonnes per year. By contrast, European countries account for only 9.5% of the total PAH emissions annually (Zhang and Tao, 2009). The contribution of the various anthropogenic sources of PAHs to the total emission

profile can vary by country and region. The global sources of PAH emissions are shown in Table 7.1, and the main sources of PAHs in six European countries are shown in Table 7.2.

The largest emission of PAHs globally comes from incomplete combustion of organic material, and the largest single source is from the combustion of biofuels. Biofuel is a single type of primary solid biomass (e.g. animal dung or peat) (Zhang and Tao, 2009). Burning biomass fuels such as wood on indoor open-pit stoves is common in developing areas, leading to harmful exposures to particulate matter < 2.5 μm in diameter ($PM_{2.5}$), carbon monoxide (CO), and PAHs, which can be significantly reduced by the introduction of modern stoves (Li *et al.*, 2011). Anthropogenic sources include PAHs that come from incomplete combustion processes (especially biofuels) and those that are made commercially, are by-products of industrial processes, or are generated from vehicle emissions, cooking, food preservation, and first- and second-hand cigarette smoke.

Anthropogenic sources of PAHs in ambient air

Commercial production

PAHs produced commercially include naphthalene, acenaphthene, phenanthrene, fluoranthene, and pyrene; however, only naphthalene is used directly without further processing, as a moth repellent.

Industrial processes

Many PAHs are released into the atmosphere during industrial processes such as coal coking and petroleum refining. It is estimated that coal coking was responsible for the release of thousands of tonnes of PAHs per year in different countries during the 1980s and early 1990s. Reduced coke production and technical improvements have led to reductions in PAH emissions from this source. Little is known about the composition of these PAH emissions (WHO, 1998). In petroleum refining, most of the emissions consist of smaller two- and three-ring compounds (94–99%, depending on the process studied) (IARC, 1989). Thus, the composition of PAHs from combustion (pyrogenic) versus the composition of PAHs from petroleum refining (petrogenic) can be widely different. Other industrial sources with significant PAH emissions are carbon black plants, wood preservation (creosote) plants, the asphalt and bitumen industry, aluminium production (Söderberg electrodes), iron and steel production, foundries, tyre production, power plants, waste incinerators, and stubble burning (WHO, 1998). Further restrictions may lead to lower PAH emissions from these industries (CORINAIR, 1997).

Estimation of the PAH emissions for six European countries indicates that the industrial sources contribute PAHs in the same range as mobile sources (Table 7.2; data from CORINAIR, 1997).

Residential sources

Domestic heating with oil and wood stoves leads to considerable PAH emissions in northern European countries, and especially in Scandinavia (Boström *et al.*, 2002). In Sweden, the emissions from wood-fired domestic heating are estimated to be about 100 tonnes per year, with minor contributions from oil combustion. Environmental tobacco smoke is also a considerable source of indoor air pollution and contamination within the home (Hoh *et al.*, 2012).

Motor vehicle emissions

The amount of PAHs released into the air from vehicles has been reduced considerably by the introduction of three-way converters. However, older diesel and gasoline cars with a

Table 7.1 Main sources of emission for the United States Environmental Protection Agency 16 priority PAHs in China, India, and the USA

Source	Global	China	India	USA
Biofuel	56.7%	66.4%	92.5%	9.1%
Wild fire	17.0%	0%	0%	3.3%
Consumer product use	6.9%	0.9%	0.6%	35.1%
Traffic oil	4.8%	2.0%	IS	23.0%
Domestic coal	3.7%	10.7%	1.3%	IS
Coke production	3.6%	14.4%	IS	IS
Petroleum refining	2.4%	1.0%	IS	8.7%
Waste incineration	1.9%	IS	IS	9.5%
Aluminium electrolysis	1.4%	IS	IS	1.9%
Open straw burning	IS	2.0%	3.2%	IS
Gasoline distribution	IS	IS	IS	3.0%
Aerospace industry	IS	IS	IS	2.5%
Other	1.5%		2.7%	3.9%
Tonnes in thousands	530	114	90	32

IS, insignificant.
Compiled from Zhang and Tao (2009).

catalytic converter of outmoded design have 5–10 times higher PAH emissions than modern cars. In addition, cold start at temperatures below the standardized cold start (23 °C), and especially at temperatures below 0 °C, results in a several-fold increase in PAH emissions. Several other technical variations lead to varying emissions, for example spark ignition engines (WHO, 1998). The total amounts of PAHs emitted from vehicles vary between countries; in the USA this can be as high as 6000 tonnes per year, and in six European countries the amount is about 400 tonnes per year (Table 7.1 and Table 7.2).

As might be expected, not all PAHs contribute equally to the emissions into ambient air. Table 7.3 lists a typical PAH profile in ambient air arising from different sources.

Human exposure

PAHs may be found in the gas and particulate phases (see Chapter 1). The levels given below frequently reflect the levels of discrete PAHs in the particulate phase and are often given as the sum of a limited number of PAH components. B[*a*]P is the traditional marker for PAH exposure. Several additional PAH components have been proposed as emission markers, for example fluoranthene, B[*a*]P, and benzo[*b*]fluoranthene. Boström *et al.* (2002) suggested the use of the following set of PAHs as emission and effect markers for monitoring air pollution: B[*a*]P, fluoranthene, phenanthrene, methylanthracenes/phenanthrenes, pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, indeno[1,2,3-*cd*]pyrene, benzo[*g,h,i*]-perylene, dibenz[*a*]anthracene, and dibenzo[*a,l*]pyrene. This list is quite similar to the 16 priority PAHs listed by the EPA (Figure 7.1). In some studies, the total PAH exposure is given as B[*a*]P toxic equivalency concentrations. In this approach, individual components are measured and ranked relative to B[*a*]P in terms of carcinogenicity. For example, chrysene has 1/1000th of the carcinogenicity of B[*a*]P and has a toxic equivalency concentration of 0.001. These calculations are used to estimate human health risk and can be used to calculate incremental lifetime cancer risk (ILCR). ILCR = exposure (μg/kg/day) × cancer slope factor (μg/kg/day). The ILCR is considered negligible when it is less than 1 in 10^5

Table 7.2 Main source sectors for PAHs in 1994 in six European countries (Austria, Denmark, Germany, Luxembourg, Norway, and the United Kingdom)

Sector	PAH emissions	
	Amount (tonnes per year)	Percentage of total
Combustion of energy and transformation industries	6.1	0.3
Non-industrial combustion plants plus wood burning	1120	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)	**1900**	

Reproduced from Boström *et al.* (2002).

(less than 1 additional cancer case per 100 000 persons), and the cancer slope factor is based on the extrapolation of a dose–response curve for tumorigenicity seen at high dose in experimental animals.

Background levels of PAHs in remote locations have been measured between 0.01 ng/m^3 and 0.1 ng/m^3 for individual PAH components (WHO, 1998). In rural districts the levels were approximately 10 times higher, whereas in city streets levels may amount to 50 ng/m^3 or more of the more abundant individual PAHs (Boström *et al.*, 2002). Total PAHs in the centre of Stockholm, Sweden, ranged from below 100 ng/m^3 to 200 ng/m^3. The most abundant PAH was phenanthrene. In other cities higher levels of individual PAHs have been measured (WHO, 1998; Binková *et al.*, 2003). PAH was measured in the gas and particulate phase over summer and winter sampling periods in Kocaeli, Turkey. Σ_{13}PAH in the gas and particulate phases ranged from 6.2 ng/m^3 dibenz[*a*,*h*]anthracene to 98.6 ng/m^3 phenanthrene in the winter, and from 3.0 ng/m^3 benz[*a*]anthracene to 35.1 ng/m^3 phenanthrene in the summer. The most abundant PAH in both sampling periods was phenanthrene, followed by fluoranthene and pyrene. B[*a*]P toxic equivalency concentrations were found to be 3-fold higher in the winter months (Gaga *et al.*, 2012). A similar outcome was observed in a study of children aged 5–6 years (n = 260) in New York City when measurements were conducted in the heating and non-heating seasons (Jung *et al.*, 2010). In the United Kingdom, the Toxic Organic Micropollutants programme measured temporal trends in PAH in the atmosphere from 1991 to 2005 at six different sampling sites. Most showed a reduction in PAH levels and had concentrations that were lower than the new air quality standard of 0.25 ng/m^3. However, this value was exceeded in urban areas in the winter months (Meijer *et al.*, 2008).

Indoor PAH levels usually range from 1 ng/m^3 to 50 ng/m^3 due to tobacco smoke and residential heating with wood, coal, and other materials (WHO, 1998). Environmental tobacco smoke is a major contributor to air pollution and dust, and surfaces remain contaminated long after the smoking has ceased (called third-hand smoke). Measurement of PAHs in settled household dust in 132 homes showed that total PAHs were 990 ng/g in smoking households versus 756 ng/g in nonsmoking households, and when corrected

Table 7.3 Mean profiles of individual PAHs in ambient air (relative to benzo[*a*]pyrene = 1.0)

Compound	Point source	Near mobile source	Home heating	Transport	Geometric mean
Anthracene	5.5	7.6	1.0	1.8	2.9
Phenanthrene	38	200	39	43	60
Fluoranthene	14	48	12	13	18
Pyrene	9.3	28	11	7.1	12
Benz[*a*]anthracene	1.4	0.82	1.0	0.78	0.97
Perylene	0.33	0.25	0.22	0.24	0.26
Benzo[*e*]pyrene	1.5	1.3	1.6	1.4	1.4
Benzo[*g,h,i*]perylene	1.4	1.5	2.4	1.3	1.6
Indeno[1,2,3-*cd*]pyrene	1.5	1.3	1.5	1.4	1.4
Anthanthrene	0.19	0.15	0.13	0.20	0.17
Chrysene and triphenylene	3.0	2.7	3.5	2.9	3.0
Benzofluoranthene	3.6	2.9	3.6	4.4	3.6

Source: WHO (1998); reproduced with permission from the publisher.

for loading (dust/m^3), the fold change was greater than 2-fold (Hoh *et al.*, 2012).

PAHs in the ambient air can react with nitrates, hydroxyl radicals, or ozone, leading to the production of more water-soluble compounds. These compounds are rarely included in routine PAH measurements. However, nitro-PAHs have been detected on soot, and the formation of B[*a*]P-nitroquinone has been identified (Schauer *et al.*, 2004). Exposure levels of nine different nitroarenes resulting from diesel and gasoline exhaust have recently been reviewed by the International Agency for Research on Cancer; diesel exhaust was ranked as a Group 1 known human carcinogen (Benbrahim-Tallaa *et al.*, 2012).

Generally the mobile sources differ in their PAH profile, with the heavy diesel vehicles being characterized by lower-molecular-weight components than gasoline vehicles. However, per driven kilometre, total emissions from a gasoline-fuelled car are much lower than emissions from a diesel car. The three-way converter does not change the PAH profile of a gasoline-fuelled car significantly but reduces the total levels considerably. PAH levels vary with season, with higher levels being observed in the winter than in the summer. Data from Stockholm, Sweden, indicate that during the winter the levels of low-molecular-weight PAHs are increased compared with the summer (Prevedouros *et al.*, 2004).

Biomonitoring

Significant progress has been made in biomonitoring of human exposure to PAH. External dose can be measured using personalized air monitoring devices where PM is trapped on filters and then analysed for PAH content. Internal dose can be assessed by measuring blood and urinary biomarkers of exposure. Different analytes have been used as biomarkers of PAH exposure and effect. These include measuring PAH metabolites in the urine and intermediate biomarkers of effect (e.g. DNA and haemoglobin adducts). Analysis using urinary metabolites has given the most clear-cut results. Particulate pyrene is well correlated with total PAH in the breathing zone.

Urinary 1-hydroxypyrene may also reflect inter-individual variation in PAH metabolism. Occupational exposure has been found to lead to a 10–100 times greater urinary 1-hydroxypyrene content. Danish bus drivers excreted more 1-hydroxypyrene than mail carriers did, but outdoor working mail carriers had more

PAH metabolites in their urine than those working indoors, indicating the impact of outdoor air pollution (Hansen *et al.*, 2004). The use of 1-hydroxypyrene as a biomarker of PAH exposure has been criticized on the grounds that pyrene is not a carcinogenic PAH. This has led to the substitution of 3-hydroxy-B[*a*]P, but sensitive methods of detection have been a challenge. The detection of 3-hydroxy-B[*a*]P has also been criticized as a biomarker since this metabolite is not derived from any of the known pathways of B[*a*]P activation.

Measurements of urinary 1-hydroxypyrene-glucuronide, 2-naphthol, and malondialdehyde by synchronous fluorescence spectroscopy or high-performance liquid chromatography were used to evaluate seasonal and regional variations in PAH exposure and oxidative stress in Korean adults and women. Higher levels were found in individuals from industrialized areas and in the winter. Further elevation of 1-hydroxypyrene-glucuronide was observed in children exposed to environmental tobacco smoke (Yoon *et al.*, 2012). In a study in Chinese children from polluted and non-polluted areas, the levels of nine urinary monohydroxylated PAH metabolites and 8-oxo-2′-deoxyguanosine (8-oxo-dG) were compared. Children from the polluted area had a higher PAH burden than those from the non-polluted area, but no significant difference in 8-oxo-dG levels was noted (Fan *et al.*, 2012). The effect of involuntary tobacco smoke exposure on urinary levels of 23 monohydroxylated metabolites of PAH in 5060 subjects aged > 6 years was studied in the National Health and Nutrition Examination Survey (NHANES). After correcting for other confounders, significant increases in urinary 1-hydroxypyerene, 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyflourene, 1-hydroxypyrene, and 1-2-hydroxy-phenanthrene were observed. Increases of 1.1–1.4-fold for involuntary exposure were noted, which increased to 1.6–6.9-fold increases when children were actively exposed (Suwan-ampai *et al.*, 2009).

As there is compelling evidence for the conversion of PAH to diol-epoxides as an activation pathway (see below), there have been recent advances in measuring their corresponding tetraol hydrolysis products in humans. Progress has been made in developing stable isotope dilution liquid chromatographic mass spectrometric methods to detect phenanthrene tetraols (Hecht *et al.*, 2010; Zhong *et al.*, 2011). Phenanthrene contains a bay region and undergoes similar metabolic transformation to B[*a*]P to form diol-epoxides, which hydrolyse to tetraols. The detection of phenanthrene tetraols has also been criticized, since it is not a carcinogenic PAH. Recently, methods have been developed to measure urinary B[*a*]P tetraols with femtomole sensitivity (Hecht *et al.*, 2010), and these techniques can now be applied to biomonitoring studies.

Efforts have also been made to detect stable covalent diol-epoxide DNA and haemoglobin adducts in exposed humans. Repaired diol-epoxide DNA adducts in blood can be measured using ELISA and chemiluminescence-based methods, while unrepaired DNA adducts can be measured in lymphocytes by [^{32}P]-postlabelling methods. For example, (+)-7β,8α-dihydroxy-9α,10α-oxo-7,8,9,10-tetrahydro-B[*a*]P-N^2-deoxyguanosine [(+)-*anti*-B[*a*]PDE-N^2-dGuo] adducts have also been detected in human maternal and umbilical white blood cells after exposure to air pollution, using ELISA-based methods (Whyatt *et al.*,1998; Santella, 1999). Total DNA and B[*a*]P-like DNA adducts were measured by [^{32}P]-postlabelling in lymphocytes of nonsmoking policemen in Prague (n = 109) working 8 hour shifts. While there was no significant change in total DNA adducts, there was a marked increase in B[*a*]P-like DNA adducts correlated to personal exposure to PAHs collected on respirable particles (Topinka *et al.*, 2007). Diol-epoxide DNA adducts are

short-lived; therefore, attention has also focused on the development of methods to detect haemoglobin diol-epoxide adducts since the half-life of the red blood cell is 7–10 days (Day *et al.*, 1990).

Toxicokinetics, including metabolic activation

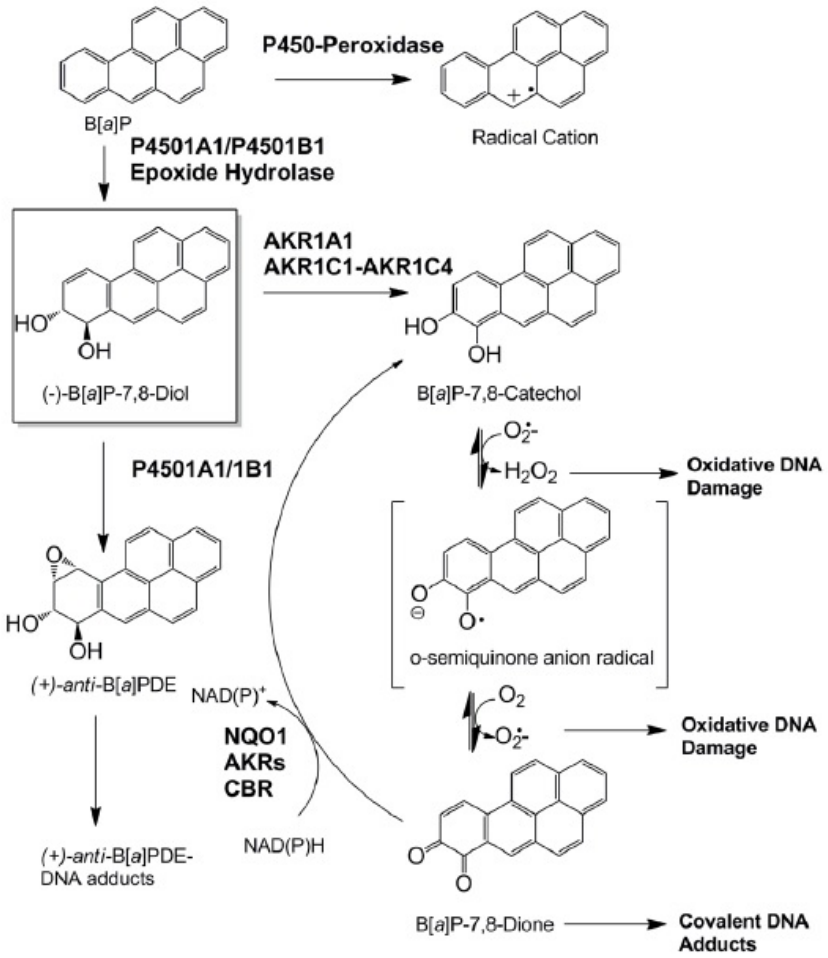
Parent PAHs have low chemical reactivity and must be metabolically activated to electrophilic intermediates to exert their carcinogenic effects (Sims and Grover, 1974; Conney 1982; Thakker *et al.*, 1985). Three pathways of PAH activation have been proposed in the literature and are best exemplified with B[*a*]P (Figure 7.2). In the first pathway, B[*a*]P is metabolically activated by either P450 peroxidase or another peroxidase by acting as a co-reductant of complex-1 (Fe^{V}). This leads to a radical cation on the most electron-deficient C6 atom, which is highly reactive and capable of forming unstable C8-guanine [8-(benzo[*a*]pyren-6-yl)guanine)], N7-guanine [7-benzo[*a*]pyren-6-yl)guanine], and N7-adenine [7-benzo[*a*]pyren-6-yl)adenine] depurinating DNA adducts (Cavalieri and Rogan, 1995). Evidence for this pathway comes from *in vitro* reactions with B[*a*]P, microsomes, and a peroxide substrate, which has led to the trapping of DNA adducts, as well as from mouse skin studies (Cavalieri *et al.*, 1990, 1991). Data exist that B[*a*]P and dibenzo[*a,l*]pyrene can exert their tumorigenicity through this mechanism in mouse skin and rat mammary gland (Cavalieri *et al.*, 1991, 2005) In addition, trace amounts of B[*a*]P-depurinating DNA adducts have been detected in the urine of smokers and in women exposed to household smoke (Casale *et al.*, 2001). However, apart from this single study, the evidence to support this mechanism due to inhalation exposure to PAH is not strong.

In the second pathway, B[*a*]P is metabolically activated to vicinal diol-epoxides (Jerina *et al.*, 1991) formed through a three-step process involving oxidation and hydrolysis reactions (Figure 7.2). In the first step, B[*a*]P is converted preferentially in the lung by the cytochrome P450 isozyme P4501B1 to the major (+)-7*R*,8*S*-epoxide and minor (–)-7*S*,8*R*-epoxide. In the second step, the 7*R*,8*R*-*trans*-dihydrodiol is predominately formed by the action of epoxide hydrolase. In the third step, diol-epoxide diastereomers are generated by another oxidation reaction via various P450 enzymes, including P4501B1 (Thakker *et al.*, 1985; Petruska *et al.*, 1992; Guengerich, 1993; Constantin *et al.*, 1994; Cavalieri and Rogan, 1995; Shimada *et al.*, 1999, 2001).

Diol-epoxides have been studied in various animal carcinogenicity models. It has been revealed that the diol-epoxides with the highest carcinogenic activity are in general the *anti*-diastereomers and especially the enantiomers with *R*-absolute configuration at the benzylic arene carbon (Thakker *et al.*, 1985; Glatt *et al.*, 1991). In studies of interactions of diol-epoxides with DNA, they demonstrate a high preference for the exocyclic amino group of deoxyguanosine and deoxyadenosine, where the major adduct derived from B[*a*]P is (+)-*anti*-B[*a*]PDE-N^2-dGuo (Jeffrey, 1985; Gräslund and Jernström, 1989; Jerina *et al.*, 1991; Geacintov *et al.*, 1997). This pathway of metabolic activation has been observed for many PAHs in ambient air, including 5-methylchrysene (Melikian *et al.*, 1983, Koehl *et al.*, 1996), benz[*a*]anthracene (Cooper *et al.*, 1980), benzo[*b*]fluoranthene (Ross *et al.*, 1992), B[*a*]P (as outlined above), dibenz[*a,h*]anthracene (Platt *et al.*, 1990), and dibenzo[*a,l*]pyrene (Luch *et al.*, 1997, 1999), in *in vitro* systems (cell extracts, microsomes, and cell culture systems), and in some cases in *in vivo* studies in animals and humans. For example, PAHs within airborne $PM_{2.5}$ produced DNA bulky stable adducts in human lung cell co-cultures (Abbas *et al.*, 2013).

In the third pathway, PAHs are metabolically activated to *o*-quinones by the action of aldo-keto reductases (AKRs) (Penning *et al.*, 1999; Penning, 2004). For B[*a*]P, the sequence involves

Fig 7.2 Pathways of PAH activation using benzo[*a*]pyrene as an example.



Source: Park and Penning (2008); reproduced with permission from John Wiley & Sons.

the NAD(P)$^+$-dependent oxidation of the 7*R*,8*R*-*trans*-dihydrodiol to a ketol catalysed by AKR1A1, AKR1C1–AKR1C4 (Figure 7.2). The ketol then spontaneously rearranges to a catechol, which undergoes air-oxidation to yield B[*a*]P-7,8-dione and reactive oxygen species (ROS) (Palackal *et al.*, 2001, 2002; Penning *et al.*, 1996). B[*a*]P-7,8-dione is both electrophilic (will react with DNA) and redox-active. In the presence of reducing equivalents and NQO1, AKRs themselves, and carbonyl reductase, the quinones can be reduced back to the corresponding catechols, and if they are not intercepted a futile redox cycle will ensue in which NADPH is depleted and ROS is amplified (Shultz *et al.*, 2011). This pathway of metabolic activation has been observed for several PAHs in ambient air, including phenanthrene, chrysene, 5-methyl-chrysene, benz[*a*]anthracene, and B[*a*]P in *in vitro* systems (recombinant enzymes) and cultures of human lung cells (Palackal *et al.*, 2001, 2002; Park *et al.*, 2008b).

Efforts have been made to assess the contribution of each of these pathways to the metabolic activation of B[*a*]P in human lung cells. Using a stable isotope dilution liquid chromatographic mass spectrometric method, signature

metabolites of each of the three pathways were measured: B[*a*]P-1,6-dione and B[*a*]-3,6-dione (radical cation metabolites), B[*a*]P-tetraol-1 (diol-epoxide metabolites), and B[*a*]P-7,8-dione (*o*-quinone metabolites) in human bronchoepithelial (H358) cells in the presence and absence of the aryl hydrocarbon receptor (AhR) agonist TCDD. It was found that each of the pathways contributed equally to B[*a*]P metabolism in the presence and absence of TCDD (Lu *et al.*, 2011).

The rate of absorption of PAHs from the tracheobronchial epithelium after inhalation exposure is determined by their high lipophilicity (Gerde *et al.*, 1993). For lipophilic carcinogens such as B[*a*]P, the delayed absorption in the airway mucosa is a result of slow passage through the airway epithelium, yielding a very high dose to these target cells. Because of the long retention time, the metabolic activation can be considerable even at low enzyme activities (Bond *et al.*, 1988).

Modes of action

Carcinogenic PAHs are generally positive in short-term tests for mutagenicity (Table 7.4), for example the bacterial *Salmonella* mutagenicity (Ames) assay and the *HPRT*-mammalian cell mutagenicity assay, provided a metabolic activation system is present (Malaveille *et al.*, 1977; MacLeod *et al.*, 1988; Chen *et al.*, 1990; Wei *et al.*, 1993). In the Ames assay, a rat liver S9 activation system is used; in the *HPRT* assay, recombinant P4501A1 and P4501B1 are co-expressed. The mutagenic species has been identified by comparing the mutagenic potency of different PAH metabolites, which demonstrates that of the known metabolites the diol-epoxides are the most potent mutagens (Malaveille *et al.*, 1977). Treatment of a plasmid containing *K-Ras* with the (+)-*anti*-B[*a*]PDE followed by transfection into NIH3T3 cells led to cell transformation with increased foci in soft agar. Rescue of the plasmid showed that there were single point mutations of the 12th and 61st codons, which could explain the transformation potential of the diol-epoxide. The dominant mutation observed was a G → T transversion, consistent with DNA-adduct formation on deoxyguanosine (Marshall *et al.*, 1984). One of the most compelling pieces of data has shown that by using ligation-mediated polymerase chain reaction, the (+)-*anti*-B[*a*]PDE preferentially forms DNA adducts in *hot spots* on the *p53* tumour suppressor gene, which is one of the most mutated genes in human lung cancer. These hot spots correspond to the same codons that are mutated in tumours obtained from humans with lung cancer. The dominant mutation observed was again a G → T transversion, consistent with DNA adduct formation on deoxyguanosine (Denissenko *et al.*, 1996; Hainaut and Pfeifer, 2001).

In a separate *in vitro* study, the mutagenic potency of (±)-*anti*-B[*a*]PDE and B[*a*]P-7,8-dione (AKR product) were compared in a yeast-reporter gene assay for *p53* mutation. It was found that B[*a*]P-7,8-dione was 80-fold more mutagenic than the diol-epoxide provided it was permitted to redox cycle (Yu *et al.*, 2002). In these experiments there was a linear correlation between (±)-*anti*-B[*a*]PDE mutagenicity and the formation of (+)-*anti*-B[*a*]PDE-N^2-dGuo adducts, and a linear correlation between B[*a*]P-7,8-dione mutagenicity and the formation of 8-oxo-dGuo adducts (Park *et al.*, 2008a). In addition, B[*a*]P-78-dione gave predominately G → T transversions, consistent with the base mispairing of 8-oxo-dGuo with adenine. The position of the point mutations within *p53* was quite random until there was biological selection for dominance, and then the spectrum of mutations was similar to that seen in lung cancer (Park *et al.*, 2008b). These data suggest that B[*a*]P-7,8-dione formed by AKRs has the potential to contribute to the carcinogenic mode of action of B[*a*]P.

Planar PAHs can induce their own metabolism. Compounds such as B[*a*]P can bind to the AhR (Nebert and Jensen, 1979; Nebert *et al.*,

Table 7.4 Genotoxicity of individual PAHs that are carcinogenic in experimental animals after inhalation or intratracheal instillation

Compound	Results
Anthanthrene	Positive, limited database
Benzo[*b*]fluoranthene	Positive
Benzo[*j*]fluoranthene	Positive
Benzo[*k*]fluoranthene	Positive
Benzo[*a*]pyrene	Positive
Chrysene	Positive
Dibenz[*a,h*]anthracene	Positive
Dibenzo[*a,i*]pyrene	Positive
Indeno[1,2,3-*cd*]pyrene	Positive
Naphthalene	Negative for gene mutations, positive for clastogenicity *in vitro*

Source: WHO (1998); reproduced with permission from the publisher.

1993, 2004). This leads to nuclear localization of the liganded AhR, where it can act as a transcription factor by binding to the xenobiotic response element to induce the *CYP1A1* and *CYP1B1* genes (Denison *et al.*, 1988a, 1988b, 1989), which will result in enhanced monoxygenation of the parent PAH. PAH metabolism leads to the production of electrophiles (e.g. quinones), which can activate the Nrf2-Keap 1 system. Nrf2 acts as a transcription factor and binds to the antioxidant response element to induce γ*GCS*, *NQO1* and *AKR1C1–AKR1C3*, and *AKR1B10* (Burczynski *et al.*, 1999; Jin and Penning 2007; Penning and Drury, 2007). Importantly, AKR1C1–AKR1C3 are involved in the metabolic activation of PAH *trans*-dihydrodiols to the electrophilic and redox active PAH *o*-quinones, which could further exacerbate PAH activation via induction of AKRs. The PAH *o*-quinones produced by this pathway are also ligands for the AhR (Burczynski and Penning, 2000). Thus, both the parent PAH and their downstream metabolites can lead to the metabolic activation of PAHs in ambient air.

PAHs may, in addition to initiating carcinogenesis via a genotoxic mechanism, exert promotional effects through various modes of action. Certain PAHs induce inflammatory processes (Casale *et al.*, 1997). The binding of PAHs to the AhR also leads to transcriptional upregulation of genes involved in growth as well as biotransformation and differentiation (Nebert *et al.*, 1993). Studies also indicate the ability of both PAHs and their metabolites to activate kinases involved in survival signalling, thus giving DNA-damaged cells a survival advantage (Burdick *et al.*, 2003). At higher concentrations some PAHs induce apoptosis (Solhaug *et al.*, 2004). In addition, PAHs show inhibitory effects on gap junctional intercellular communication (Upham *et al.*, 1996; Weis *et al.*, 1998).

Carcinogenicity studies in animals

Most investigations of PAH carcinogenesis by the respiratory route are intratracheal instillation studies (WHO, 1998). In all, 10 PAHs have been found to be carcinogenic in experimental animals after inhalation or intratracheal instillation (WHO, 1998; NTP, 2000) (Table 7.5). Only B[*a*]P and naphthalene have been studied by the inhalation route. In one inhalation study in hamsters, groups of 24 males were 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 hours per day, 7 days per week for the first 10 weeks, then for 3 hours per day for 2 years. Exposure was by nose breathing only. There were no tumours in the controls or in the low-exposure

group. In the other two groups, exposure-related tumours were found in the nasal cavity, larynx, trachea, pharynx, oesophagus, and forestomach, but not in the lung (Thyssen *et al.*, 1981). RIVM (1989) cites two other inhalation studies with B[*a*]P not found in the open literature: one in mice (Knizhnikow *et al.,* 1982; see RIVM, 1989) and one in rats with co-exposure with sulfur dioxide (Laskin *et al.,* 1970; see RIVM, 1989). In both studies malignant lung tumours were observed.

In recent bioassay inhalation studies with naphthalene, Fischer 344/N rats developed neuroblastomas of the nasal olfactory epithelium after being exposed in inhalation chambers to 0, 10, 30, or 60 ppm (80, 52, 157, or 314 mg/m^3) for 6 hours per day, on 5 days per week, for 105 weeks (NTP, 2000). The observed rates in males were 0/49, 0/49, 4/48, and 3/48, respectively, and in females 0/49, 2/49, 3/49, and 12/49, respectively. In addition, adenomas of the nasal respiratory epithelium were observed in 0/49, 06/49, 8/48, and 15/48 males and in 0/49, 0/49, 4/49, and 2/49 females, respectively. In the study with B6C3F$_1$ mice subjected to whole-body exposure of 0, 10, or 30 ppm (0, 52, or 157 mg/m^3) naphthalene in inhalation chambers for 6 hours per day, 5 days per week, for 104 weeks, a statistically significant increase in the incidence of bronchioloalveolar adenomas in high-dose female mice was observed (NTP, 2000). Increased incidences of bronchioloalveolar adenomas and carcinomas were observed in the male mice, but the increases were not statistically significant.

PAHs and their metabolites will also cause lung cancer in animals when administered by other routes. Classically, the newborn mouse model of lung cancer was used to rank the tumorigenicity of different B[*a*]P metabolites, given that the developing lung is more susceptible to carcinogen exposure. Studies such as these showed that the (+)-*anti*-B[*a*]PDE was the most potent lung tumorigen of the known B[*a*]P metabolites (Buening *et al.*, 1978; Kapitulnik *et al.*, 1978). Similarly, in the A/J mouse lung model of B[*a*]P-induced carcinogenesis, *anti*-B[*a*]PDE-DNA adducts were early lesions that could be detected in the initiation phase (Nesnow *et al.*, 1998).

Carcinogenesis experiments with mixtures containing PAHs have also been reported. Heinrich *et al.* (1994) exposed groups of 72 female Wistar rats to a coal tar/pitch aerosol containing either 20 or 46 µg/m^3 B[*a*]P for 17 hours per day, 5 days per week, for 10 or 20 months, followed by a clear 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, 143, 158, and 321 mg B[*a*]P/m^3 hours, and the corresponding lung tumour rates were 4.2%, 33.3%, 38.9%, and 97.2%, respectively, whereas there were no tumours in the control group. In similar experiments in which rats were exposed to coal tar/pitch vapour condensed on the surface of fine carbon black particles, the resulting lung tumour rate was about twice as high.

Pott and Heinrich (1990) have also performed a lifelong inhalation study with rats exposed to diesel exhaust. In this study, tumour rates similar to those in the study with pitch pyrolysis vapours were induced, although the PAH content (measured as B[*a*]P) was 100–1000 times lower. This result indicates that diesel exhaust contains other potent carcinogenic or tumour-promoting compounds besides unsubstituted PAHs.

Numerous carcinogenicity studies have been performed using dermal application and subcutaneous and intramuscular injection (for overview, see WHO, 1998). An oral gavage study with B[*a*]P revealed tumour development in the liver, forestomach, auditory canal, oral cavity, skin, and intestines in both sexes of rats, and additionally the kidney in males and the mammary gland and oesophagus in females (RIVM, 2001). However, no lung tumours were observed after this route of administration. In a feeding study of B[*a*]P in mice, tumours in the tongue,

Table 7.5 Carcinogenicity of individual PAHs in experimental animals after inhalation or intratracheal instillation

Compound	Carcinogenicity (weight of evidence)	Species	No. of studies with positive, negative, and questionable results		
			+	–	±
Anthanthrene	Positive	Mouse	1		
Anthracene	Negative	Rat		1	
Benzo[*b*]fluoranthene	Positive	Rat Hamster	1	1	
Benzo[*j*]fluoranthene	Positive	Rat	1		
Benzo[*k*]fluoranthene	Positive	Rat	1		
Benzo[*g,h,i*]perylene	Negative	Rat		1	
Benzo[*a*]pyrene	Positive	Mouse Rat Hamster	1 9 11	1	1
Benzo[*e*]pyrene	Negative	Rat		1	
Chrysene	Positive	Rat	1		
Dibenz[*a,h*]anthracene	Positive	Rat Hamster	1 1	1	
Dibenzo[*a,i*]pyrene	Positive	Hamster	2		
Indeno[1,2,3-*cd*]pyrene	Positive	Rat	1		
Naphthalene	Positive	Mouse Rat	1		2
Phenanthrene	Negative	Rat		1	
Pyrene	Negative	Hamster		1	

Source: WHO (1998); reproduced with permission from the publisher; IARC (2002).

oesophagus, forestomach, and larynx, but not lung, were observed (Culp *et al.*, 1998).

Carcinogenicity studies in humans

Occupational exposures

A review and meta-analysis on the association between occupational exposure to PAHs and lung cancer development in 39 cohorts found an average relative risk of 1.20 per 100 μg/m^3 years cumulative B[*a*]P (Armstrong *et al.*, 2004). For some occupations relative risks were considerably higher, but confidence intervals were very wide. For exposures in coke ovens, gas works, and aluminium industries, the risk is equivalent to a relative risk of 1.06 for a working lifetime of 40 years at 1 μg/m^3.

Ambient air exposures

Few studies have addressed the impact of exposure to PAHs in ambient air on human cancer. Studies using other exposure indicators (PM or NO_2) have shown associations between air pollution and lung cancer; however, no PAH exposure information was available (Pope *et al.*, 2002; Hoek *et al.*, 2002; Nafstad *et al.*, 2003). An analysis of the United States data on lung cancer, PM exposure, and older PAH and metal air concentration data, supports the plausibility that known chemical carcinogens may be responsible for the lung cancer attributed to $PM_{2.5}$ exposure in the American Cancer Society study (Harrison *et al.*, 2004). A study by Cordier *et al.* (2004) found an increased risk of childhood brain cancer associated with PAH exposure. Both paternal

preconception occupational PAH exposure and paternal smoking were associated with increased risks for childhood brain tumours.

Human susceptibility

PAHs are metabolically activated by phase I P450 isozymes (*CYP1A1*, *CYP1B1*) in combination with epoxide hydrolase (*EPHX*) and phase I AKR isozymes (*AKR1A1*, *AKR1C1-AKR1C4*) and are detoxified by phase II enzymes including *GSTs*, *UTGs*, *SULTs*, and *COMT*. In addition, bulky covalent diol-epoxide DNA adducts can be repaired by nucleotide excision repair proteins (*XPD* [helicase], *XPA*, and *XPC* [damage recognition]), and oxidative DNA lesions can be repaired by base excision repair enzymes (*hOGG1* and *APE*). Each of these genes is highly polymorphic in the human population. (A complete list of these variants is available at the NCBI database: http://www.ncbi.nlm.nih.gov/.) Many of these variants are non-synonymous single-nucleotide polymorphisms (nSNPs) that can affect enzyme activity. Combinations of these nSNPs rather than an individual SNP may affect human genetic susceptibility to PAH emissions in ambient air.

In a study of Prague policemen occupationally exposed to polluted air, B[*a*]P-like DNA adducts were detected and found to be positively associated with SNPs in *XPD* and *GSTM1* (Binková *et al.*, 2007). In another lung cancer case–control study, exposure to environmental tobacco smoke and polymorphisms in *CYP1B1 Leu(432)Val* was significantly associated with lung cancer susceptibility, with an odds ratio for at least one allele of 2.87 (95% confidence interval [CI], 1.63–5.07) (Wenzlaff *et al.*, 2005a). Combinations of the polymorphism in this phase I enzyme gene along with those selected from either phase II enzyme genes (*GSTM1* null, *GSTP1 Ile(105)Val*) or NADPH-quinone oxidoreductase (*NQO1*) *C(609)T*) were also evaluated. Here the combination of the *CYP1B1 Leu(432)Val* allele and the *NQO1 C(609)T* allele was associated with the highest risk of lung cancer (odds ratio [OR], 4.14; 95% CI, 1.60–10.74) (Wenzlaff *et al.*, 2005a). In the same study cohort, variants in *GSTM1*, *GSTT1*, and *GSTP1* were examined to determine whether there was an association of the genotype with lung cancer incidence in never-smokers. Individuals who had been exposed to household environmental tobacco smoke for > 20 years, and who were carriers of either the *GSTM1* null allele or the *GSTP1* Val allele, were at a 4-fold increased risk of developing lung cancer (OR, 4.56; 95% CI, 1.21–17.21) (Wenzlaff *et al.*, 2005b). In a lung cancer case–control study in China, women who were never-smokers were found to be at a significant increased risk of adenocarcinoma if they were carriers of the variants in the nucleotide excision repair variant *XRCC1* 399 Gln/Gln versus the Arg/Arg genotype (OR, 14.12; 95% CI, 2.14–92.95). The OR of lung adenocarcinoma for the *XRCC1* 399Gln allele with exposure to cooking oil smoke was 6.29 (95% CI, 1.99–19.85) (Li *et al.*, 2005). DNA integrity was investigated in 50 bus drivers, 20 garage men, and 50 controls in the Czech Republic and associated with variants in the base excision repair gene *hOGG1*. Carriers of at least one variant (Cys allele) had a higher degree of DNA damage (Bagryantseva *et al.*, 2010). To date, no molecular epidemiological study has been performed whereby combinations of polymorphic variants in phase I, phase II, and DNA repair genes have been pooled. However, based on the studies described, carriers of variants in all three classes of genes might be at higher risk of developing lung cancer from emissions of PAHs in ambient air.

Conclusions

PAHs generated from the incomplete combustion of organic material are ubiquitous contaminants in urban air. There are numerous unsubstituted PAHs (pyrogenic) and substituted PAHs (petrogenic). The pyrogenic PAHs may occur in the gas phase, particulate phase,

or mixtures of both phases. The major worldwide source is the combustion of biofuels, while other sources such as combustion plants, various industrial and production processes, road transport, and waste incineration can contribute. Total PAH levels in some urban areas are in the range of 100–200 ng/m^3 but may be even higher in more polluted areas and can show distinct seasonal variation. However, measurements of total PAHs are relatively scarce. B[*a*]P is the traditional marker for PAHs, but various other individual PAHs have also been proposed, such as fluoranthene, B[*a*]P, and benzo[*b*]fluoranthene. Biomarkers of exposure include 1-hydroxypyrene, 3-hydroxy-B[*a*]P, and tetraols, but DNA and protein adducts can also be measured as intermediate cancer biomarkers. The major disease end-point of interest is lung cancer, and approximately 10–15% of all lung cancer cases are seen in never-smokers. Parent PAHs must be metabolically activated to electrophilic intermediates (radical cations, vicinal diol-epoxides, and *o*-quinones) to act as lung carcinogens. All three routes have been observed in human lung cells. Various promotional effects of PAHs may contribute to their carcinogenic action. In all, 10 PAHs have been found to be carcinogenic in experimental animals after inhalation or intratracheal instillation. Naphthalene seems to be an exception compared with other carcinogenic PAHs as it appears to not be genotoxic. A meta-analysis of occupational cohort studies found a 20% increase in relative risk per 100 μg/m^3 years cumulative B[*a*]P exposure. Studies of ambient air pollution and cancer have demonstrated an association between carriers of polymorphic variants in phase I, phase II, and DNA repair enzyme genes.

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