PART 1.

CONCORDANCE BETWEEN CANCER IN HUMANS AND IN EXPERIMENTAL ANIMALS

CHAPTER 7.

Polycyclic aromatic hydrocarbons and associated occupational exposures

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Properties of PAHs

Most polycyclic aromatic hydrocarbons (PAHs) with potential biological activity have been determined to have a molecular structure that ranges in size from two to six fused aromatic rings (IARC, 2010). The physicochemical properties of these PAHs that are critical to their biological activity vary greatly, because their molecular weights cover a vast range.

Aqueous solubility of PAHs decreases approximately logarithmically with increasing molecular mass (Johnsen et al., 2005). Two-ring PAHs, and, to a lesser extent, three-ring PAHs, dissolve in water; this makes them more readily available for biological uptake and degradation (Mackay and Callcott, 1998; Choi et al., 2010). Furthermore, two- to four-ring PAHs volatilize sufficiently to appear in the atmosphere predominantly in gaseous form, although the physical state of four-ring PAHs can depend on temperature (Atkinson and Arey, 1994; Srogi, 2007).

In contrast, PAHs with five or more rings have low solubility in water and low volatility. They therefore occur predominantly in solid form, bound to particulates in polluted air, soil, or sediment (Choi et al., 2010). In the solid state, these compounds are less accessible for biological uptake or degradation, which means that their persistence in the environment is increased (Johnsen et al., 2005; Haritash and Kaushik, 2009).

The properties that influence the biological activity of PAHs include their vapour pressure, their adsorption on surfaces of solid carrier particles, their absorption into liquid carriers, their lipid–water partition coefficient in tissues, and their limits of solubility in the lipid and aqueous phases of tissues. These properties are linked with the metabolic activation of PAHs, as well as their deposition and disposition.

PAHs share a similar mechanism of carcinogenic action in both humans and experimental animals.

This includes metabolic conversion to oxides and dihydrodiols, which in turn are oxidized to diol epoxides. These oxides and diol epoxides are the ultimate DNA-reactive metabolites of PAHs. The oxides form stable DNA adducts, and the diol epoxides form stable adducts but also unstable adducts (so-called depurinating adducts) with DNA through formation of electrophilic carbonium ions.

Occupational exposure to PAHs

Occupational exposure to PAHs occurs predominantly through inhalation and dermal contact. Industrial processes that involve the pyrolysis or combustion of coal and the production and use of coal-derived products, including coal tar and coal tar-derived products, are major sources of occupational exposure to PAHs. Workers at coal-tar production plants, coking plants, bitumen production plants, coal-gasification sites, smokehouses, aluminium production plants, coal-tarring facilities, and municipal waste incinerators are exposed to PAHs. Exposure may also result from inhalation of engine exhaust and from use of products that contain PAHs in a variety of other industries, such as mining, oil refining, metalworking, chemical production, transportation, and the electrical industry (Vanrooij et al., 1992).

Studies in Germany measured concentrations of PAHs in the breathing zone of chimney sweeps during "black work"; the PAHs in the air samples varied depending on the type of fuel burned (oil, oil/solid, or solid) (Knecht et al., 1989). Concentrations of PAHs in coal-tar products may range from less than 1% to 70% or more (ATSDR, 2002). Occupational exposure can lead to PAH body burdens among exposed workers that are considerably higher than those in the general population.

There is growing awareness that uptake of PAHs through the skin is substantial (Jongeneelen, 2001). Dermal uptake has been shown to contribute to the internal exposure of workers to PAHs; a study in the creosote industry found that the total internal dose of PAHs did not necessarily correlate with levels of inhalation exposure alone, and that dermal exposure contributed significantly (Vanrooij et al., 1992).

Classification of PAHs

The *IARC Monographs Programme* has reviewed experimental data for 60 individual PAHs (IARC, 2010). Of these 60 PAHs, one, benzo[*a*]pyrene, is classified as *carcinogenic to humans* (Group 1). Other PAHs reviewed by IARC include cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, and dibenzo[*a,l*]pyrene, which are classified as *probably carcinogenic to humans* (Group 2A), and benz[*j*]aceanthrylene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*c*]phenanthrene, chrysene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, indeno[1,2,3-*cd*]pyrene, and 5-methylchrysene, which are classified as *possibly carcinogenic to humans* (Group 2B). It should be noted that in the evaluations of benz[*j*]aceanthrylene, benzo[*c*]phenanthrene, benzo[*a*]pyrene, cyclopenta[*cd*]pyrene, dibenzo[*a,h*]anthracene, and dibenzo[*a,l*]pyrene, the mechanistic data available for these compounds were critical for determining the overall evaluation for each one (IARC, 2010).

The remaining 45 PAHs reviewed by IARC were acenaphthene, acepyrene (3,4-dihydrocyclopenta[*cd*]pyrene), anthanthrene, anthracene, 11*H*-benz[*bc*]aceanthrylene, benz[*l*]aceanthrylene, benzo[*b*]chrysene, benzo[*g*]chrysene, benzo[*a*]fluoranthene, benzo[*ghi*]fluoranthene, benzo[*a*]fluorene, benzo[*b*]fluorene, benzo[*c*]fluorene, benzo[*ghi*]perylene, benzo[*e*]pyrene, coronene, 4*H*-cyclopenta[*def*]chrysene, 5,6-cyclopenteno-1,2-benzanthracene, dibenz[*a,c*]anthracene, dibenz[*a,j*]anthracene, dibenzo[*a,e*]fluoranthene, 13*H*-dibenzo[*a,g*]fluorene, dibenzo[*h,rst*]pentaphene, dibenzo[*a,e*]pyrene, dibenzo[*e,l*]pyrene, 1,2-dihydroaceanthrylene, 1,4-dimethylphenanthrene, fluoranthene, fluorene, 1-methylchrysene, 2-methylchrysene, 3-methylchrysene, 4-methylchrysene, 6-methylchrysene, 2-methylfluoranthene, 3-methylfluoranthene, 1-methylphenanthrene, naphtho[1,2-*b*]fluoranthene, naphtho[2,1-*a*]fluoranthene, naphtho[2,3-*e*]pyrene, perylene, phenanthrene, picene, pyrene, and triphenylene. These compounds were determined to be *not classifiable as to their carcinogenicity to humans* (Group 3), because of limited or inadequate experimental evidence (IARC, 2010).

As noted above, benzo[*a*]pyrene is the only PAH classified by IARC in Group 1. A review of the data available for this PAH indicates that the complete sequence of steps in the metabolic activation pathway of benzo[*a*]pyrene to mutagenic and carcinogenic diol epoxides has been demonstrated in humans, in human tissues, and in experimental animals. After exposure, humans

Table 7.1. Group 1 agents associated with dermal exposures to polycyclic aromatic hydrocarbons (PAHs) that cause squamous cell carcinoma of the skin in humans and in rodents

Agent	Target organ		
	Humans	**Mice**	**Rats**
Benzo[*a*]pyrene	No data	Skin	Skin
Chimney sweep soots	Skin, including scrotum	Skin	No data
Coal tar	Skin, including scrotum	Skin	No data
Coal-tar pitch	Skin, including scrotum	Skin	No data
Mineral oils, untreated and mildly treated	Skin, including scrotum	Skin	No data
Shale oils	Skin, including scrotum	Skin	No data

metabolically activate benzo[*a*]pyrene to benzo[*a*]pyrene diol epoxides that form DNA adducts. The *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide–deoxyguanosine adduct has been measured in populations (e.g. coke-oven workers and chimney sweeps) exposed to PAH mixtures that contain benzo[*a*]pyrene. The reactive *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide induces mutations in rodent and human cells. Mutations (G → T transversions) in the K-*ras* proto-oncogene in lung tumours from mice treated with benzo[*a*]pyrene are associated with *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide–deoxyguanosine adducts. Similar mutations in the *KRAS* proto-oncogene and mutations in the tumour suppressor gene *TP53* were found in lung tumours from non-smokers exposed to PAH-rich products of coal combustion that are known to contain benzo[*a*]pyrene (as well as many other PAHs). In an in vitro study, the codons in *TP53* that are most frequently mutated in lung cancer in humans were shown to be targets for DNA adduct formation and mutation induced by benzo[*a*]pyrene. The strong and extensive experimental evidence for the carcinogenicity of benzo[*a*]pyrene in many animal species, supported by the consistent and coherent mechanistic evidence from studies in exposed humans and in experimentally exposed animals, and from in vitro studies in human and animal tissues and cells, provides biological plausibility to support the overall classification of benzo[*a*]pyrene as *carcinogenic to humans* (Group 1) (IARC, 2010, 2012).

Studies of cancer in humans

There are no epidemiological studies on human exposure to individual PAHs, because these chemicals never occur in isolation in the environment but are present as components of complex chemical mixtures. PAHs are very widespread environmental contaminants, because they are formed during incomplete combustion of materials such as coal, oil, gas, wood, or waste, or during pyrolysis of other organic materials, such as tobacco. Data on the carcinogenicity of PAHs to humans are available primarily from studies in occupational settings where workers are exposed to mixtures containing PAHs. It is difficult to ascertain the carcinogenicity of the component PAHs in these mixtures, because of potential chemical interactions and the presence of other carcinogenic substances.

Certain occupations associated with high exposure to PAHs have been classified by IARC as *carcinogenic to humans* (Group 1); these include coal gasification, coke production, coal-tar distillation, chimney sweeping, paving and roofing with coal-tar pitch, and work involving mineral oils, shale-oil production, and aluminium production. In most cases the classification is based on epidemiological studies of increased cancer incidence without reference to supporting evidence from bioassays in experimental animals. The roles of individual PAHs in the genesis of cancer observed in these occupations could not be defined (IARC, 2010).

Tumour site concordance

There are six IARC Group 1 agents that cause non-melanoma tumours of the skin (Rice, 2005). Five of these are related to occupations where PAH exposures are high and are believed to be the causative agents (Table 7.1). There is a precise correlation between carcinogenicity to human skin and carcinogenicity to mouse skin for these five

Table 7.2. Group 1 carcinogens associated with inhalation exposures to polycyclic aromatic hydrocarbons (PAHs) that cause lung cancer in humans and in rodents

Agent	Target organ	Route/target organ	
	Humans	**Mice**	**Rats**
Benzo[*a*]pyrene	No data	Intraperitoneal injection of and oral exposure to soot extracts/ lung	Intratracheal and intrapulmonary instillation of soot extracts/lung
Chimney sweep soots	Lung	No data	Intratracheal instillation of soot extracts/ lung
Coal-tar vapours from coke ovens	Lung	Inhalation/lung	Inhalation/lung
Soots and vapours from aluminium production	Lung, bladder	No data	No data

PAH-associated exposures when the complex mixtures isolated from the occupational environment are applied topically.

In 1775, Pott made the pioneering observation that cancer of the scrotum in chimney sweeps was an occupational disease resulting from direct contact with soot (Pott, 1775). All five established PAH-based chemical carcinogens for human skin to which exposures occur by direct dermal contact are complex mixtures: coal tar, coal-tar pitch, untreated and mildly treated mineral oils, shale oils, and soots. Because these mixtures contain PAHs, all have a genotoxic component to their mode of action in rodents. Most of the individual PAHs classified by IARC as either *probably carcinogenic to humans* (Group 2A) or *possibly carcinogenic to humans* (Group 2B) (listed above) are genotoxic and have been shown to cause skin cancer and/or be initiators of skin cancer in rodents (IARC, 1983, 2010).

Soots and vapours from coke production, aluminium production, and related industries also cause lung cancer in humans, but only extracts of soot and vapours from coke production have been tested in rodents by an appropriate route (Table 7.2). Both mice and rats developed lung tumours after inhalation of coal-tar vapours from coke ovens. Soot extracts caused lung tumours in rats after intratracheal instillation. There appears to be a good correlation between lung cancer in humans and in rodents for these two mixtures when studied by an appropriate route in mice and rats. All these complex mixtures have genotoxic activity, which is recognized to underlie their carcinogenic activity in the lung. In summary, many of the individual PAHs in these complex mixtures that have been classified by IARC as either *probably carcinogenic* or *possibly carcinogenic* to humans are also genotoxic and have been shown to cause lung tumours in rodents when administered by an appropriate route (IARC, 2010).

The various tissue compartments of the respiratory tract are metabolically active towards exogenous chemicals in both humans and experimental animals and are clearly capable of transforming many metabolism-dependent chemicals, including carcinogenic PAHs, to their chemically reactive metabolites (Rice, 2005). In the lung, metabolically active cell types include pulmonary macrophages as well as epithelial cells.

Benzo[*a*]pyrene is the only PAH that has been classified by IARC as *carcinogenic to humans* (Group 1). As indicated above, the basis for this classification is the extensive knowledge of the mechanism of carcinogenic action of benzo[*a*]pyrene in humans and experimental animals. None of the many remaining PAHs shown to be carcinogens in animals have been classified as an IARC Group 1 carcinogen, most likely because much less mechanistic information is available for these agents than for benzo[*a*]pyrene. These other PAHs are classified as either *probably carcinogenic to humans* (Group 2A) or *possibly carcinogenic to humans* (Group 2B). Most marked human occupational exposure to these compounds involves complex mixtures that contain more than one of these PAHs and that often contain other, non-PAH carcinogens. Therefore, the carcinogenic activity of these mixtures cannot confidently be ascribed to any one of their individual components.

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