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Polycyclic Aromatic Hydrocarbons and Petroleum Industry

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CHEMISTRY AND STRUCTURES

The term polycyclic aromatic hydrocarbons (PAHs) generally refers to a group of chemical compounds consisting of carbon and hydrogen atoms arranged as planar compounds whose principal structural feature is fused rings. Their nomenclature has evolved over many decades and is complex. A comprehensive listing, including traditional synonyms and chemical structures, is given by Sander and Wise (1).

PAHs are produced during the incomplete combustion of organic material and are among the most ubiquitous environmental pollutants. The combustion processes that release PAHs invariably produce a variety of compounds, and in fact, it is difficult or impossible to ascribe health effects in humans to particular members of the PAH family. Hence, PAHs are usually treated as a group for the purpose of risk assessment. However, the relative amounts of individual PAHs released vary from one source to another. The PAH "fingerprint" of diesel exhaust, for example, is markedly different from that of mainstream tobacco smoke (2). Thus, environmental concentrations of PAHs reported in the literature often consist of lists with varying numbers of compounds. Polycyclic organic matter is defined as a group of 16 individual PAH species (acenaphthene, acenaphthylene, anthracene, **benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene**, benzo(ghi)perylene, **benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene**, fluoranthene, fluorene, **indeno(1,2,3-cd)pyrene**, naphthalene, phenanthrene, pyrene) that includes a group of seven PAHs (**in bold**) that are probable human carcinogens. Figure 81.1 illustrates structures of key PAHs. The best-known PAH is benzo(a)pyrene (BaP), due to its early identification in coal tar and later use as a model compound for investigating the carcinogenic properties of tobacco smoke.

SOURCES OF POLYCYCLIC AROMATIC HYDROCARBONS IN THE ENVIRONMENT

PAHs enter the environment through both natural and manmade processes. The principal natural sources of environmental PAH are forest fires and volcanic activity (3,4). Forest fire emissions are particularly severe in Indonesia, where they are often lit to clear forests in preparation for agricultural activities. During the 1997 Indonesian haze disaster, concentrations of PAH were 6 to 14 times higher than in unaffected areas (5). Malaysia, relatively unaffected until recently, has had severe haze problems. Fires in peat forests in Malaysia are thought to contribute 25% to 35% of atmospheric PAH (6). Burning of wood for heating and cooking has always been an important manmade source of atmospheric PAH. Since the Industrial Revolution there have

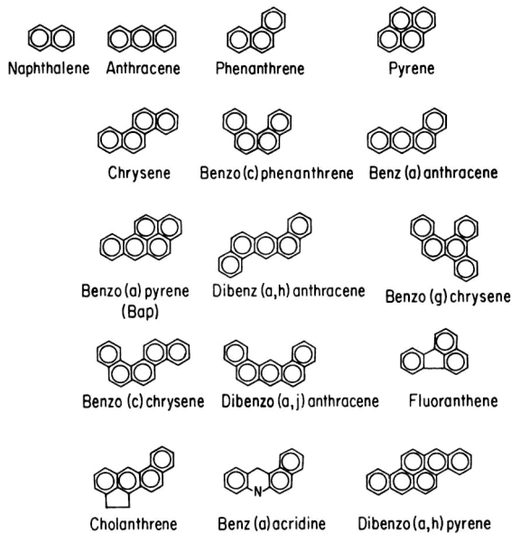

Figure 81.1 PAHs.

been important stationary sources, such as manufacturing and power generation, and since the early 20th century, mobile sources in the form of gasoline and, later, diesel-fueled engines also became important contributors to total environmental PAHs.

Stationary Anthropogenic Sources of Polycyclic Aromatic Hydrocarbons Emissions

Stationary sources of anthropogenic PAH emissions arise from industrial and household activities and account for about 80% of total annual PAH emissions in the United States (7). Industrial sources include power generation, municipal incinerators, and industrial manufacturing processes.

It is difficult to estimate precisely the contribution to total atmospheric PAH from its many different sources, and few such estimates are available. A 1982 report by Ramdahl et al. (8) put the proportion of PAH emissions in the United States from industrial sources at 41%; residential heating 16%; mobile sources 25%; open burning 13%; and power generation and incineration 5% and 1%, respectively. Total PAH emissions were estimated at about 11,000 metric tons. Boström et al. (10) cite tabulations from the European Environmental Agency that break down an estimated 1,900 tons of PAH emissions in 1992 according to emission source: 60% (1,120 tons) was attributed to nonindustrial combustion plants, including domestic wood burning; 20% (383 tons) was from road transport; and lesser amounts were from production processes and combustion in manufacturing industries (9).

Residential heating, including wood burning

Boström et al. (10) note that "residential burning of wood is regarded as the largest source of PAHs" in both the United States and Sweden. In Sweden, between 1990 and 1995, domestic heating sources including district heating contributed up to one third of total emissions of PAHs to air (101 out of 153 total tons per year in 1995).

In the United States there has been considerable progress in improving the efficiency of outdoor wood-burning furnaces for heating homes and hot water. The U.S. Environmental Protection Agency (EPA) reported in 1998 that two different wood furnace designs emitted 0.2 g to 0.4 g PAH per kg wood fuel under various conditions. Emissions in relation to energy output were less than 17 mg per MJ input, which was less than a certified wood stove but several orders of magnitude greater than a natural gas furnace (11). Measurements of PAH in domestic wood emissions were dominated by phenanthrene (690 μg per MJ), followed by fluoranthene (148 μg per MJ), pyrene (114 μg per MJ), and anthracene (97 μg per MJ). BaP content was minor (10 μg per MJ) (12). Burning of heating oil for home heating is a minor source of PAH, especially compared with wood burning (13).

Power Generation

Coal-fired power plants have represented a source of environmental PAH, at least in the past. In a 1982 study, high concentrations of PAH were reported in sediments taken in southwestern Lake Erie near a large coal-fired power plant (14). However, increasingly stringent regulations over the years have reduced their importance (15,16).

Municipal Incinerators

Municipal incinerators are a troublesome source of PAH emissions, in part because it is difficult for municipal authorities to exercise stringent control over the content and composition of the refuse that they must collect for legal and public health reasons. PAH measured in fly ash from municipal waste incinerators usually includes phenanthrene, benzo(g,h,i)perylene, fluoranthene, benzo(a)fluoranthene, indeno(1,2,3-c,d)pyrene, and chrysene (17–19). The relative abundance of specific PAH has been reported to differ considerably between incinerators operated in the United States and in the United Kingdom: Shane et al. (20) reported phenanthrene to be the most abundant and frequently detected PAHs in samples of fly ash and bottom ash colleted from 18 U.S. sites, whereas British data favored benzo(g,h,i)perylene.

Industrial Manufacturing

Several manufacturing activities have been responsible for large environmental emissions. These include

manufacture or processing of coal tar, coke, asphalt, and petroleum catalysts/cracking operations. Coal tars are byproducts of destructive distillation (carbonization) of coal to produce coke or gas and may contain hundreds to thousands of individually identifiable chemicals (21,22). Coal tars are used in the manufacture of industrial products, including pesticides and pharmaceuticals, and have been used as auxiliary blast-furnace fuels in the production of steel (23). Coal tars result from the cooling and purification of manufactured gas, a process that can also produce waste products known as "purifier waste," which could contain sulfur and cyanide impurities, and may persist in the environment for many years (24). Coal-tar pitches, which are formed as residues during distillation of coal tars, are used as a binder in preparing anodes used in the smelting of aluminum. It has been noted that in the United Kingdom, aluminum production and anode baking (part of the anode manufacture process) were the largest sources of PAH emissions until 1996, contributing about half of all emissions. However, as a result of the 1990 Environmental Protection Act, which led to heavy investment in abatement equipment, emissions were eventually reduced to about 5% of the total (25).

Mobile Sources of Polycyclic Aromatic Hydrocarbon Emissions

Automotive exhaust from cars and trucks is a major contributor to atmospheric PAH, particularly in urban environments (26). As Boström et al. (27) note, "vehicle exhaust is the largest contributor to PAH emissions in central parts of large cities." PAH composition varies by type of vehicle fuel (gasoline vs. diesel) and is further affected by the presence or absence of a catalytic converter. Furthermore, PAHs are emitted from automobile exhaust in the vapor phase, as well as in particulate matter (28). Because some PAHs occur primarily in the vapor phase (e.g., phenanthrene), whereas others are almost exclusively bound to particles (e.g., coronene), characterization of the composition of an atmospheric mixture is best done by presenting as complete PAH profiles as possible. Boström et al. (27) compare PAH emissions by vehicle type, fuel, and catalytic converter use, for up to 25 individual PAHs, to demonstrate a decrease in total emissions by a factor of five upon changing from the nonenvironmentally classified diesel fuel (MK3) to the environmentally classified fuel (MK1). They also point out that cold-start emissions from gasoline vehicles may account for more than 50% of total PAH emissions from gasoline vehicles (29).

Indoor Environment

Indoor sources of PAH can also contribute to an individual's total air exposure, especially in episodic events, including smoking (30,31), and for three-ringed PAH compounds (32). Indoor air concentrations of PAH generally reflect both indoor and outdoor sources. Data from the Total Human Environmental Exposure Study, which examined human exposure to BaP via inhalation and food pathways for 13 households in Philipsburg, New Jersey, suggested that up to 50% of the outdoor particulate concentration of BaP could penetrate indoors (33). Studies by Sheldon et al. (34,35) also found outdoor BaP highly correlated with indoor levels in California, contributing more than 50% on average to indoor levels. Studies done elsewhere have found similar results: the contribution of outdoor sources to the heavier PAHs was 63% to 80% for five- to seven-ringed compounds in U.S. cities and 76% for BaP in Japanese cities (36). In one study, homes with gas heating systems were found to have higher average indoor PAH than homes with electric heating systems (37).

HUMAN EXPOSURES

Environmental

Individuals are exposed to complex mixtures of pollutants that may have arisen from a multitude of sources. It is rarely possible to track down specific atmospheric sources, especially in urban environments. Attempts have been made to characterize the relative abundance or "fingerprints" of atmospheric PAH in a variety of settings. Khalili et al. (2), for example, measured the concentration of 20 PAHs near specific sources in the Chicago metropolitan area. They found two- and three-ringed PAHs responsible for up to 98% of the total measured concentration near coke ovens and in highway tunnels, but for only 73% to 76% of the total in auto (gasoline) and bus (diesel) garages.

Air Pollution

Besides direct exposure to automotive exhaust, secondary exposure may occur to PAHs that have been previously deposited in soils, highways, and other locations of human activities. Instrumentation and methods have been developed that make it possible to measure both PAHs and volatile organic compounds in indoor air (38). The EPA Toxic Release Inventory for 1992 contained a partial list of releases of anthracene to the environment from manufacturing or processing facilities, showing amounts of up to 11,090 pounds of PAH per year (39). Besides "ordinary" air pollution, exposure to PAH may occur following natural or manmade disasters. Pleil et al. (40) reported significant levels of airborne PAH associated with the collapse of the World Trade Center towers on Sept. 11, 2001, as well as from subsequent use of diesel-powered equipment during the cleanup operation. For further information on air

pollution in general, see Chapters 93 to 96, which deal with outdoor and indoor sources, epidemiology, human clinical studies, and toxicological studies.

Water Pollution

PAH may be found as contaminants of both surface and ground water, with atmospheric deposition providing the major contribution (7,41). The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for PAH catalogs the following sources of PAH in surface waters: deposition of airborne PAH, municipal wastewater discharge, urban stormwater runoff, runoff from coal storage areas, effluents from wood treatment plants and other industries, oil spills, and petroleum pressing (7). ATSDR notes that data on PAH in groundwater are scant, citing an American Petroleum Institute estimate of 1 to 2 tons of BaP released from municipal sewage effluents and 0.1 to 0.4 tons of BaP from petroleum refinery wastewaters for 1977 (42). The EPA National Urban Runoff Program, which operated between 1978 and 1983, reported concentrations of PAH above 1,000 ng per L (43). Reports over the past several decades have documented the occurrence of PAH in surface water samples taken from geographically disparate areas, including four cities in the eastern United States (Huntington, West Virginia; Buffalo, New York; Pittsburgh, Pennsylvania; and Philadelphia, Pennsylvania—with a PAH concentration of 600 ng per L in Pittsburgh) (44); 11 locations along the Mississippi River, with the highest concentration of phenanthrene at 34 ng per L measured near New Orleans (45); and the St. Lawrence River and tributaries, where Pham et al. detected phenanthrene, benzo(b)fluoranthene, fluoranthene, and pyrene (46). As might be expected, much higher concentrations of PAH have been found in industrial effluents, such as refinery wastewaters (47,48).

Levels of PAH in finished drinking water are generally very low, because overall water quality is strictly regulated and monitored in most heavily populated areas. Nevertheless, drinking water may occasionally be contaminated with PAH or with chlorinated derivates of naphthalene, phenanthrene, fluorene, and fluoranthene, as has been reported in a Japanese study (49).

Soil

Airborne PAH originating in both stationary and mobile sources may be deposited near the source but can also travel a considerable distance. Heavy soil contamination has been documented on current and former industrial sites, including those of former manufactured gas plants (50). Contributions to PAH in residential soil are primarily from deposition of particulate matter from highway traffic, with localized contributions from barbecuing and operation of gasoline-powered lawnmowers (51). PAH along highway rights of way are mainly from automotive exhaust as well as from wearing of tires and asphalt. In a Dutch study, Van Brummelen et al. (52) sampled four soil layers at 10 sites at increasing distances from a blast-furnace plant, and were able to estimate the relative contribution of PAH from the plant and from "background" sources.

The presence of PAH in residential soils does not automatically imply a specific level of human exposure, because this would depend on many factors related to human activities around the home. In recent years methods have been developed to estimate potential exposure to PAH from soil that has been brought into households from outdoors by their occupants. Chuang et al. (54,55) obtained profiles of PAH in house dust and tracked-in soil, gathered using a specially designed vacuum cleaner (high-volume surface sample = HSV3) (53). They found PAH concentrations greatest in entryway soil > house dust > pathway soil > foundation soil (54,55). Beyea et al. (56) used measurements of yard soil around the households of participants in a case–control study of breast cancer to optimize models of exposure to traffic sources of PAH. Estimates of PAH exposure using these methods may permit assessment of risk in future epidemiological studies.

Marine Sediment

Sediments are major sinks for PAH, primarily due to their low solubility and strong affinity for organic carbon in particulate matter (57). Numerous studies of PAH in sediment cores have been carried out over the years. Hites et al. (58) identified anthropogenic combustion of fossil fuels as the primary source of PAH in cores taken to a depth of 42 cm from Buzzard's Bay, Massachusetts. Wenning et al. (59) took 13 core sediments from the Passaic River in Newark, New Jersey, and concluded that primary sources of PAH, as well as polychlorinated biphenyls, were discharges of industrial effluents either directly into the waterway or through combined sewer overflows. The accumulation of PAHs and other industrial pollutants in marine sediments is an important factor contributing to the bioaccumulation of these compounds in fish and shellfish, which are eventually consumed by humans. Eisler (60) has tabulated bioconcentration factors in selected species of aquatic organisms for anthracene, BaP, and several other PAHs, reporting, for example, a factor between 4,400 and 9,200 in rainbow trout.

Personal

Dietary

Food. Exposure to PAH can be through preparation of food and in the food itself. PAH have been measured in emissions from charcoal grilling of meat by Dyremark et al. (61). They identified PAH levels of 23 μg per kg in the smoke emanating from grilling of minced lean pork, but attributed most of the PAH in the local air

environment to combustion of the charcoal rather than the meat itself, and concluded that the overall contribution to air pollution of this source was relatively minor. Kazerouni et al. (62) measured BaP in composite samples of commonly consumed foods in the second National Health and Nutrition Examination Survey and found the highest levels (about 4 ng per g cooked meat) in grilled/barbecued, very well-done steaks and hamburgers and in similarly prepared chicken with skin. BaP in nonmeat items was low. Consumption of bread/cereal/grain and grilled/barbecued meat was estimated to contribute to about one fourth of the mean daily dietary intake of BaP. The database of PAH measurements in food was later used by Sinha et al. (63) to relate estimated dietary exposure to risk of colorectal adenocarcinoma in a clinic-based case-control study, with a 5-fold risk associated with individuals in the highest quintile of dietary consumption.

Cigarette Smoking

Cigarette smoke contains an abundance of PAH, which contribute to its carcinogenic properties. The carcinogenicity of these PAHs were already well-known at the time of publication of the landmark 1964 Surgeon General's report, which listed the concentration in cigarettes, cigars, and pipes of BaP, acenaphthylene, anthracene, and pyrene (64).

Literally thousands of publications since that time have confirmed cigarette smoking as a cause of many types of cancer, including lung, larynx, oral cavity, esophagus, bladder, hematopoietic system, and other organ systems (65). Cigarette smoke is a highly complex mixture, which includes not only PAHs, but also other carcinogens such as nitrosamines; aromatic amines; heterocyclic amines; a variety of other miscellaneous organic compounds; and heavy metals such as arsenic, nickel, chromium, cadmium, and lead (66). Consequently, it is not possible to ascribe the carcinogenic effects of tobacco use to specific PAH, but these undoubtedly play a role in human health effects.

Occupation

Exposure to PAH occurs in numerous industries, including coke production and downstream industries like steel manufacture, aluminum, petroleum refining, coal gasification, and manufacture. The primary routes of exposure to coal tars and coal-tar products are inhalation, ingestion, and dermal contact. Actual numbers of exposed workers are difficult to estimate; outdated estimates from the National Occupational Hazard Survey and the National Occupational Exposure Survey, both done in the 1970s, put the number of workers directly or indirectly exposed to coal tar products at 145,000. Besides in heavy industry such as coke, steel, and aluminum, exposure occurs in occupations in which asphalt (also called bitumen) is used, such as road paving and roofing (68). Burstyn et al. (69) have developed a methodology for incorporating exposure measurements among asphalt workers into a database that is well-suited to epidemiological studies of health risks. Both professional and volunteer firefighters are also exposed to PAH in the course of their duties (70), although such work also entails exposure to many complex mixtures of natural and synthetic combustion products. Concerns have been raised that military personnel stationed in Kuwait during the Gulf War experienced lengthy exposures to PAH from the hundreds of deliberately set oil well fires (71).

Occupational exposure to PAH may also affect workers engaged in both diesel and gasoline-powered motor transport, including automobiles, trucks, heavy equipment such as that used in mining and construction, and marine. Actual exposures obviously depend upon individual circumstances, such as the portion of the workday spent in or near vehicles, and time spent outdoors versus indoors, underground, or in tunnels. The number of workers employed in the trucking industry in the United States alone is estimated to be more than 9 million, the largest single employer being the United Parcel Service. Exposures to such workers do not include additional exposures off the job. Health consequences of occupational exposures are discussed later in a separate section.

The Oil-and-Gas Industry and Petroleum Fuels

Many sources of PAH exposure are directly related to the oil-and-gas industry and the use of petroleum as a fuel. Petroleum, or crude oil, is the most heavily consumed form of energy, comprising 42.7% of total world energy consumption. Petroleum provides gasoline for transportation and heating oil and for a variety of nonenergy products, such as lubricating oil and chemical feedstocks from which plastics are made. PAH, being produced whenever organic material is combusted, are emitted in the form of air pollution in either volatile (gaseous) or particle form.

The petroleum (and gas) industry is divided into two major segments: the "upstream" (drilling, well servicing, pumping, maintaining collecting systems) and the "downstream" (refining, product manufacturing, marketing).

Crude oil is a mixture of more than 1,000 compounds, some of which are PAHs. Quantities of the single-ring aromatic hydrocarbon benzene, and substituted and saturated PAHs, called naphthalenes, are present in all but the lightest crude oils, and the content of PAHs increases in heavier crudes to about 7%. Although a variety of hydrocarbon products produced from petroleum have specific toxic effects, the toxicity of crude petroleum itself to humans is relatively low. Despite this

relative reduced toxicity, PAHs are responsible for most of the toxicity of crude oil in the ecosystem when a spill occurs. After a spill, the volatile hydrocarbons evaporate quickly, leaving the PAH-enriched heavier fraction behind. Production water, which is also rich in metals and brine, also contains PAH and represents a major disposal problem for the industry.

The downstream segment of the industry is more likely to present opportunities for occupational exposure to PAH. Refining is a closed process with limited opportunities for exposure to PAH. Crude petroleum first is washed with solvent, which removes salts, heavy hydrocarbons, sulfur compounds, and impurities. Then it is distilled to recover the lighter, low-molecular-weight fractions that are used as fuels and lubricating oils. Cracking is a process that breaks down heavy alkanes into lighter fractions more suitable as fuels. Thermal cracking, which is done using heat, generates PAH that may be left behind in residual material, called coke, although not in large quantities. The coke itself may be recycled in the process. Exposure may occur during maintenance of cracking facilities. Thermal cracking has been replaced in many applications by steam cracking, catalytic cracking, and lower-temperature methods. Cracking is a closed process, and under normal circumstances workers are not exposed to PAH, although that possibility exists during maintenance work.

Asphalt is made from the heavy residual fraction left and is rich in PAH. Exposure to PAH is a hazard in roofing, street paving, and other activities where asphalt is applied in open air.

Natural gas provided 16% of energy consumed worldwide in 1999. It is primarily used for heating, generating electricity, and industry. Due to its chemical structure, mostly methane, it produces less carbon dioxide for the energy it produces than any other fossil fuel. Natural gas does not contain PAH. Most of the hydrocarbon content in natural gas consists of short-chain alkanes, which are generally not toxic. Excess gas may be "flared" on site, ignited in a controlled fashion on top of a stack. When flares burn inefficiently, with rich mixtures exceeding available oxygen, incomplete combustion occurs, and PAHs are produced.

Coalbed methane is a form of natural gas arising from coalbeds. Although the gas itself is free of PAH, the methods used to produce it may result in wastewater contaminated with PAH, which has raised environmental concerns.

Oilsands and oil shale are minerals containing large quantities of a hydrocarbon substance called bitumen. These fossil fuels currently have a small share of world energy consumption but represent a potentially huge supply, especially in North America, where large deposits of oilsands exist in western Canada. The content of PAH in both forms of bitumen and the synthetic hydrocarbon product derived from processing bitumen is higher than in crude oil. The PAH compounds are not necessarily the same as in combustion products, however. Shale oil was extensively evaluated in the 1980s for health risks, and the historic industry appears to have experienced an increased rate of skin cancer. The sites where oilsands are mined and extracted, as well as oilsands processing facilities, do not appear to show unusually high rates of injury or disease, but a comprehensive study has not been performed. Sensitive to the environmental and human health risks of the product, the oilsands industry has made a concerted effort to reduce production of coke and to eliminate sources of exposure in production. The oilsands are a natural geological formation that lies exposed on the surface in the Athabasca region, however, and PAH from bitumen naturally enter some surface waters.

Large oil-and-gas facilities, especially refineries, have large energy requirements that are met by fossil fuels and by cogeneration, making them important stationary sources of PAH emissions.

HUMAN HEALTH EFFECTS

Because PAH almost always occur in the environment as mixtures rather than as individual compounds, it is difficult to ascribe adverse human health effects to individual compounds. Most assessments of the health risks of exposure to PAH, such as that done by ATSDR, are inferred from studies involving exposure to complex mixtures, such as those encountered in occupational settings (e.g., coke oven work and roofing) or cigarette smoking (7).

Toxicity

The largest effort by far toward elucidating human health effects of PAH has been directed toward studies of carcinogenicity. Considering their near omnipresence in occupational and environmental settings, there are surprisingly few available studies of other health effects. This may due be in large part to the fact that exposure to PAH often occurs with other toxic substances, making it difficult to determine the effects of PAH alone. There is certainly ample evidence of serious adverse health effects associated with exposure—mostly by inhalation but by other routes as well—to complex particulate mixtures, of which PAHs frequently make up a substantial proportion. A comprehensive ATSDR toxicological profile of PAH failed to discover specific reports of neurological, reproductive, or developmental effects in either animals or humans (7). Szczeklik et al. (72) found a "marked depression" of mean serum immunoglobulin G (IgG) and IgA in coke oven workers, with some decrease in IgM but an increase in IgE. The coke oven workers had order-of-magnitude-greater measured exposure to PAH relative to comparison workers.

There is limited experimental evidence in rats (73) and cockerels (74) that exposures associated with PAH-producing industries may affect cardiovascular function. Few epidemiological studies have reported PAH-associated cardiovascular risks. In a multicountry collaborative study Burstyn et al. (75) found a dose-related increase in fatal ischemic heart disease (IHD) in a cohort of 12,367 male asphalt workers for whom BaP could be estimated quantitatively and exposure to coal tar semiquantitatively. Both cumulative and average exposure indices for BaP and coal tar were positively associated with mortality from IHD. The highest relative risk was observed for average BaP exposures of at least 273 ng per m^3 [RR = 1.64; 95% confidence interval (CI), 1.13 to 2.38].

Carcinogenicity

The International Agency for Research on Cancer (IARC), in its periodic evaluation of carcinogenic agents and exposures, has summarized the extensive evidence that exposure to a number of PAH sources is carcinogenic (IARC Group I). These include coal tar pitches and coal tars, which are mixtures of PAH and other compounds, exposure to industrial processes such as coal gasification and coke production, aluminum production, iron and steel founding (76,77), and of course tobacco smoking (78). Sources judged carcinogenic by IARC also include mineral oils, shale oils, and soots. Several other sources of exposure are classified by IARC as "probably carcinogenic to humans" (IARC Group IIA), including creosote, diesel exhausts, and petroleum refining (79). Assessment of human cancer risk to coal tar derivatives is based upon a number of occupational studies, some dating back many decades. Lloyd's (80) classic paper on mortality of coke plant workers, for example, documents a 10-fold risk of lung cancer for men employed 5 or more years at full-time topside jobs (i.e., at or near the tops of the ovens). Redmond et al. (81) reported increased risk of cancer of the lung, kidney, and skin in workers exposed to coal tar pitch volatiles. More recently, Boffetta et al. (82) reviewed cancer risks associated with PAH exposure in a variety of occupations, including aluminum production, coal gasification, coke production, iron and steel foundries, tar distillation, shale oil extraction, wood impregnation, roofing, road paving, carbon black production, carbon electrode production, chimney sweeping, and calcium carbide production. They concluded that "heavy exposure to PAHs entails a substantial risk of lung, skin, and bladder cancer, which is not likely to be due to other carcinogenic exposures present in the same industries." Target organs were most consistently the lung, skin, and bladder.

An extensive literature on cancer risks in workers in various industries involving exposure to PAH has shown clear excess of lung cancer and suggestive excesses of bladder cancer (83,84). As noted above and elsewhere (85), studies of coke oven workers were among the earliest to establish PAH mixtures as human carcinogens. In a study of cancer mortality among European asphalt workers, Boffetta et al. (86) noted a small excess of lung cancer in workers employed in road paving, asphalt mixing, and other jobs involving exposure to bitumen fumes, although confounding by related exposures such as to coal tar could not be ruled out. Overall mortality from head and neck cancer was elevated for bitumen workers (87). Exposure to PAH also occurs in the construction industry. Kurtz et al. (88) have measured exposure to coal tar pitch volatiles, PAHs, and total particulates in excess of established standards.

Excess cancer in roofers was first reported by Hammond et al.(89). There have been subsequent reports of increased lung cancer risk in roofers [e.g., Zahm et al. (90) and Morabia et al.(91)] but few have been statistically significant. A meta-analysis by Partanen and Boffetta (92), however, demonstrated an overall statistically significant excess of lung cancer among roofers (RR = 1.78; 95% CI,1.5 to 2.1). It is uncertain to what extent the risk is related to specific exposures, because such workers were exposed in the past to coal tar and asbestos, as well as asphalt.

Epidemiological studies have generally characterized risks according to broad job title or industry, because specific exposure measurements over workers' lifetimes are rarely available. Nevertheless, with reasonable assumptions and approximations, it is possible to make lifetime exposure estimates by gathering and synthesizing industrial hygiene data from a variety of sources. A recent meta-analysis based upon such a synthesis has been done by Armstrong et al. (93), who estimated the average equivalent "unit relative risk" per 100 μg per m^3-years of BaP at 1.20 (95% CI, 1.11 to 1.29). Estimated means in coke ovens, gas works, and aluminum production works were similar (95% CI, 1.15 to 1.17). In other industries, they were much higher, but precision was substantially poorer (e.g., asphalt, RR = 18; 95% CI, 4 to 73).

Although the cancers most often investigated have been those traditionally associated with employment in heavy industry, such as lung and bladder cancer, el-Bayoumy (94) has pointed out that breast cancer can also be induced by a number of PAH, including 7,12-dimethylbenz(a)anthracene, a synthetic compound used primarily in carcinogenesis research. On the basis of experimental research and structural grounds, he proposed that PAH and nitro-PAH be considered potential factors in human breast cancer. Gammon et al. (95) have investigated this hypothesis in a population-based case-control study of 576 women with breast cancer and 427 controls conducted in Long Island, New York. Peripheral blood was used for assays of PAH diol-epoxide-DNA adducts via competitive ELISA. An adjusted odds ratio of 1.49 (95% CI, 1.00 to 2.21) was observed in the

highest adduct quintile (>21.9 per 10^8 nucleotides); no dose-response was seen.

Mechanisms for PAH carcinogenesis have been investigated in considerable detail. As with many xenobiotics, metabolism usually proceeds via an activation phase with formation of electrophilic intermediates. Conjugation reactions leading to deactivation of reactive electrophiles may occur in a second phase. The metabolic activation stage usually proceeds via formation of 7,8-diol epoxides, catalyzed by enzymes in the cytochrome P450 family such as CYP1A1, as well as other isoenzymes such as CYP1A2, CYP1B1, and CYP3A4. Diol epoxides, in turn, form adducts with DNA, which may give rise to mutations following DNA replication. A variety of mutation formats has been described, which may vary with the structure and number of rings of the specific PAH. Smith et al. (96) mapped the distribution of adducts induced by diol epoxides of a number of PAHs within the p53 gene in human bronchial epithelial cells. The codons most strongly involved in adduct formation were also those with the highest mutational frequency. An extensive discussion of mechanisms for adduct formation and alternative metabolic pathways is given by Boström et al., and extensive reviews have been presented by Wogan et al. (97), Baird et al. (98), and Xue and Warshawsky (99).

BIOMARKERS AND BIOMONITORING

During the past several years there has been considerable progress in development and use of biomarkers for assessing past exposure to PAH. Although the concentration of PAH in tissue has occasionally been determined (100), it is more practical to determine the concentration of PAH reaction products in urine. The pyrene metabolite 1-hydroxypyrene (1-OHP), and sometimes its glucuronidation product, 1-hydroxypyrene glucuronide, are often used to demonstrate past exposure to PAH and to estimate body burden for use in epidemiological risk analysis. 1-OHP has been measured consistently in the urine of cigarette smokers and has been used [by Hecht et al. (101), for example] to track the effects of smoking cessation.

There is increasing use of 1-OHP to assess worker exposure to PAH in occupational studies. Caux et al. (102) found elevated levels of 1-hydroxypyrene in the urine of firefighters exposed to PAH during the course of their duties, compared with levels in their own urine after a nonexposed period, and Kang et al. (103) found 1-OHP measurements higher in PAH-exposed steelworkers than in nonexposed workers. van Schooten et al. (104) measured urinary 1-OHP in groups of workers in an aluminum plant but having different measured exposures to PAH. 1-OHP was correlated with PAH exposure among groups but not at the level of the individual. Overbo et al. (105) reported a significant increase in urinary 1-OHP workers exposed to measured PAH in an electrode paste plant relative to control workers.1-OHP has also been found to be elevated in the urine of miners exposed occupationally to diesel exhaust (106). Measurement methods for 1-OHP are now relatively routine (107). They have been called "robust and nonlaborious (108) but use of 1-OHP as a quantitative biomarker of exposure has not yet been established, and health-based exposure limits cannot yet be set.

PAH-DNA adducts have been used extensively for biomonitoring of exposure. As early as 1988, Perera et al. (109) measured the levels of PAH-DNA adducts in peripheral blood cells of 35 Finnish foundry workers with an enzyme-linked immunosorbent assay using a polyclonal anti-BaP diol epoxide-I-DNA antibody known to cross-react with DNA modified by diol epoxides of structurally related PAH. They found higher levels in exposed workers compared with controls, and adduct levels were dose-related to BaP exposure. Their group subsequently used ^{32}P-postlabelling and immunoassay methods to demonstrate higher adduct levels in residents of a Polish region heavily polluted by coke plant emissions relative to rural controls (110). The continuing development of assay methods has enabled studies in residential groups not thought to be so highly exposed as industrial workers or those who live close to industrial sources of PAH pollution. The majority of nonindustrial exposures comes from food and motor vehicle exhaust. Shantakumar et al. (111) recently combined PAH-DNA adduct measurements with data from environmental home samples of dust and soil, dietary history data, and PAH exposure estimates based on geographic modeling of vehicular traffic patterns. They found a strong association with levels measured in outdoor soil (which reflects in part deposition of vehicle-related particulate matter) but a negative association with PAH in indoor house dust.

As adduct measurements become more widespread, they are being used as dosage markers in a variety of cancer studies. Adduct levels were associated with risk of development of lung cancer in a case–control study nested in the European Investigation into Cancer and Nutrition study. The overall odds ratio was not statistically significant, however (odds ratio = 1.86; 95% CI, 0.88 to 3.93) (112). Furthermore, adduct levels were dichotomized as detectable and nondetectable; when adduct level treated as a continuous variable to predict risk, its regression coefficient was not significantly different from zero, and the authors stated that the level of measurement error "seems to be high."

DNA-adduct assay results at present still have somewhat limited sensitivity. A set of interlaboratory trials undertaken between 1994 and 1997 to evaluate interlaboratory disparities found substantial differences in reported BaP-DNA adduct levels by different methods, but also found improved reproducibility after circulation and

adoption of uniform protocols (113). Schoket et al. (114) found a lack of correlation between adduct levels and urinary 1-OHP among workers in a Hungarian aluminum plant. Mensing et al. (115) have observed a reduction in adduct levels in PAH-exposed factory workers following a change in production materials (binding pitch) but found no differences between adducts in current smokers compared with nonsmokers. deKok et al. (116) has noted that the sensitivity of the assay varies with the method used and stated: " Recent developments in the application of capillary electrophoresis in combination with either immunochemical or mass spectrometric detection techniques may offer new and promising approaches, with higher selectivity as compared to TLC-^{32}P postlabeling."

In a recent review, Vineis and Perera (117) argued that bulky DNA adducts "express cumulative exposure to PAHs and other aromatic compounds after the action of metabolizing enzymes and despite the intervention of DNA repair enzymes" and, thus, should be considered to be "markers of cumulative DNA damage" rather than strictly dosage surrogates.

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