Review

The Applied Biology & Chemistry Journal
https://www.theabcjournal.com
eISSN: 2582-8789

Benzo[a]pyrene: A carcinogen, its sources, adverse effects, and preventions

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Received April 25, 2024
Revised July 02, 2024
Accepted July 21, 2024
Published September 30, 2024

Abstract: A polycyclic aromatic hydrocarbon called benzo[a]pyrene (B[a]P) is produced during incomplete burning of fuels. The most common way humans consume B[a]P is through food products, particularly grilled or smoked foods. B[a]P is also frequently detected in the sediments, soil, surface water, and air. Once bioactivated, it produces a highly reactive epoxide monomer that can create adducts by chemically reacting with biological molecules, such as DNA. B[a]P is implicated in various cancers due to its interaction with the aromatic hydrocarbon receptor (AhR). Apart from its detrimental impacts on development and reproduction, this substance also suppresses the immune system. Microbes, however, are critical to cleaning up the B[a]P-contaminated environment. This review focuses on forming B[a]P in different compartments of the environment and human surroundings, and the mechanisms responsible for its harmful effects and carcinogenic risk. This review also discusses the strategies for the deterioration of B[a]P.

Keywords: benzo[a]pyrene; cancer; metabolism; micro-organisms; polycyclic aromatic hydrocarbon

1. Introduction

Benzo[a]pyrene, or B[a]P is a compound that is responsible in inducing cancer and has been investigated thoroughly for its respective health risks. It usually occurs in a variety of environments, including coal tar, automotive exhaust, charred or burned food, and smoke of tobacco [1]. According to the International Agency for Research on Cancer (IARC), B[a]P has categorized to type 1 of human carcinogen. Numerous studies have explored the mechanisms through which B[a]P leads to cancer [2, 3]. Biochemical conversion of B[a]P occurs in liver by the help of cytochrome P450 enzyme. The metabolic reaction catalyzed by cytochrome P450 (CYPs) results in the production of one of the activated forms of B[a]P which is BaP-7,8-dihydrodiol-9,10-epoxide (BPDE). This BPDE has the capacity to make reaction with DNA and result in the formation of adduct most preferably at the residue of guanine. Moreover, B[a]P metabolism carried out by dihydro-diol dehydrogenase results in the generation of different intermediates that ultimately leads to the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The increased concentration of RNS and ROS may change the activity of protein kinase and signalling cascades that impacts the normal growth and differentiation of cell [4]. Thus, it has been determined that B[a]P causes oxidative stress, inflammatory responses, and disruption of cell signalling processes, all of which are linked to the onset of malignancies along with other illnesses [5].

The concentration of B[a]P is a potent marker that determines the possible carcinogenicity of different sources. However, B[a]P is commonly found in seafood, smoked fish, fruits, cereals, grain, oils, vegetables, and barbecued meat. Various animal investigations revealed that the exposure to B[a]P is associated with various health effects [6]. Thus, this review covers the causes, mechanisms, health effects, prevention tactics, and degradation approaches for B[a]P exposure.

2. Sources of Benzo[a]pyrene

Benzo[a]pyrene is highly bound to the organic portion of soil and builds up in flora and mammal fat tissue, but it does not reach lower levels of soil. As a result, the underground portion of the plant absorbs it badly [7]. According to current studies, plant B[a]P levels were influenced by the soil's initial B[a]P content. Cultivating spring barley in soil that had been contaminated with B[a]P was found to collect this chemical. Lower than 1-6 days in the environment, and less than 1-2 hours in water, yet over 5–10 years in sediments as well as more than 14–16 months in land (for full deterioration) are the anticipated half-life periods for B[a]P [8]. The half-life of B[a]P in blood is less than 5

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minutes, while in the liver, it is 10 minutes. The half-life of the B[a]P/DNA adduct was discovered to be 4.5-5.5 days. The persistence of B[a]P in soil is likely to vary depending on the nature of the chemicals surrounding it and the type. The concentration of PAHs in relation with air generated particles alters significantly due to their source of emission such as combustion processes and traffic. The ratio of PAH is utilized to determine the appropriate emission sources. Exposure to indoor particulate matter (PM) was identified as a major health issue as majority of individuals spends nearly 90% of their time period indoors. Particles of major concern to the health of a human being are those that are called as inhalable particles [7]. Most of the particulate-phase PAH are gathered into fine particles and settled down slowly based on the condition of atmosphere and chemical reactivity which results their transportation over a long distance and pollute even remote places. It is well determined that the lower molecular weight PAHs present in air usually in vapor form while multiple ringed are converted to particles. Intermediate size PAHs are divided between particulate and vapor phases based on the temperature of atmosphere [9].

2.1 Air

2.1.1 Outdoor air

Benzo[a]pyrene is one of the major PAHs that participate significantly to the contamination of the air. The majority of PAH emissions come from human activities such as insufficient combustion, burning of biomass, and decomposition of petroleum and other fossil fuels. Significant portions of semi-volatile organic compounds contain PAHs. Because of their low boiling temperatures, PAHs with lower molecular mass are more frequently found in the gaseous state, while those with a large molecular weight, such as B[a]P, are mostly found in the particulate stage and have greater carcinogenic potential [10]. B[a]P is an essential tool used in ecological surveillance, which includes quality of the air assessment since it is thought to be a marker for identifying a PAHs group. While greater quantities of this material have been found in different parts of the globe, including EU member states, the European Union (EU) that the levels of B[a]P in the atmosphere is limited to 1 ng/m^3 [11].

In metropolitan air outside, the average concentrations of different PAHs range from one to a few hundred ng/m^3. The areas with the greatest B[a]P concentration, identified in tunnels under roads and large towns that heavily rely on coal and other fuels for home heating, were those with many hundreds of tiny particles per cubic meter. According to estimates, 20% of Europeans are subjected to B[a]P at levels greater than the EU yearly acceptable limit of 1 ng/m^3, whereas 7% of those surveyed reside in areas where B[a]P levels are below the threshold of acceptable risk, which is 0.12 ng/m^3 [12]. In a similar way the median B[a]P level in Genoa, Italy, was found to be 2 ng/m^3 in areas near busy streets, but it was found to be significantly greater at 14 ng/m^3 on the roof of a structure 300 meters away from a coal furnace. Poland has one of the worst air quality conditions in Europe, with high B[a]P level seen outside, especially during the summertime. The researchers found that B[a]P concentration in Nowy Sącz, Tarnów, and Kraków cities in Poland were consistently higher than the recommended ranges of 10 to 11, 4 to 6, and 4 to 10 ng/m^3 [13]. Likewise, B[a]P was found in the atmosphere of Linzhou, China, ranging in quantity from 5.1 to 20.2 ng/m^3. Thailand's pollution levels revealed that average B[a]P contents (absorbed at the particles phase) were 6 and 11 times greater in the PM 2.5 fraction throughout moderate and heavy haze periods, respectively, at 0.052 and 0.095 ng/m^3 [14].

2.1.2 Indoor air

Research has demonstrated a robust correlation between urban pollutants and illnesses of the respiratory system. The investigation determined the levels of various PAHs in gaseous samples collected from 35 homes stoves of rural North China during frying. Both the gases and particle phase had substantial level of B[a]P, including 14.3 ng/m^3 and 6.7 ng/m^3, respectively [15]. According to the investigators, B[a]P levels were greatly affected by the type of gasoline that burned and the system efficiency for ventilation. In some research studies, the PAHs formed in the different culinary processes in China was examined and reported the level of PAHs with in the level of 105-783 ng/m^3. The outcomes of this research explained that when culinary process was done by utilizing oil in place of water, the concentration of B[a]P was found to be higher amount [16].

Another research studies on the in the Temple of Tibet reported the B[a]P level in the range of 17-18.5 ng/m^3. This increased level of B[a]P was due to the absence of proper ventilation, and excessive combustion of plant substances [17].

Because of the not fully developed respiratory and immunological systems, children are more specifically prone to be exposed from the B[a]P present in the indoor sources. They are found to be in more exposure of B[a]P in winter (0.05-10.3 ng/m^3), as observed in the classes of China due to the heating of rooms. Some studies also discovered that the major reason of B[a]P exposure in the inside of the buildings were the application of gasoline and coal for heating purpose. In a different investigation, the researchers found B[a]P at an extremely elevated average level of 163.87 ng/m^3. They also observed that, in Saudi Arabia, average PAH concentrations were greater in educational institutions of city rather than in rural and resident school settings [18].

2.2 Surface water

The water on the surface has also been shown to contain B[a]P. Surface water directly deposited B[a]P is a significant environmental input. After settling on urban

land, PAHs including B[a]P are subsequently carried into waterways by surface runoff and erosion. Because B[a]P is poorly soluble in aqueous environments, it binds to organic matter and becomes present in the hydrosphere [19]. According to an Indian study, the overall amount of 17 PAHs was 157.96 ng/L, while the B[a]P level was 8.61 ng/L in river water. In addition, investigators measured B[a]P concentrations in 44 lakes in China, ranging from 0.07 to 2.26 ng/L. Like this, the calculated B[a]P level and median overall PAHs was found to be 1.37 ng/L and 26.2 ng/L, respectively from the Karst River in Hubei [20].

On the examination of surface water of Southeast Sea in Japan, it was found that it was infected with PAHs within the range of 6-13 ng/L. In the dissolved phase of the sea around 13 types of PAHs and in solid phase about 12 types of PAHs were reported which were ranged from 0.12-0.076 ng/L. This inference and conclusion that the combination of pyrogenic and petrogenic sources was the primary cause of this exposure [21].

2.3 Soil

Waste generated by various industries is a major contribution to the creation of PAHs, which in turn affects the quality of soil. Research findings indicate that the primary cause of pollution and health problems associated with it in Taiyuan's soil is the coal-burning process. According to the analysis of Poland soil, the amount of B[a]P was determined to be between 0.0001-3.030 mg/kg, with house furnaces and cars having the largest contributions [22]. The amount of B[a]P in the soil was determined to be between 0.3 and 0.9 mg/kg in the Bialystok area of Poland, and between 0.28 and 5.50 mg/kg in Cleveland City. According to data, the concentration of B[a]P in Turkish greenhouse soil was found to be between 1-2 µg/kg. [2].

2.4 Food contamination

When food products are consumed that cause PAHs to develop during meal processing, humans are easily exposed to B[a]P. This B[a]P is commonly available in a wide diversity of dietary sources, involving Alwana olive oil (31.3 ± 0.3 ppb), olive oil (2.19 ± 0.2 ppb), fish/meat-based baby foods (0.00–1.66 µg/kg), and milk (0.06–2.09 µg/kg) [23]. B[a]P has also been identified in cucumbers (4.35 ng/kg), Iranian bread samples (mean 0.1 µg/kg), fresh shellfish (0.31 ± 0.42 µg/kg), mussels (0.24 ± 0.18 µg/kg), oysters (1.26 ± 1.22 µg/kg), charcoal-grilled chicken (1.19 ± 0.31 µg/kg; 2.22 ± 0.13 µg/kg) but not in chocolate [24]. Burgers (0.9 µg/kg), barbecued/grilled chicken (0.9 µg/kg), and well-done steaks (4.15 µg/kg) had the greatest B[a]P values. In general, nonmeat items had low B[a]P contents. On the other hand, B[a]P levels in some vegetables and grains (such vegetable cabbage and kale) were as high as 0.5 µg/kg. It was discovered that the investigated average everyday consumption of individuals of B[a]P was made up of 21% and 29%, respectively, of grain, cereal, bread, barbecued or grilled meat [25]. B[a]P can come from a variety of sources (Figure 1), but how it is metabolized in the human body is covered in the following sections.

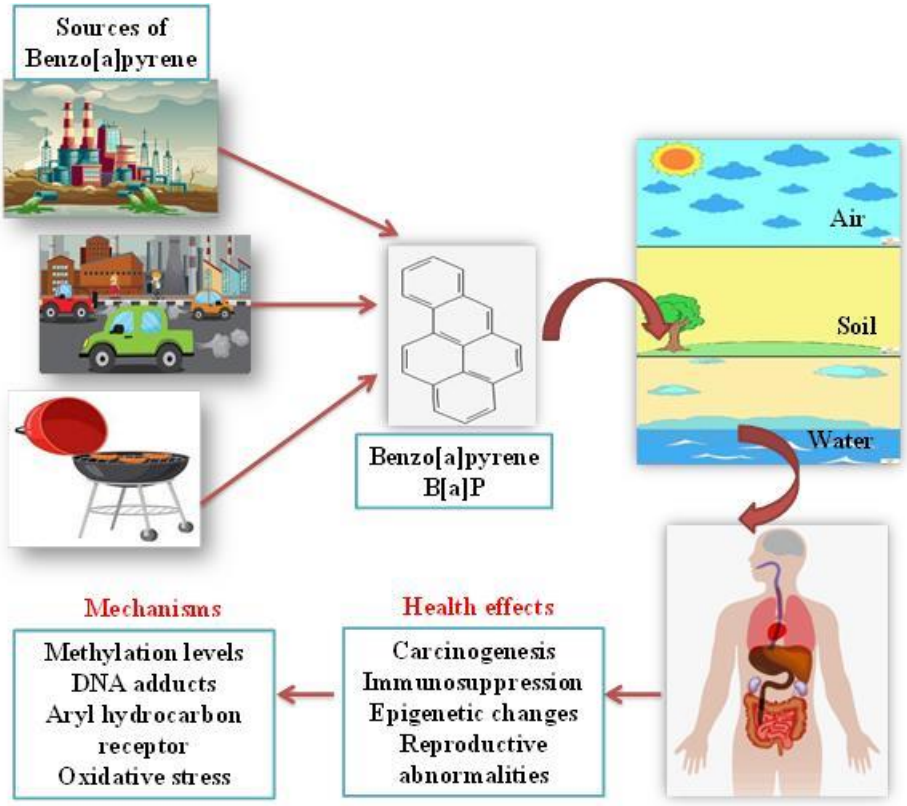

Figure 1. Sources and health risk of B[a]P.

3. Metabolism and mechanism of carcinogenesis resulted by benzo[a]pyrene

B[a]P is broken down by phase-I and phase-II processors into a variety of chemicals, such as phenols, quinones, arene oxides, and dihydrodiols, as well as their hydrophilic mixes with glutathione, glucuronide, and sulfate. Benzo[a]pyrene-7,8-diol is one significant metabolite that is generated by epoxide hydrolase during its reaction with benzo[a]pyrene-7,8-epoxide. This dihydrodiol can be further converted by CYPs to a series of benzo[a]pyrene-7,8-diol-9,10-epoxides, which make up one class of B[a]P eventual carcinogenic metabolites. B[a]P can be oxidized with the aid of peroxidases, such as CYPs and prostaglandin-H synthase [26]. CYP1A1, CYP1A2, and CYP1B1 are the major cytochrome P450s that controls the generation of diolepoxides and diols. Benzo[a]pyrene and other PAHs can induce cytochrome P450s by interacting to the AhR nuclear complex. This can result in alterations to the transcription of phase-II and CYP enzyme genes [27]. The carcinogenesis produced by B[a]P is resistive in mammals lacking the AhR receptor. Both CYPs and peroxidases have the ability to produce radical cations by oxidizing a single electron. This cation is part of another class of carcinogenic chemicals. A person's susceptibility to carcinoma is altered by changes in phase-II enzymes and human CYPs, including uridine 5′-diphosphate glucuronosyltransferases, glutathione S-transferases, and sulfotransferases [28]. Certain variations in phase-II enzymes and Aldo-keto reductase (AKR1) family enzymes oxidize benzo[a]pyrene-7,8-dihydrodiol to benzo[a]pyrene-7,8-quinone in a different metabolic pathway. Gene variations that affect sensitivity have been found among them. The decomposition of B[a]P quinones to hydroquinones, which can then be reoxidized and produce oxygen species that are reactive, is catalyzed by NAD(P)H quinone oxidoreductase-1 (NQO1) [29-31]. Currently available research on the process of B[a]P-directed carcinogenesis in lab animals mostly relies on two independent pathways: radical cation and diolepoxide pathways. Each offers a distinctive rationale for the modifications seen in particular tissues in animal models. The mechanism of diolepoxide for B[a]P includes a series of metabolic reaction: B[a]P to B[a]P-7,8-oxide then to B[a]P-7,8-diol to B[a]P-7,8-9,10-epoxides. It has been demonstrated that each kind of metabolic intermediate is carcinogenic and genotoxic [32]. The radical-cation pathway for B[a]P has only been explored in relation to mouse skin carcinogenesis. Because of the ionization potential and geometric structure, one-electron oxidation of B[a]P by CYPs or peroxidases results in the formation of a radical cation on carbon 6 as an outcome of geometric configuration and ionization potential. In the skin of mouse, this radical cation forms adducts with adenine and guanine. These adducts are very transient and resulted to cause apurinic sites in the skin of mouse [33]. Some of the other activation mechanisms of B[a]P are listed in Table 1.

4. Health effects of benzo[a]pyrene

Several investigations confirm that B[a]P is carcinogenic. For example, a groundbreaking study reported that B[a]P causes cancers in different animal models, such as rats and mice, by means of mechanism including mutation and damage to DNA. Strong evidence for B[a]P's carcinogenic potential and its participation in the growth of carcinoma was presented by Onaciu et al. [34]. Exposure to B[a]P is associated to various other harmful health outcomes beside cancer. Studies have created a connection between exposure of B[a]P and lung illness such as asthma [35].

Table 1. Other activation mechanism of benzo[a]pyrene.

Activation method	Mechanism	References
Meso-region activation	Both CYPs and sulfotransferases participate in B[a]P biomethylation through S-adenosylmethionine to produce 6-methyl-B[a]P.	[36]
Ortho-quinone/ reactive oxygen species activation	Aldo-keto reductase (AKR) enzyme system will both produce ROS and DNA adducts when it oxidizes B[a]P-7,8-diol oxidation to produce B[a]P-7,8-quinone.	[37]
Aryl hydrocarbon-receptor (AhR) activation	B[a]P together with other AhR-ligands regulate xenobiotic metabolism, including production of ROS, which causes DNA damage as well as oxidative stress to cellular systems.	[38]
Immunosuppression activation	Additionally, there is evidence that PAHs reduce immune defense through oxidative damage, non-genotoxic mechanisms that alter lymphocyte signaling pathways, and p53-dependent processes.	[39]
Epigenetic activation	B[a]P promotes cell proliferation, affecting normal human bronchial epithelial cells during squamous development and lung cancer progression	[40]

Moreover, B[a]P has also been related to cardiovascular ailments. According to a report, B[a]P ingestion is related with dysfunction of endothelial cells, which is an important factor in the aetiology of heart diseases such as atherosclerosis and hypertension [41].

Epigenetic alterations are considered as one of the mechanisms that is included in the process of carcinogenicity. It involves alterations in the organization and composition of chromatin, post-translational patterns of histone proteins, and DNA methylation process [42]. Various investigations have showcased how the environment impacts the methylation of DNA which ultimately altered the specific as well as global methylation of a particular gene. In vitro investigations confirm B[a]P as an epigenetic modifier. The mutagenic metabolite (BPDE) of B[a]P binds with DNA and caused methylated DNA formation and caused alterations in DNA methyltransferase (DNMT). Treatment of immortalized bronchial epithelial cells with BPDE caused increase in the level of cytosine-DNA-1 methyltransferase which is related with the hypermethylation of 5-10 gene promoters comprising member of cadherin gene family [43, 44]. However, treatment of untransformed cells with BPDE in vitro results no significant alterations in the status of methylation. The reports of B[a]P on global methylation of DNA are quite contradictory and limited. For instance, treatment of TK6 cells with B[a]P showed no major global DNA methylation alterations whereas other investigations have reported that the exposure to B[a]P directs global hypomethylation in the DNA of zebrafish embryo [45].

The control of reproduction at neuroendocrine level is seriously controlled at the central level by the adequate secretion of gonadotropin-releasing hormone (GnRH) by the GnRH neurons in the hypothalamus. A change in the network of GnRH mainly at developmental stage directs to long term systemic and reproductive consequences which results to infertility. B[a]P play a crucial role as an endocrine disrupter that affects gamete maturation, and gonadal function. B[a]P treatment to the fetal ovary prior the formation of follicle decreased the germ cell number and ultimately up the number of primordial follicles by 76% [46]. B[a]P decreased total progressive and hyperactivated migration and motility in a viscous medium in both unselected and swim-up spermatozoa. Swim-up spermatozoa had no major effect on viability whereas unselected spermatozoa have a reduction [47]. Table 2 includes a few of the other health impacts caused by B[a]P.

Table 2. Other health effects caused by B[a]P.

Effect	Model	Dose(s)	References
Decline in cortical neuron function	Long Evans rats	300 µg/kg body weight (bw); taken orally between 14 and 17 days of pregnancy	[48]
Behavioral deficiencies and plasticity	Long Evans rats	0, 25, and 150 µg/kg bw; taken orally between 14 and 17 days of pregnancy	[49]
Fetal damage, restricted growth, and bleeding	Rat	50, 100, and 200 mg/kg bw; intraperitoneal; on 10^{th}, 12^{th}, and 14^{th} day of gestation	[50]
Altered pregnancy hormones and fetal viability	F-344 rats	25, 75, and 100 µg/m^3, inhaled for 4 hrs a day for 10 days	
Hematopoietic changes in fetal	Mice	0, 50, 100, and 150 mg/kg/day; taken orally throughout the 13^{th}-17^{th} week of pregnancy	[51]
Ovarian toxin inhibiting corpus luteum formation	C57BL/6N mice	0-500 mg/kg; intraperitoneal	[52]
Reduced sperm production and hormonal activity in testes	Rats	Inhalation of 75 µg/m^3; 4 h daily a day for sixty days at 24, 48, and 72 hrs	[53]
Negative impact on Autism risk gene activity and cognitive effects during pregnancy	In utero children	Orally during days 14–17 of embryonic development at a dosage of 0, 150, 300, and 600 µg/kg bw	[54]
Increased lesions from atherosclerosis	$ApoE^{-/-}$ mice	12.5 mg/kg/day and 5 mg/kg/bw, twice a week for two weeks.	[41]
Increased MCP1 gene expression in aortic tissue	$ApoE^{-/-}$ mice	12.5 mg/kg/day and 5 mg/kg/bw, twice a week for two weeks.	
Amplify the hypertrophy of the heart	Sprague-Dawley rats	During seven days at dosage of 20 mg/kg/bw	
Organelle dysfunction and mis-localization in mouse oocytes	ICR mice	40 mg/kg/bw for 10 days	[55]

5. Different types of cancers caused by benzo[a]pyrene

5.1. Lung cancer

Vázquez-Gómez et al. showed that exposure of rats for longer period of time to B[a]P responsible in inducing squamous cells cancer and adenocarcinomas, which have resemblance with the histopathological features observe in human lung cancer cases [56]. The pathological significance of lung cancer in human beings is quite comparable to that of B[a]P-directed cancer of the lungs in rats. In the rats, the biochemical transformation of B[a]P creates reactive species that bind strongly to DNA, creating DNA adducts and later resulting mutations in the genome [57].

An investigation by Pesatori et al. discovered a strong correlation among increased cancer of the lungs prevalence between employees in sectors like aluminum smelting and coke manufacture and workplace exposure to B[a]P [58]. In a comparable manner, a meta-analysis done by Famiyeh et al. reported the substances harmful potential in humans by confirming a dose-response association between contact with B[a]P and the development of lung cancer [59]. B[a]P causes lung cancer in humans through a number of pathways, including destruction of DNA and activation of metabolism. After inhalation, cytochrome P450 enzymes in the liver break down benzophene to produce highly reactive intermediates such as benzo[a]pyrene diol epoxide (BPDE), that can covalently bond to nucleic acid to form DNA adducts. These adducts can interfere with regular repair and replication of DNA processes, which can result in alterations in important suppressors of tumors and oncogene genes linked to the growth of lung cancer [60].

5.2. Liver cancer

B[a]P has been related to the initiation of damage to DNA in the liver cancer, majorly through the formation of chemically changed nucleic acid molecules referred as DNA adducts. These adducts can affect regular repair mechanisms and replication procedures, which may be responsible in inducing mutations and the growth of cancer [61]. In the event of cancer, B[a]P has the ability to limit the apoptotic process and control the activation of various enzymes and signaling pathways that activate AhR, which is necessary for the ongoing development and multiplication of hepatic carcinoma cells [62]. Additionally, B[a]P modifies the metabolism of glucose and lipids, leading to liver cell dysregulation and, eventually, accelerated tumor growth and metastasis [63]. In addition, epidemiological research has reported a relation between long term exposure to B[a]P and a higher risk of liver cancer. Numerous investigations confirmed the link between prolonged exposure to B[a]P and a higher risk of developing liver cancer. This is corroborated by a Chinese study that found that people who consume contaminated food or breathe in polluted air are significantly more likely to develop liver cancer than people who are not exposed to high levels of B[a]P [64].

5.3. Colorectal adenoma

The colorectal adenoma is a benign tumor also referred as a colorectal polyp which was originate from the epithelial cells that line the colon and rectum. Even though the large number of adenomas cases does not show any symptoms, if they do not receive treatment, they may directly progress to colorectal cancer. Various research has looked into the part that environmental pollutant, such as B[a]P, play a significant part in the spread and emergence of colorectal adenomas [65]. High Dietary Inflammatory Index (DII) scores were positively related with a greater risk of developing colon tumors. Additionally, it was emphasized that how inflammatory agents like B[a]P contribute in the process of development of irritation in the colon [66].

A meta-analysis study emphasized the fatal effects of B[a]P exposure on colorectal health by finding a positive link between higher concentrations of urine PAH compounds and a higher risk of colorectal adenomas [67]. Ozaki and Nakagawara reported that the molecular pathways underpinning B[a]P-directed colorectal carcinogenesis [68]. This study clarified how exposure to B[a]P results the promoter region of the tumor suppressor gene p53 to get methylated, which ultimately silences the gene and results to the dysregulation of cell cycle control and DNA repair. This dysregulation ultimately emphasizes the exact function of B[a]P in driving the development of adenomas by converting colorectal cells to malignant cell. A study by Harris et al. revealed the role of westernized diet in the development of colon cancer directed by B[a]P via biotransformation, which in turn results in the binding of the metabolites with DNA forming adducts that ultimately forms colon polyps determined by dysplasia, tumor size, and number [69].

5.4. Laryngeal cancer

High amounts of B[a]P were associated to a greater likelihood of laryngeal cancer, according to research findings that showed a direct correlation between B[a]P consumption and the disease. Hecht, in his investigation, emphasized B[a]P cancerous ability by highlighting its potential to create mutations in laryngeal cells, which can result in the initiation of cancer [60]. Additionally, laryngeal irritation and respiratory problems might be caused due to B[a]P exposure. According to an investigation, inhalation of B[a]P may be responsible in the onset of inflammation reaction in the mucosa of larynx, which in turn further aggravates respiratory symptoms. Some reports indicated that the exposure of B[a]P was related to the production of oxidative stress in the larynx which results in inflammation and issues related with respiration [70]. B[a]P is well known to mutate and damage DNA of the laryngeal cells, increasing the risk of cancer. Another study that investigated into the genotoxic capacity

of barium paraffin in the larynx reported that after being exposed to B[a]P, forms DNA adduct, which can result mutations and affects genome stability [60].

5.5. Oral cancer

B[a]P serves as an element for starting oral cancer according to Jiang et al. [71]. Researchers established that B[a]P exposure strengthens cancer risks in the mouth primarily among tobacco users who started using tobacco earlier. B[a]P facilitates oral cancer development through its mechanisms that enhance inflammatory responses along with oxidative damage in addition to its main mutagenic properties [72]. Furthermore, epidemiological studies have showcased that the incidence of oral cancer and B[a]P exposure are correlated with each other in positive manner. For instance, a meta-analysis that analyzed information from different population-based research concluded that people who were in direct exposure with the higher B[a]P levels had a greater chance of getting oral carcinoma [73]. Carcinogenic properties of B(a)P in oral tissues have generated significant findings through studies that employed animal models. In a study, mice were administered with B[a]P orally and the researchers saw the development of oral carcinoma that is identical with the histology and microscopic features of human oral cancer. The results of human epidemiological studies were supported by this practical work, indicating that B[a]P in the oral cavity has the potential to result cancer [74].

6. Biomarkers for the estimation of benzo[a]pyrene

Biomarkers can be identified in tumors, surrogate tissues, and target organs. These fall into three categories: indicators of exposure, which are often unique to the polycyclic aromatic hydrocarbons (PAHs) in question (such as peptide or nucleotide adducts), detoxification enzymes e.g. glutathione S-transferases, biomarkers of effect such as 8-oxo-deoxyguanosine, micronuclei, cytogenetic effects, genotoxic effects, mutations in indicator genes, oncogenes, and tumor-suppressor genes, and susceptibility biomarkers including DNA-repair enzymes, and bioactivation enzymes e.g. cytochrome P450 isoenzymes. The majority of biomarkers providing evidence about damage and sensitivity serve without specificity to any specific type of PAH contact yet selected parameters offer possibilities to explain cancer-causing mechanisms from PAH exposure in humans [75]. Certain precautions can be taken to prevent against the detrimental consequences of B[a]P exposure, which are briefly described in the next section.

7. Safety measures related to benzo[a]pyrene handling and storage

B[a]P is a harmful polycyclic aromatic hydrocarbon that demonstrates carcinogenic, mutagenic along with teratogenic properties. The necessity of strict safety protocols becomes critical during all stages of B[a]P handling because of its toxic qualities and documented lasting health risks. The document establishes essential protective measures together with appropriate operational methods that aim to maintain safe operations while reducing contact with B[a]P.

The atmosphere around lignite and pitches combustion plants in Czech Republic should contain less than 100-200 ug/100 m^3 of B[a]P. The USSR Ministry of Health set the maximum allowable concentration (MAC) for B[a]P in the operational area as 15 ug/100 cu-m and in atmospheric air at 0.1 ug/100 cu-m [76]. Protective safety protocols should be rigorously enforced during B[a]P work processes to reduce possible health dangers [77]. The staff working with chemicals must use proper personal protective equipment (PPE) that includes both respiratory protections together with safety goggles and lab coats and disposable nitrile or neoprene gloves to safeguard their skin. The reduction of B[a]P vapor inhalation needs engineering controls including fume hoods and ventilation systems as essential provisions. The storage of B[a]P must occur in sealed containers while required safe handling methods must be kept when working in fume hoods for pipetting. The laboratory must have protocols for decontamination that involve suitable disinfectants to rapidly clean contaminated areas and materials using designated washing solutions or alcohol wipes. Additionally, all laboratory members should receive adequate training and be made aware of the potential hazards, correct PPE usage, and appropriate handling techniques related to B[a]P exposure [78].

Furthermore, the evaluation of polycyclic aromatic hydrocarbon (PAH) substances including B[a]P exposure through human biomonitoring (HBM) requires urine samples as the main biological matrix because of the short half-life period of their compounds. 1-hydroxypyrene (1-OHPYR) functions as a common biomarker used in such assessments [79]. 1-OHPYR levels in urine respond to the effects from smoking cigarettes and industrial pollutant exposure and person's eating behavior. The research shows that 1-OHPYR measures correlate with smoking behaviors in unexposed populations but it has been linked to B[a]P contamination in the air which supports its usefulness as a biomarker in measuring PAH exposure [11]. Oilfield chemicals that contain B[a]P have developed into a substantial environmental issue. The development of a double T-line mode immunochromatographic strip made from gold nanoparticles enables B[a]P detection in oilfield samples with a measurement range from 0.42 to 300 mg/kg while reaching detection sensitivities between 0.23 and 1.07 mg/kg [80].

The correct storage conditions for B[a]P are necessary to stop its quality decline and protect it against pollutants and unauthorized use. A secure well-ventilated area should contain B[a]P when stored in sealed glass containers which display all required labels including its name and concentration and hazards details along with source date. Storage conditions need to prevent non-desired substances from contacting B[a]P while maintaining temperatures between low to dark range for light protection [78]. B[a]P

can be destroyed through degradation protocols in addition to standard safety procedures.

8. Biodegradation of benzo[a]pyrene

The broad variety of microbial species that may degrade B[a]P is contributing to the growing popularity of the biodegradation process of B[a]P. Enzymes like oxygenases and hydrolases are produced by microorganisms like *Staphylococcus haemoliticus*, and they can convert hazardous B[a]P into non-toxic forms [81]. Very few microorganisms including *Ochrobactrum* sp., *Novosphingobium pentaromativorans*, *Bacillus subtilis*, *B. licheniformis*, *Mesoflavibacter zeaxanthinifaciens*, *Sphingomonas yanoikuyae* JA, *Stenotrophomonas maltophilia*, and *Mycobacterium vanbaalenii* have been able to degrade B[a]P under non-halophilic circumstances [82]. The amount of B[a]P in the soil and its quality are the two main elements that affect how quickly B[a]P degrades in the soil. However, the two most often used techniques for the degradation of B[a]P are bio-augmentation and bio-stimulation.

Furthermore, some new methodology for the effective decomposition of B[a]P and other related PAHs have been possible by using nanotechnology and omics-technology. The natural breakdown of PAHs in the atmosphere, however, also has negative affect on species of bacteria. More harmful constituents could emerge while biodegradation, which can cause harm to microbial biological membranes, allow the organisms to enter, and restrict their ability to perform important functions [83]. Functional enzymes including naphthalene dioxygenase (NahAC) and catechol 2,3-dioxygenase (C23O) that are formed due to the extensive exposure to petroleum plays a crucial function in directing the transformation of B[a]P. Most of the major degrading enzymes are encoded by greatly conserved genes such as phn, nid, phd, and nah. In a study, Pan et al. reported the biodegradation of B[a]P utilizing a genetically engineered *B. lichenformis* with removal rate of 78.21-80.16% [84]. Dong et al. reported the high-efficiency ability of *Pseudomonas benzopyrenica* BaP3 in degrading the B[a]P due to *rhd1* [85]. Photocatalytic degradtion of B[a]P upto 86% was achieved utilizng a nanocomposite g-C3N4-SnS in 4 hrs of time period [86]. Chen et al. reported the remediation of B[a]P polluted soil by medium chemical oxidation linked with microbial degradation including dominant species such as *Oxalobacteraceae*, *Alicyclobacillacea*, *Enterobacteriaceae*, and *Burkholderiaceae* [87]. Immobilized *Acineotobacter baumannii* and *P. taiwanensis* PYR1 on cinder beads degrades the B[a]P by 81% under petroleum polluted aerobic soil [88]. The Synergy of algal and bacteria such as *Rhodococcus wratislaviensis* and *Chlorella* sp. MM3 had the B[a]P degradation capacity of 100% under the aerobic soil slurry [89].

9. Other methods of B[a]P degradation

A green and cost effective peroxymonosulfate directed catalyst (CG-Ca-N) was developed with melamine, calcium chloride, and coal gangue as activator. Under suitable condition, the CG-Ca-N can eliminate the 100% of B[a]P from an aqueous solution after 20 min, and 72.06% from the medium of slurry within 60 min [90]. Lu et al. reported the elimination of B[a]P from the sausages and related particulate matter while the smoking of sausages by the help of film developed by the combination of corn starch (CS) with sodium alginate (SG)/K-carrageenan (KC) [91]. The elimination ability of both the composite film (CS-SA and CS-KC) were found to be 41.1%-56.5% with excellent biodegradability and recyclability. Laccase is a green biocatalyst which is broadly utilized for the elimination of various types of organic contaminants. However, laccase in its free form is unstable and problematic to recover that restricts its practical utilization. A specialized structure of Fe_3O_4@d-SiO_2@p-SiO_2 allows the better immobilization of laccase. This immobilized laccase had remarkable elimination activity for B[a]P with an elimination efficiency of 99%. Effective degradation of organic contaminants in complex environment of soil through using the non-radical pathways is important but quite challenging. Biochar related nZVI formed by carbothermal reduction method was developed for the activation of persulfate which exhibits superfast decomposition of B[a]P with efficiency of 71.80% within the time period of 5 min [92].

10. Conclusion

Alteration in the blood sugar metabolic process may Common sources of B[a]P include food, dust, soil, surface water, air, and smoke of cigarette. Owing to its strong hydrophobicity, B[a]P is found in greater levels in soil and aquatic debris, whereas it is found in tiny amounts in surface water bodies. B[a]P is frequently present in outdoor air at quantities that regularly surpass permissible limits. Particularly, children in preschool and school, as well as employees of aluminum companies or coke ovens, are in grave danger of significant health problems from breathing indoor air having extremely elevated B[a]P concentrations. This material is classified as a group I carcinogen and is highly hazardous. In addition to being neurotoxic, teratogenic, mutagenic, genotoxic, and mutagenic, B[a]P also reduces fertility. The production of DNA adducts, the production of ROS, the stimulation of AhR, and several epigenetic modifications are all part of the B[a]P-action process. Excessive B[a]P atmospheric pollution is today one of the biggest threats to environmental health in many countries. Given the current state of B[a]P air pollution, the governments of those countries must take new steps to reduce it in the environment. However, B[a]P that has already entered the atmosphere, particularly in heavily contaminated soils, must be removed as soon as possible using bacterial strains capable of breaking down this substance. The discovery of novel enzymes and their functions in chemo-, regio-, and enantioselective chemical

reactions for degradation of B[a]P may contribute to the creation of novel techniques for organic compounds via biocatalysis, particularly given current developments in biotechnology such as controlled evolution and the engineering of proteins. Overall, this study has emphasized the existing gaps in the knowledge of B[a]P degradation, and the suggested study routes will make significant contributions to bridging these gaps.

Declarations

Author Contribution: Both authors contributed equally in the preparation of the manuscript.

Funding: Not Applicable

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: Not applicable

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