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Exposure to polycyclic aromatic hydrocarbons with special focus on cancer

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PEER REVIEW

Peer reviewer

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Comments

This review is a valuable work in which authors have explained the sources and the emissions of PAHs. PAHs and their epoxides emission create cancer and other adverse effects to living organisms. Authors have explained that PAHs is toxic, mutagenic and carcinogenic. It is urged to develop strategies aimed to minimizing the content of PAHs in environment.
Details on Page 187

ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are a group of compounds consisting of two or more fused aromatic rings. Most of them are formed during incomplete combustion of organic materials such as wood and fossil fuels, petroleum products, and coal. The composition of PAH mixtures varies with the source and is also affected by selective weathering effects in the environment. PAHs are ubiquitous pollutants frequently found in a variety of environments such as fresh water and marine sediments, the atmosphere, and ice. Due to their widespread distribution, the environmental pollution due to PAHs has aroused global concern. Many PAHs and their epoxides are highly toxic, mutagenic and/or carcinogenic to microorganisms as well as to higher forms of life including humans. The main aim of this review is to provide contemporary information on PAH sources, route of exposure, worldwide emission rate, and adverse effects on humans, especially with reference to cancer.

KEYWORDS
PAH, Environmental pollution, DMBA, Benzo(a)pyrene, Cancer

1. Introduction

The term polycyclic aromatic hydrocarbon (PAH) refers to a ubiquitous group of several hundred chemically-related, environmentally persistent organic compounds having various structures and varied toxicity. Most of them are formed by a process of thermal decomposition (pyrolysis) and subsequent recombination (pyrosynthesis) of organic molecules. PAHs enter the environment through various routes and are usually found as a mixture containing two or more of these compounds, *e.g.*, soot[1]. However, some PAHs are manufactured, and these pure PAHs usually exist as colorless, white or pale yellow solids. PAHs affect organisms through various toxic actions. The mechanism of toxicity is considered to be interference with the normal function of cellular membranes as well as with enzyme systems associated with the membrane[2]. They have been shown to cause carcinogenic and mutagenic effects and are potent immunosuppressants[3]. Their effects have been documented with respect to immune system development, humoral

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immunity, and host resistance. The most extensively studied PAHs are 7,12-dimethylbenzo anthracene (DMBA) and benzo(a)pyrene (BaP). PAHs have two or more single or fused aromatic rings with a pair of carbon atoms shared between rings in their molecules. The term "PAH" refers to compounds consisting of only carbon and hydrogen atoms. PAHs containing up to six fused aromatic rings are often referred to as "small" PAHs and those containing more than six aromatic rings are called "large" PAHs. The majority of research on PAHs has been conducted on the small PAHs due to the availability of samples of them[4]. The general characteristics of PAHs are high melting and boiling points (therefore making them solid), low vapor pressure, and very low aqueous solubility, the latter two tending to decrease with increasing molecular weight. Whereas their resistance to oxidation and reduction increases with higher molecular weight. PAHs are highly lipophilic and therefore very soluble in organic solvents. PAHs also manifest various properties such as light sensitivity, heat resistance, conductivity, emittability, and resistance to corrosion, as well as have a variety of physiological actions. PAHs possess very characteristic UV absorbance spectra. Each ring structure has a unique UV spectrum, and thus each isomer has a different UV absorbance spectrum. This characteristic is especially useful in the identification of PAHs. Most PAHs are also fluorescent, emitting characteristic wavelengths of light when they are excited (when the molecules absorb light). Aqueous solubility decreases with each additional ring. The simplest PAHs, as defined by the International Union of Pure and Applied Chemistry (IUPAC), are phenanthrene and anthracene, both of which contain three fused aromatic rings. Smaller cyclic molecules, such as benzene, are not PAHs. Naphthalene, which consists of two coplanar six-membered rings sharing an edge, is another aromatic hydrocarbon[5]. By formal convention, it is not a true PAH, though naphthalene is referred to as a bicyclic aromatic hydrocarbon. Although the health effects of individual PAHs are not exactly alike, 17 PAHs have been identified as being of greatest concern with regard to potential exposure and adverse health effects on humans and are thus considered as a group (profile issued by the Agency for Toxic Substances and Disease Registry, ATSDR). The primary purpose of this review is to provide public health officials with information about the carcinogenicity of PAHs, including its mechanisms. Also addressed are the sources of PAHs, routes of exposure to them and evaluations of toxicological studies and epidemiological investigations. Recommendations for the protection of human health and the environment against PAHs are also given.

2. Sources

2.1. Industrial emissions

PAH emissions from industries are produced by the burning of fuels such as gas, oil, and coal. PAHs can also be emitted during the processing of raw materials such as primary aluminum. Additional sources of PAHs include emissions from industrial activities such as the production of primary aluminum, coke, petrochemicals, and rubber tires, as well as the manufacturing of cement, bitumen, and asphalt. Wood preservation, commercial heat and power generation, and waste incineration are yet other sources. Inomata *et al.* studied emissions of PAHs from the pyrolysis of scrap tires[6]. Total PAH emissions from a scrap tire plant via pyrolysis were 42.3 g/day with an emission factor (EF) of 4 mg/kg. To study the thermal degradation of organic materials, Lee and Vu investigated PAH emissions from pyrolysis products[7]. EFs of PAHs from thermal decomposition of organic materials ranged from (0.40±0.13) mg/g for cellulose to (9.0±0.5) mg/g for tires. Estrellan and Iino reported that EFs for joss paper furnaces average 71.0 mg/g[8]. With the application of devices such as adsorption towers for the control of air pollution, removal efficiencies of total PAHs are 42.5% and 11.7% for particulate and gaseous PAHs, respectively[9]. Mu *et al.* reported emissions of PAHs from various industrial stacks: blast furnace, basic oxygen furnace, coke oven, electric arc furnace, heavy oil plant, power plant, and cement plant[10]. The coke oven, electric arc furnace, and heavy oil combustor were shown to produce large amounts of high molecular weight PAH emissions. EFs of PAHs from these industrial stacks ranged from 0.08 to 3.97 mg/kg feedstock, whereas those for BaP ranged from 1.87 to 15.5 μg/g feedstock. The highest EFs of total PAHs and BaP were found for the combustion of heavy oils. Recently, PAH emissions from waste incineration have been investigated in many studies. According to the Italia Agency for Environmental Protection, total EFs of PAHs range from 91 to 414 μg/g of waste burned in incinerators of municipal and industrial waste facilities. PAHs are mainly emitted from exhaust fumes of vehicles, including automobiles, railways, ships, aircrafts, and other motor vehicles. PAH emissions from mobile sources are associated with the use of diesel fuel, coal, gasoline, oils, and lubricant oil.

2.2. Agricultural sources

Open burning of brushwood, straw, moorland heather, and stubble are agricultural sources of PAHs. All of these activities involve burning organic materials under suboptimum combustion conditions. Thus, it is expected that a significant amount of PAHs would be produced from the open burning of biomass. In fact, EFs of PAHs from wood combustion range from 16.4 to 1282 mg/kg wood[11]. PAH concentrations released from wood combustion depend on wood type, kiln type, and combustion temperature.

2.3. Air

The background levels of some representative PAHs present in the air are reported to be 0.02-1.2 ng/m^3 in rural areas and 0.15-19.3 ng/m^3 in urban areas[12]. Cigarette smoking and environmental tobacco smoke are other sources of airborne PAHs. Smoking a single cigarette can yield an intake of 20–40 ng of benzo (a) pyrene[13]. Smoking one pack of unfiltered cigarettes per day yields 0.7 μg/day BaP exposure; whereas in the case of filtered cigarettes, the value is 0.4 μg/day[14]. The main sources of PAHs are related to combustion processes (domestic solid fuel burning, motor vehicles, *etc*.) and the use of solvents and aerosols.

2.4. Water

PAHs can leach from soil into water. Water contamination also occurs from industrial effluents and accidental spills during oil shipment at sea[15]. Concentrations of B(a)p in drinking water are generally lower than those in untreated water and about 100-fold lower than the standard value for drinking water designated by the U.S. Environmental Protection Agency (EPA) [EPA's maximum contaminant level for B(a)p in drinking water is 0.2 parts per billion].

2.5. Soil

Soil contains measurable amounts of PAHs, primarily from airborne fallout. Documented levels of PAHs in soil near oil refineries have been reported to be as high as 200000 μg/kg of dried soil. Levels in soil samples obtained near cities and areas with heavy

traffic are typically less than 2000 μg/kg[16].

2.6. Foodstuffs

In non-occupational settings, up to 70% of PAH exposure for a nonsmoking person can be associated with their diet. PAH concentrations in foodstuffs vary. Charring meat or barbecuing food over a charcoal, wood, or other type of fire greatly increases the concentration of PAHs. For example, the PAH level for charred meat can be as high as 10–20 μg/kg[17]. Charbroiled and smoked meats and fish contain more PAHs than do their uncooked counterparts, with up to 2.0 μg/kg of B(a)p detected in smoked fish. Tea, roasted peanuts, coffee, refined vegetable oil, cereals, spinach, and many other foodstuffs contain PAHs (Figure 1). Some crops, such as wheat, rye, and lentils, may synthesize PAHs or absorb them from water, air or soil[18].

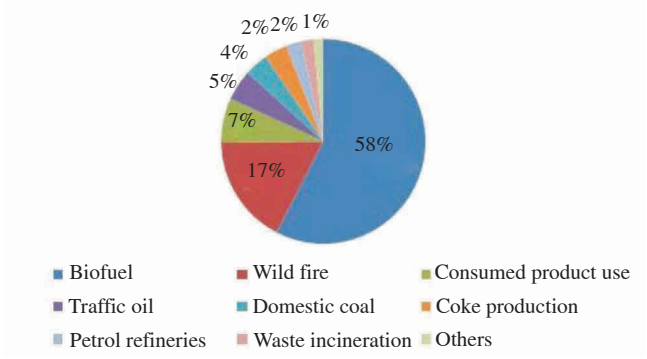

Figure 1. Environmental sources of PAHs.

2.7. Other sources

Some PAHs are found in medicines, dyes, plastics, pesticides, and wood preservatives. Because these hydrocarbons are highly lipophilic in nature, PAHs in the environment are found primarily in soil, sediment, and oily substances, as opposed to being in water or air. However, they are also a component of concern in particulate matter suspended in the air[19]. The EPA has identified 1408 hazardous waste sites as the most serious in the U.S. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. PAHs have been found in at least 600 of the sites on the NPL. However, the number of NPL sites evaluated for PAHs is not known. As the EPA evaluates more sites, the number of sites at which PAHs are found may increase. This information is important because exposure to PAHs may cause harmful health effects and because these sites are potential or actual sources of human exposure to PAHs. The National Institute for Occupational Safety and Health (NIOSH) has determined that PAHs are a "potential occupational carcinogen". Although the health effects of individual PAHs are not exactly alike, the following 17 PAHs are profiled as a group of those detrimental to health: acenaphthene, acenaphthylene, anthracene, benz[a]anthracene, BaP benzo[e]pyrene, benzo[b] fluoranthene, benzo[g,h,i]perylene, benzo[j]fluoranthene, benzo[k] fluoranthene, chrysene, dibenz[a,h]anthracene, fluoranthene, fluorene, indeno[1,2,3-c,d]pyrene, phenanthrene, and pyrene.

2.8. Routes of exposure

PAH exposure through air, water, soil, and food sources occurs on a regular basis for most people. Routes of exposure include ingestion, inhalation, and dermal contact in both occupational and non-occupational settings. Some exposures may involve more than one route simultaneously, affecting the total absorbed dose (such as dermal and inhalation exposures from contaminated air). All non-workplace sources of exposure, such as diet, smoking, and burning of coal and wood, should be taken into consideration[20].

2.9. PAH emission worldwide

The total global atmospheric emissions of PAH16 in 2004 were estimated to be 520 giga grams per year (Gg y^{-1}) and a full list of the emissions from individual countries in 2004 is presented in the supporting information, along with socioeconomic parameters including area, population, and gross domestic product. The annual PAH emission from Asian countries in that year was 290 Gg y^{-1}, contributing 55% of the global total. China and India were the top two PAH-emitting countries, emitting 114 Gg y^{-1} and 90 Gg y^{-1}, respectively. Africa, North America, Europe, South America, and Oceania contributed 18.8%, 8.0%, 9.5%, 6.0%, and 1.5% of the total global PAH emissions, respectively (Figure 2). The United States was the third largest emitter of PAHs at 32 Gg y^{-1}. The PAH emissions from Nigeria, Indonesia, Brazil, Pakistan, Democratic Republic of the Congo, and Russia ranked 4th to 9th on a global basis; and the total PAH emissions from the top nine countries accounted for over 60% of the global PAH emissions in 2004. Figure 3 compares the calculated PAH emission rates for the United States, the United Kingdom, countries of the former USSR, and a number of European countries with those reported in the literature[21].

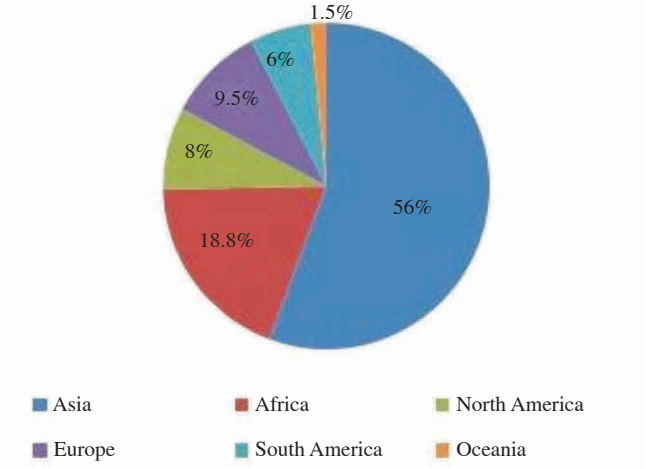

Figure 2. PAH emission from all over world.

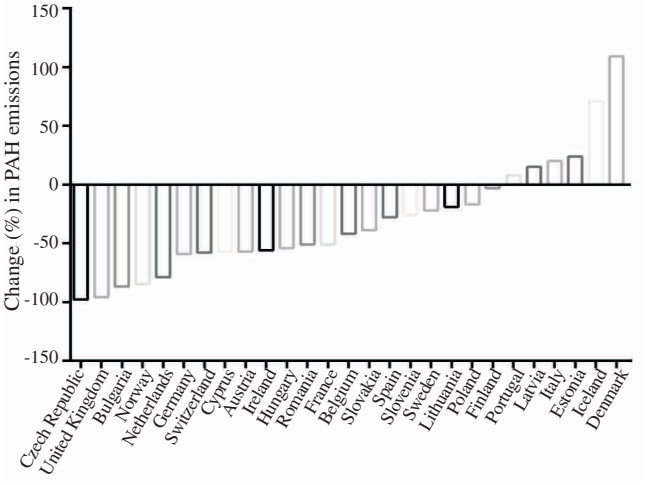

Figure 3. PAH emission from European Economic Area countries (1990-2010).

3. Adverse effects of PAHs

3.1. Acute health effects

The effects on human health depend mainly on the length and route of exposure, the amount or concentration of PAHs one is exposed to, and of course the innate toxicity of the PAHs[22]. A variety of other factors can also impact health, including subjective factors such as pre-existing health status and age. The ability of PAHs to induce short-term health effects in humans is not clear. Occupational exposure to high levels of pollutant mixtures containing PAHs results in symptoms such as eye irritation, nausea, vomiting, diarrhea, and confusion[23]. However, it is not known which components of the mixture were responsible for these effects; and other compounds commonly found with PAHs may be the cause of these symptoms. Mixtures of PAHs are also known to cause skin irritation and inflammation. Anthracene, B(a)p, and naphthalene are direct skin irritants; and the former two are reported to be skin sensitizers, *i.e.*, to cause an allergic skin response in animals and humans[24].

3.2. Chronic health effects

Health effects from chronic or long-term exposure to PAHs may include decreased immune function, cataracts, kidney and liver damage (*e.g.*, jaundice), breathing problems, asthma-like symptoms, lung function abnormalities; and repeated contact with the skin may induce redness and skin inflammation[25]. Naphthalene, a specific PAH, can cause the breakdown of red blood cells if inhaled or ingested in large amounts. With exposure to PAHs, the harmful effects that may occur largely depend on the way in which the individual is exposed.

3.3. Teratogenicity

Embryotoxic effects of PAHs have been described in experimental animals exposed to PAHs such as benzo(a)anthracene, BaP, and naphthalene. Laboratory studies conducted on mice have demonstrated that ingestion of high levels of BaP during pregnancy results in birth defects and a decreased body weight in the offspring[26]. It is not known whether these effects can occur in humans. However, the Center for Children's Environmental Health reports studies demonstrate that exposure to PAH pollution during pregnancy is related to adverse birth outcomes including low birth weight, premature delivery, and heart malformations. High prenatal exposure to PAH is also associated with a lower IQ at age three, increased behavioral problems at ages six and eight, and childhood asthma[27].

3.4. Immunotoxicity

PAHs have also been reported to suppress immune reactions in rodents. The precise mechanisms of PAH-induced immunotoxicity are still not clear; however, it appears that immunosuppression may be involved in the mechanisms by which PAHs induce cancer[28].

3.5. Genotoxicity

Genotoxic effects of some PAHs have been demonstrated in both rodents and *in vitro* tests using mammalian (including human) cell lines. Most PAHs are not genotoxic by themselves and must be metabolized to their diol epoxides, which then react with DNA to induce genotoxic damage. Genotoxicity plays an important role in the carcinogenicity process and maybe in some forms of developmental toxicity as well[29].

3.6. Carcinogenicity

Although unmetabolized PAHs can have toxic effects, a major concern is the ability of their reactive metabolites, such as epoxides and dihydrodiols, to bind to cellular proteins and DNA. The resulting biochemical disruptions and cell damage lead to mutations, developmental malformations, tumors, and cancer[30]. Evidence indicates that mixtures of PAHs are carcinogenic to humans, which come primarily from occupational studies on workers exposed to mixtures containing PAHs, and these long-term studies have shown an increased risk of predominantly skin and lung, but also bladder and gastrointestinal cancers[31]. However, it is not clear from these studies whether exposure to PAHs was the main cause, as these workers had been simultaneously exposed to other cancer-causing agents (*e.g.*, aromatic amines). Animals exposed to high levels of certain PAHs over long periods in laboratory studies develop lung cancer from inhalation, stomach cancer from ingesting PAHs in food, and skin cancer from skin contact. BaP is the most common PAH to cause cancer in animals, and this compound is notable for being the first chemical carcinogen to have been discovered. Based on the available evidence, both the International Agency for Research on Cancer[32] and the US EPA (1984)[33] classified a number of PAHs as carcinogenic to animals and some PAH-rich mixtures as carcinogenic to humans. The EPA has classified the following seven PAH compounds as being probable human carcinogens: benz(a) anthracene, BaP, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenz(ah)anthracene, and indeno(1,2,3-cd)pyrene.

3.7. Cancer

PAHs are ubiquitous environmental agents commonly believed to contribute significantly to the development of human cancers. Like many other carcinogens, these hydrocarbons are metabolized enzymatically to various metabolites, of which some are reactive. In the large group of enzymes involved in the metabolism of carcinogens[34], cytochrome P450 enzymes CYP 1A1, 1A2, 1B1, and 3A4 are the most important enzymes in the metabolism of PAHs[35]. PAHs undergo metabolic activation to diol-epoxides, which bind covalently to DNA. The DNA binding of activated PAHs is considered to be essential for the carcinogenic effect[36,37]. DNA adducts have been found in various human tissues[38]. In epidemiological studies, a positive correlation between the level of PAH exposure and the number of PAH-DNA adducts has been found, including that between coke oven exposure and PAH-DNA adducts in blood cells[39] and that between cigarette smoking and PAH-DNA adducts also in blood cells[40]. A refined repair system has evolved to eliminate DNA adducts from the genome. PAH adducts are eliminated by nucleotide excision repair[41]. If the adducts are left unrepaired, they may cause permanent mutations[42]. If these mutations are situated at critical sites, including tumor suppressor genes or oncogenes, they may lead to cellular transformation and the development of tumors. In some cases, specific mutations found in the Tp53 gene, the most commonly mutated gene in human cancers, are associated with exposure to certain carcinogens[43]. For example, the PAHs in cigarette smoke bind preferentially to the Tp53 gene sites called "hotspot" codons, where most smoking-associated mutations are also found[44]. Such studies give support to the link between DNA adducts and the cancer risk in humans (Figure 4).

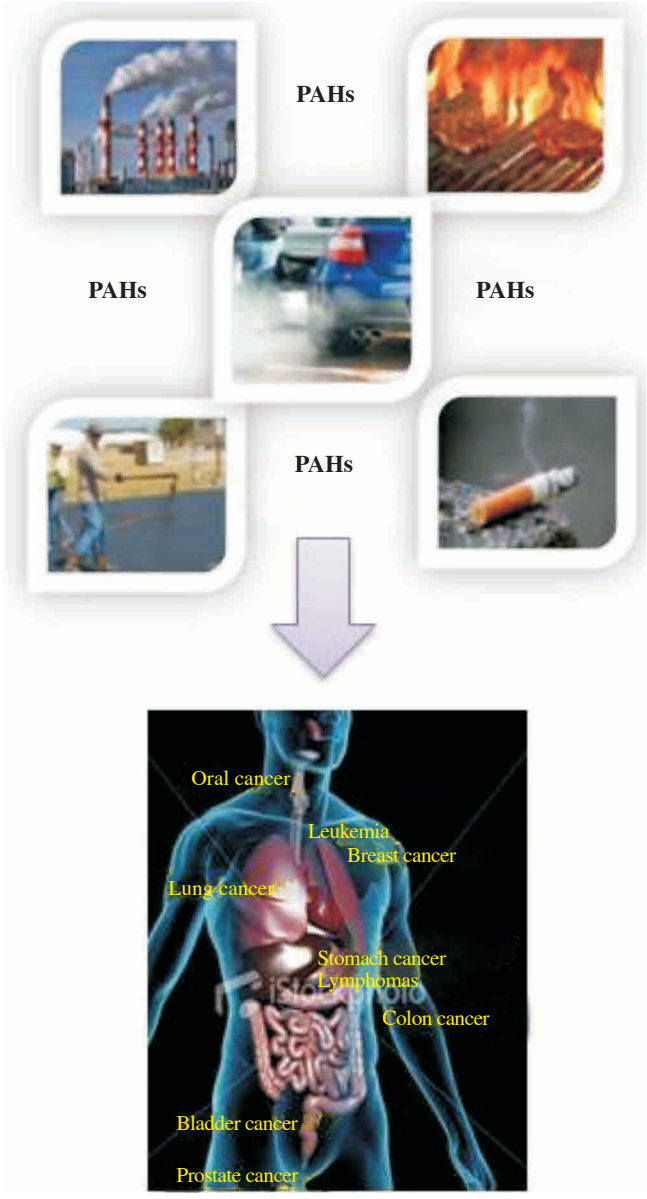

Figure 4. PAH harmful effects on humans.

3.8. BaP

According to the International Agency for Research on Cancer (IARC), there is sufficient evidence to show that BaP is carcinogenic in laboratory animals, and probably also in humans. Rajendran *et al.* reported that BaP has the potential to cause lung cancer in experimental animals[45]. The ability of BaP to induce tumors upon local administration is well documented[46]. BaP is metabolically activated, and the ultimate carcinogenic product is formed via a three-step process. The first step includes the formation of (7R,8S)-epoxy-7,8-dihydrobenzo(a)pyrene (B(a)P-7,8-oxide), catalyzed by cytochrome P450 enzymes[42]. The second step, catalyzed by epoxide hydrolase, is the conversion to (7R,8R)-dihydroxy-7,8-dihydrobenzo(a)pyrene (B (a)P-7,8-diol). Finally, cytochrome P450 enzymes catalyze the reaction, producing four possible isomers of 7,8-dio1-9,l0-epoxide. Quantitatively the most important of them is (7R,8S)-dihydroxy-(9S,10R)-epoxy-7,8,9,10-tetrahydrobenzo(a) pyrene (BPDE). BPDE, which is the ultimate carcinogen, binds to DNA at guanine residues[36,47] and produces BPDE-DNA adducts. BaP induces cytochrome P4501A1 (CYP1A1) by binding to the aryl hydrocarbon receptor in the cytosol[48,49] (Figure 5). Upon being bound, the transformed receptor is translocated to the nucleus where it dimerizes with aryl hydrocarbon receptor nuclear translocator. This dimer then binds to xenobiotic response elements located in the promoter region of certain genes. This process increases the transcription of certain genes, notably CYP1A1, resulting in increased production of the CYP1A1 protein[48] and is similar to the induction of CYP1A1 by certain polychlorinated biphenyls and dioxins. Seemingly, CYP1A1 activity in the intestinal mucosa prevents major amounts of ingested B(a)P from entering the portal blood and systemic circulation[50]. Intestinal, but not hepatic, expression of CYP1A1 depends on Toll-like receptor 2[51].

3.9. DMBA

PAHs have been shown to increase the risk for breast cancer through a variety of mechanisms. DMBA, one of them, is commonly found in our environment and can be isolated from diesel exhaust, barbequed meat, tobacco smoke, overheated cooking oil, *etc*[52]. DMBA has the potential to cause breast cancer in experimental rats[53]. Reactive oxygen species are potentially dangerous by-products of cellular metabolism and also the predominant reason for many oxidative stress-mediated diseases generated by various environmental contaminants among which DMBA is an important one. DMBA is a fat-soluble compound, and because of this property it accumulates and persists in the adipose tissue of the mammary gland, thus increasing the exposure of mammary epithelium to this chemical carcinogen[54]. DMBA, like BaP, is also an indirect-acting carcinogen, requiring metabolic activation to yield its ultimate carcinogenic form[55]. DMBA is oxidized to DMBA-3-4-epoxide by phase I enzymes, especially CYP[56].

3.10. Metabolic activation of DMBA

Epoxide hydrolase, another phase I enzyme, then converts the epoxide to DMBA-3,4 diol, the proximate carcinogen. Subsequent oxidation by CYP leads to the formation of DMBA-3,4-diol-1,2-epoxide, the ultimate carcinogen[57] (Figure 6), which then reacts with DNA to form the adducts that are responsible for its mutagenicity and carcinogenicity. According to the International Agency for Research on Cancer (IARC) and the U.S. EPA, anthracene, benzo(g,h,i)perylene, benzo(e)pyrene, chrysene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to their carcinogenicity in humans and are considered potentially to act as immunosuppressants. Although there are still technical, financial, as well as management difficulties in technique development and popularization, the potential for reducing PAH emissions is enormous.

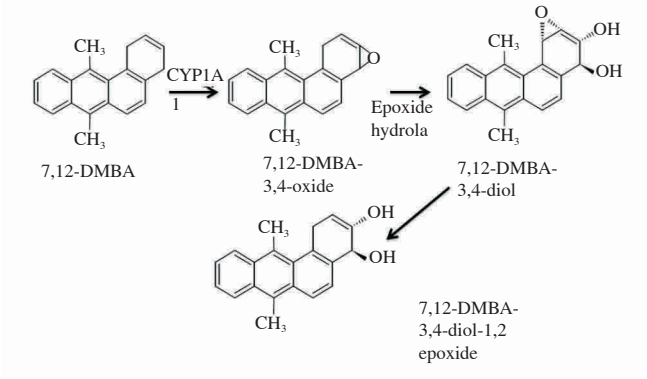

Figure 6. Metabolic activation of DMBA.

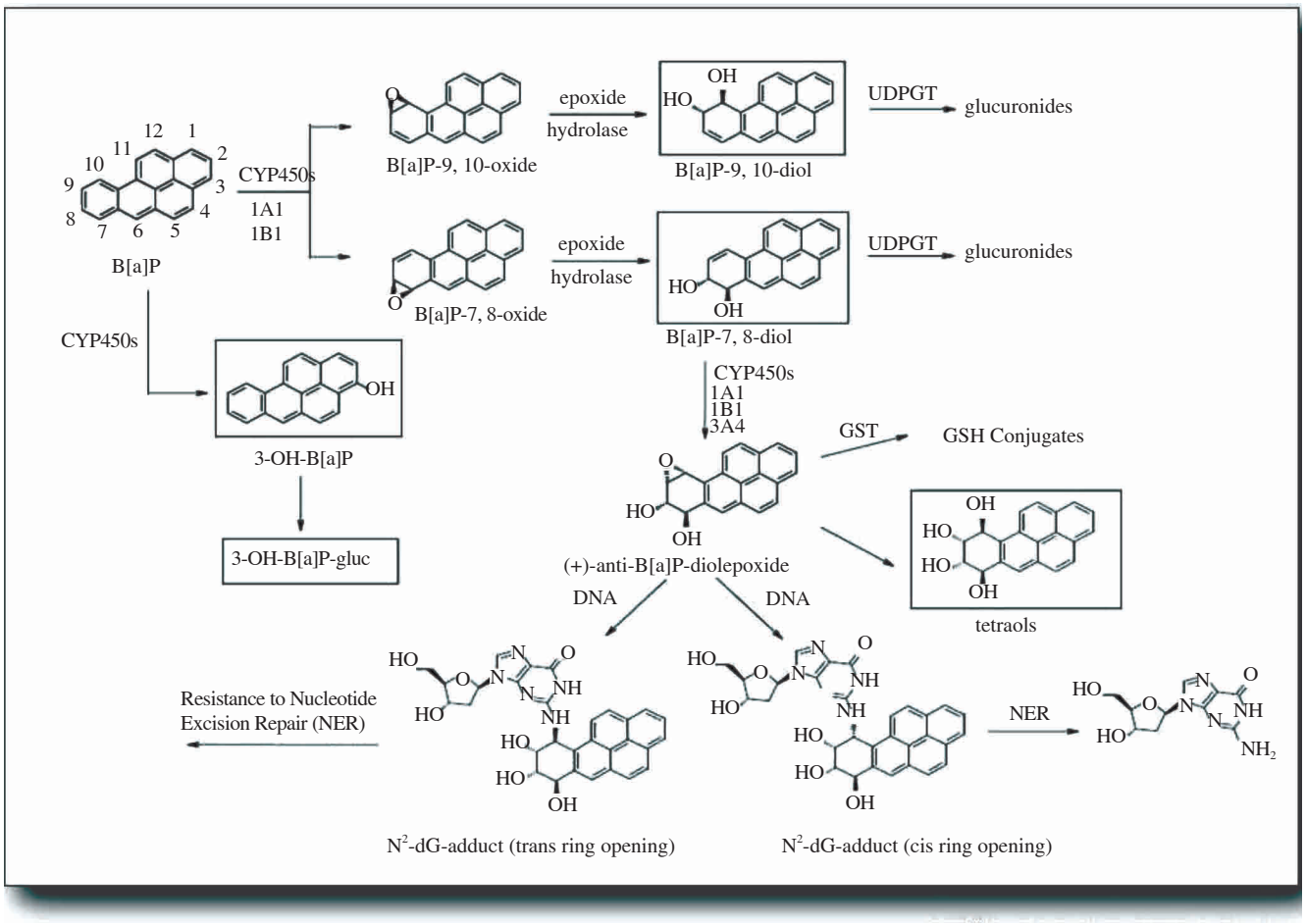

Figure 5. Metabolic activation of BaP[49].

4. Conclusions

In conclusion, the concentrations and fate of PAHs in the environment were reviewed. The partitioning of these compounds in the atmosphere was also evaluated, with reference to the historical trends in PAH emissions. In addition, the main anthropogenic sources of PAHs were discussed. Domestic coal combustion, coal-fired power stations, industrial processes, and vehicles were indicated to make major contributions to contemporary national-regional PAH emissions, although the relative proportions attributed to these sources would vary for different PAH compounds and among countries. The information presented here indicates that large uncertainties still exist in terms of atmospheric sources, loads, fates, and degradation rates of PAHs and that further data enabling a more accurate general model for evaluations are needed. Companies are urged to develop strategies aimed at minimizing the content of PAHs in industrial exhaust gases and products that exceed legal requirements, thereby reducing PAH contamination as much as possible.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgement

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Comments

Background

PAHs are a group of compounds consisting of two or more fused aromatic rings. Most of them are formed during incomplete combustion of organic materials such as wood and fossil fuels, petroleum products, and coal. Due to their widespread distribution, the environmental pollution caused by PAHs has aroused global concern.

Research frontiers

The present review article explains the toxic effects of PAHs. Many PAHs and their epoxides are highly toxic, mutagenic and/or carcinogenic to all living organisms.

Related reports

The sources of PAHs such as industrial emissions, agricultural sources, air, water, soil, foodstuffs and other sources were reviewed.

Innovations and breakthroughs

In this present article, authors have reviewed the sources, emissions and the adverse effects of PAHs. The sources of PAHs and their epoxides emission create cancer and other adverse effects to living organisms worldwide.

Applications

From this review article, it has been found that PAHs is toxic, mutagenic and carcinogenic. It is urged to develop strategies aimed to minimizing the content of PAHs in industrial and agricultural products thereby reducing PAHs accumulation in the environment.

Peer review

This review is a valuable work in which authors have explained the sources and the emissions of PAHs. PAHs and their epoxides emission create cancer and other adverse effects to living organisms. Authors have explained that PAHs is toxic, mutagenic and carcinogenic. It is urged to develop strategies aimed to minimizing the content of PAHs in environment.

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