Review

1-Hydroxypyrene Glucuronide & 8-Hydroxy-2'-deoxyguanosine: A Key Biomarker Bridging Polycyclic Aromatic Hydrocarbons (PAHs) Exposure to Malignancy— Mechanistic and Epidemiological Perspectives

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1-Hydroxypyrene Glucuronide & 8-Hydroxy-2'-deoxyguanosine: A Key Biomarker Bridging Polycyclic Aromatic Hydrocarbons (PAHs) Exposure to Malignancy— Mechanistic and Epidemiological Perspectives

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Abstract

Polycyclic aromatic hydrocarbons (PAHs) are pervasive environmental carcinogens whose health impacts depend on both exposure burden and downstream molecular damage. However, a major limitation in current risk assessment is the lack of integrated biomarker strategies that link exposure to early carcinogenic events. This review focuses on two critical and complementary biomarkers; 1-Hydroxypyrene Glucuronide (1-OHPG), a validated indicator of internal PAH exposure, and 8-Hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage and mutagenesis. While these biomarkers are individually well-established, their combined application remains underexplored. Mechanistically, PAH metabolism generates reactive intermediates and reactive oxygen species that induce DNA lesions, with 8-hydroxy-2'-deoxyguanosine reflecting cumulative oxidative genomic injury. Epidemiologically, elevated levels of both biomarkers have been associated with increased cancer risk in exposed populations, yet they are often assessed independently, limiting their predictive power. This review critically evaluates existing evidence and highlights the disconnect between exposure assessment and biological effect monitoring. It proposes that the simultaneous integration of 1-hydroxypyrene glucuronide and 8-hydroxy-2'-deoxyguanosine provides a more robust framework for linking PAH exposure to carcinogenic outcomes. Bridging this gap could significantly enhance early detection, mechanistic interpretation, and risk stratification in PAH-related malignancies.

Keywords: polycyclic aromatic hydrocarbons; 1-hydroxypyrene glucuronide; 8-hydroxy-2'-deoxyguanosine; biomarker integration; oxidative DNA damage; cancer risk

Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with a substantial proportion of cases attributable to environmental exposures [1]. According to the World Health Organization, cancer accounted for nearly 10 million deaths globally in recent years, highlighting its enormous public health burden [2]. Increasing epidemiological evidence suggests that environmental pollutants including chemical contaminants in air, water, and food, play a significant role in the initiation and progression of various malignancies [3]. Environmental carcinogenesis is therefore a critical area of investigation, particularly as rapid industrialization, urbanization, and changes in lifestyle continue to increase human exposure to toxic compounds.

Among environmental carcinogens, Polycyclic Aromatic Hydrocarbons (PAHs) have attracted considerable scientific attention due to their widespread distribution and well-established toxicological properties [3]. PAHs constitute a large class of organic compounds formed primarily

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through the incomplete combustion of organic materials such as fossil fuels, biomass, tobacco, and industrial emissions [4,5]. These compounds are ubiquitous in the environment and are commonly detected in ambient air, contaminated soil, aquatic systems, and certain food products, particularly those subjected to high-temperature cooking processes such as grilling or smoking [6]. Human exposure to PAHs occurs predominantly through inhalation of polluted air, ingestion of contaminated food or water, and dermal contact with contaminated materials [7].

Several polycyclic aromatic hydrocarbons (PAHs) are well-established as potent carcinogens, mutagens, and teratogens [8]. Among them, benzo[a]pyrene (BaP) is one of the most extensively studied and has been classified as a Group 1 human carcinogen due to its strong association with cancers of the lung, skin, and bladder [4,9]. Emerging evidence also implicates PAH exposure in breast carcinogenesis, which is particularly significant given that breast cancer remains one of the most prevalent malignancies among women worldwide [3,10,11]. The carcinogenic potential of PAHs arises largely from their metabolic activation within the body, leading to the formation of reactive intermediates capable of interacting with cellular macromolecules, including DNA [12]. This metabolic process is often mediated through signaling pathways such as the Aryl Hydrocarbon Receptor signaling pathway, which regulates the expression of cytochrome P450 CYP1A1 enzymes responsible for the biotransformation of PAHs into reactive metabolites [13,14]. These metabolites can generate reactive oxygen species (ROS), resulting in oxidative stress, DNA damage, and ultimately mutagenesis, key events in the multistep process of carcinogenesis [15,16].

Despite the recognized carcinogenicity of PAHs, accurately assessing human exposure and its biological consequences remains a major challenge in environmental health research. Traditional exposure assessment approaches, such as environmental monitoring of pollutants, often fail to capture individual variability in absorption, metabolism, and susceptibility [17]. Consequently, the use of biomarkers has become an essential tool in environmental toxicology and molecular epidemiology. Biomarkers provide measurable indicators of biological processes, exposures, or disease states and allow researchers to establish more precise relationships between environmental contaminants and adverse health outcomes [18,19]. In the context of environmental carcinogenesis, biomonitoring enables the evaluation of both the internal dose of a toxicant and the early biological effects resulting from exposure [20].

One of the most widely used biomarkers of PAH exposure is 1-Hydroxypyrene Glucuronide (1-OHPG), a conjugated metabolite of pyrene that is excreted in urine following hepatic metabolism. Because pyrene is commonly present in PAH mixtures, urinary 1-OHPG is considered a reliable indicator of internal PAH exposure in both occupational and environmental settings [21–23]. Numerous studies have demonstrated that elevated levels of urinary 1-OHPG correlate strongly with exposure to PAHs in populations such as industrial workers, traffic police officers, smokers, and residents of highly polluted urban environments [21,24–27]. The measurement of 1-OHPG therefore provides valuable insight into the internal dose or concentration of PAHs that has entered the body and undergone metabolic processing.

While exposure biomarkers such as 1-OHPG provide evidence of pollutant uptake, they do not necessarily indicate whether the exposure has resulted in biological damage [19,23]. For this reason, biomarkers that reflect early molecular effects are equally important. One such biomarker is 8-Hydroxy-2′-deoxyguanosine (8-OHdG), a product of oxidative modification of the DNA base guanine. This lesion arises when reactive oxygen species generated during cellular metabolism or toxicant exposure attack DNA molecules, leading to oxidative damage [28]. The accumulation of 8-OHdG is particularly significant because it can cause G→T transversion mutations during DNA replication, thereby contributing to genomic instability and carcinogenesis [29–32]. Elevated levels of 8-OHdG have been detected in biological fluids such as urine and blood in individuals exposed to various environmental pollutants, including PAHs, suggesting its usefulness as a biomarker of oxidative DNA damage [33–35].

Although both 1-OHPG and 8-OHdG have been extensively studied individually, increasing attention is being directed toward their combined application as complementary biomarkers in

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environmental health studies [36]. Existing studies often evaluate biomarkers in isolation, creating a gap in understanding the interconnected molecular pathways linking PAH exposure to disease outcomes, particularly through oxidative stress and gene regulation mechanisms. .In this framework, 1-OHPG serves as an indicator of internal exposure to PAHs, while 8-OHdG reflects the downstream biological effects of that exposure in the form of oxidative DNA damage. Integrating these two biomarkers simultaneously provides a more comprehensive understanding of the continuum linking environmental exposure to molecular injury and ultimately disease development. This approach aligns with contemporary strategies in molecular epidemiology, which emphasize the importance of combining exposure biomarkers with effect biomarkers to strengthen causal inference between environmental toxicants and cancer risk [37].

The integration of 1-hydroxypyrene glucuronide (1-OHPG) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) is grounded in their ability to represent sequential events in environmental carcinogenesis, linking PAH exposure to metabolic activation, oxidative stress, and subsequent DNA damage (Figure 1). While PAH metabolism generates reactive intermediates that induce oxidative lesions such as 8-OHdG, the combined assessment of exposure and effect biomarkers provides a clearer understanding of the mechanistic pathway leading to carcinogenic outcomes. This review therefore synthesizes current evidence on PAH sources, exposure pathways, metabolic processes, and oxidative damage, emphasizing the complementary roles of 1-OHPG and 8-OHdG in bridging environmental exposure to biological effects. Such an integrated biomarker framework enhances risk assessment, supports the identification of vulnerable populations, and underscores its relevance in environmental health surveillance and cancer prevention strategies.

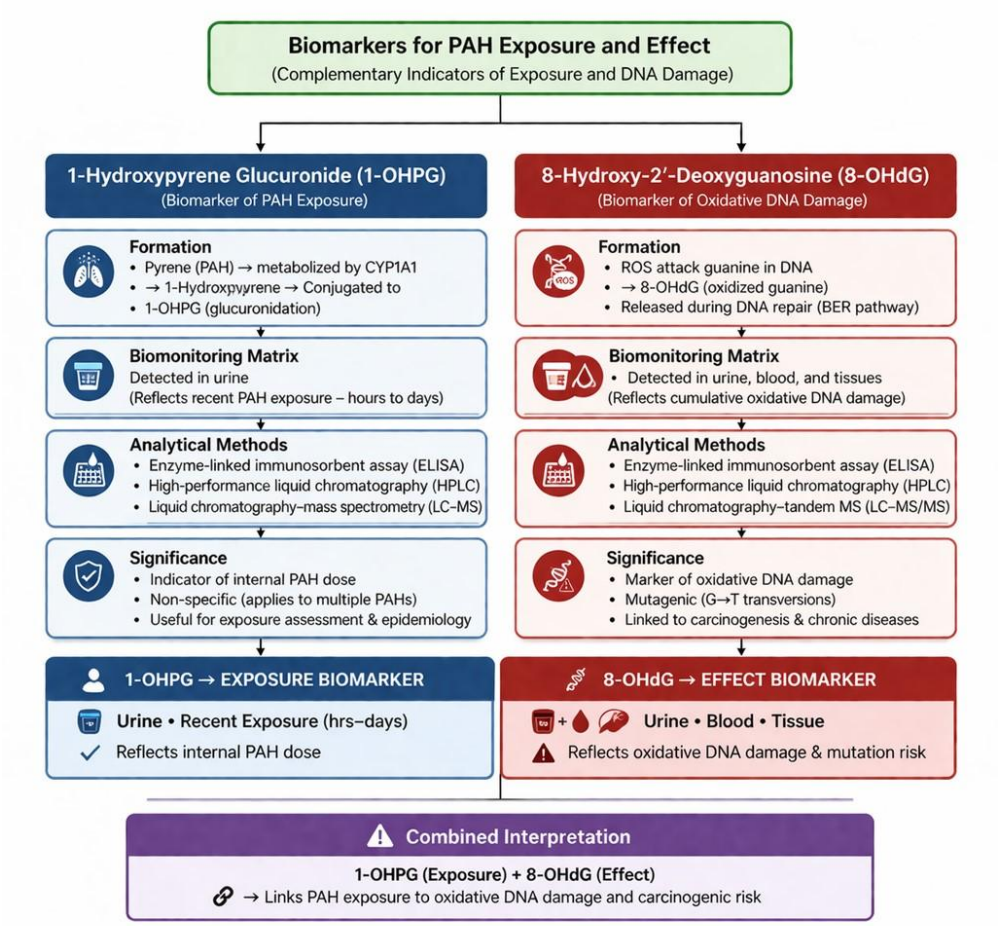

Figure PAHs biomarkers and cancer risk comparison [33,38].

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Environmental Sources, Human Exposure Pathways, and Toxicological Significance of PAHs

Polycyclic Aromatic Hydrocarbons (PAHs) are a large group of organic compounds composed of two or more fused aromatic rings and are generated primarily through the incomplete combustion of organic matter [39]. These compounds are widely distributed in the environment and are considered important environmental pollutants due to their persistence, bioaccumulation potential, and carcinogenic properties. Anthropogenic activities such as industrial combustion, transportation emissions, tobacco smoking, and high-temperature cooking processes represent major contributors to PAH contamination in air, water, soil, and food systems [40]. Consequently, humans are continuously exposed to PAHs through multiple environmental pathways, raising significant concerns regarding their potential health effects, including carcinogenesis (Figure 2) [6,9].

2.Environmental and Anthropogenic Sources of PAHs

Industrial Combustion

Industrial activities constitute one of the primary anthropogenic sources of PAHs in the environment. Processes involving coal combustion, petroleum refining, coke production, and metallurgical operations generate large quantities of PAHs as by-products of incomplete combustion [41]. These compounds are released into the atmosphere through industrial emissions and subsequently deposited in surrounding soils and aquatic systems through atmospheric fallout. Occupational settings such as aluminum production, coal tar processing, asphalt production, and coke ovens have historically been associated with elevated PAH exposure levels and increased cancer risk among workers [9,41].

In industrialized regions, emissions from fossil fuel combustion remain a dominant source of atmospheric PAHs. Once released into the atmosphere, PAHs can bind to particulate matter and undergo long-range transport before depositing onto terrestrial and aquatic environments, thereby expanding their geographical distribution and potential exposure risks [8].

Vehicular Emissions

Vehicular traffic is another major contributor to environmental PAH pollution, particularly in urban environments. PAHs are generated during the incomplete combustion of gasoline and diesel fuels in internal combustion engines. Roadside environments often exhibit elevated concentrations of PAHs in air and soil due to continuous exposure to exhaust emissions from automobiles, trucks, and buses [42,43]. Studies examining urban environmental contamination have demonstrated that vehicular emissions represent a dominant source of PAHs in urban soils and atmospheric particulate matter, highlighting the role of traffic density in determining local PAH pollution levels [25].

In addition to exhaust emissions, other vehicular-related sources include tire wear, brake lining degradation, and the volatilization of petroleum-based products used in road construction. As a result, individuals living or working near high-traffic areas may experience significantly higher exposure to airborne PAHs [44].

Tobacco Smoke

Tobacco smoke represents an important indoor source of PAH exposure. During cigarette smoking, the pyrolysis of tobacco components generates numerous toxic compounds, including PAHs. More than 500 PAH compounds have been detected in tobacco smoke, several of which possess carcinogenic properties [45–47].

Both mainstream smoke (inhaled by smokers) and sidestream smoke (released into the surrounding environment) contain substantial levels of PAHs such as benzo[a]pyrene, benz[a]anthracene, and chrysene [48]. These compounds contribute significantly to the carcinogenic potential of cigarette smoke and are strongly associated with the development of lung cancer and other smoking-related diseases [45]. Epidemiological studies have shown that exposure to tobacco smoke-derived PAHs correlates with increased cancer risk among smokers, emphasizing the importance of tobacco control in reducing PAH exposure [46].

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Dietary Sources (Charred and Smoked Foods)

Dietary intake represents a major route of polycyclic aromatic hydrocarbon (PAH) exposure in the general population. PAHs are formed during high-temperature cooking processes such as grilling, roasting, frying, and smoking, particularly when fat and juices from meat drip onto hot surfaces or open flames, leading to incomplete combustion and the subsequent deposition of PAHs onto the surface of foods [49,50]. Common dietary sources associated with elevated PAH concentrations include charbroiled meats, smoked fish, roasted coffee, grilled vegetables, and various smoked or preserved foods. For individuals who are non-smokers and not occupationally exposed, dietary intake is often considered the predominant route of PAH exposure, underscoring the critical role of food preparation methods in determining overall PAH intake [9].

2.Routes of Human Exposure

Human exposure to PAHs occurs through several pathways, primarily inhalation, dietary ingestion, and dermal absorption. The relative importance of each route depends on environmental conditions, lifestyle habits, and occupational factors.

Inhalation

Inhalation of contaminated air is a major exposure pathway, particularly in urban and industrial areas. PAHs are often adsorbed onto fine particulate matter such as $PM_{2.5}$ and PM_{10}), allowing them to be inhaled deep into the respiratory tract [51]. Major sources of airborne PAHs include vehicle exhaust, industrial emissions, tobacco smoke, and residential biomass combustion. Inhaled PAHs can deposit in the lungs and undergo metabolic activation within pulmonary tissues, potentially initiating carcinogenic processes [52].

Dietary Ingestion

Dietary ingestion represents one of the most significant exposure routes for PAHs in the general population [49]. Contaminated foods may contain PAHs formed during cooking or introduced through environmental contamination of soil and water. PAHs can accumulate in agricultural crops, fish, and livestock products, particularly in regions affected by industrial pollution or oil spills [53]. Studies have shown that the ingestion pathway may contribute substantially to total PAH exposure, particularly in populations with diets rich in smoked or grilled foods [54,55].

Dermal Absorption

Dermal contact with PAH-contaminated materials also contributes to human exposure. Occupational groups such as asphalt workers, chimney sweeps, firefighters, and petroleum industry workers are particularly vulnerable to dermal exposure. PAHs present in contaminated soils, oils, coal tar, and soot can penetrate the skin and enter systemic circulation [56,57]. Environmental exposure can also occur through contact with contaminated sediments, soils, or industrial products containing PAHs [58,59].

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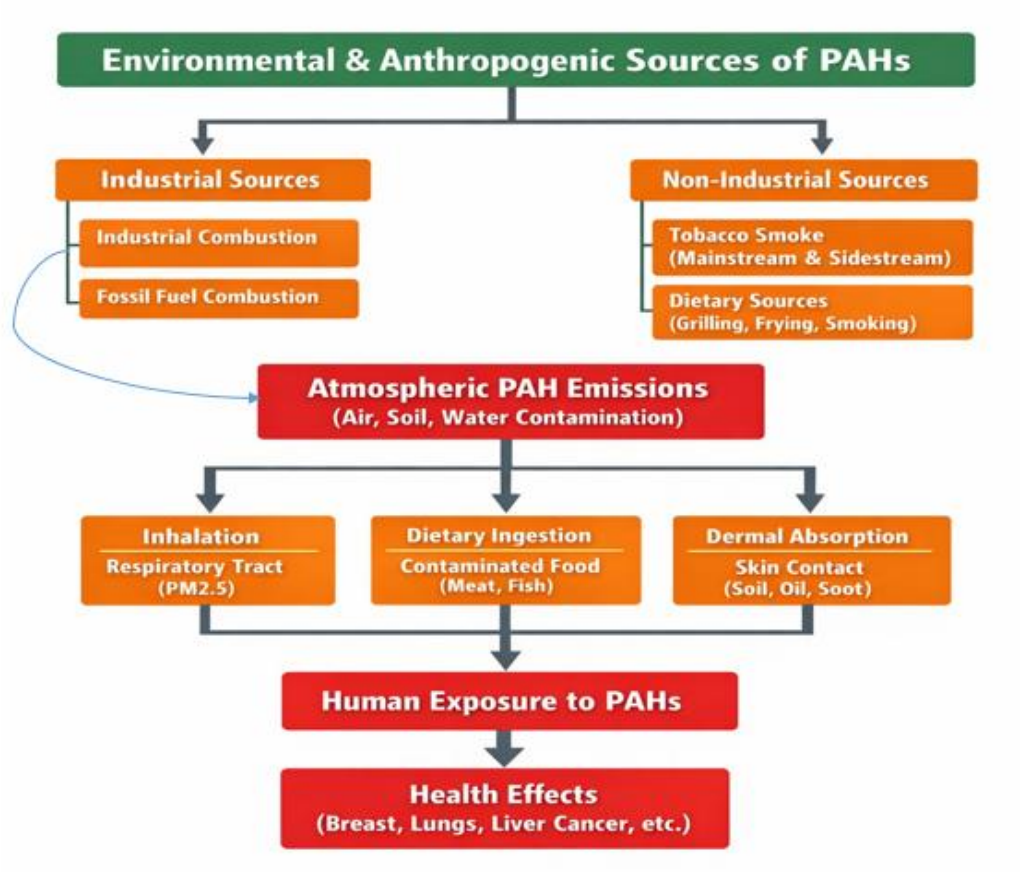

Figure Pathways of Environmental and Anthropogenic PAH Exposure and Health Effects [39,60,61].

2.Toxicological and Carcinogenic Significance

The toxicological importance of PAHs lies in their ability to undergo metabolic activation within the body, producing reactive intermediates capable of damaging cellular macromolecules.

Metabolic Activation of PAHs

PAHs themselves are relatively inert in their parent form; however, their toxicity arises after metabolic transformation within the body. Once absorbed, PAHs undergo enzymatic biotransformation primarily in the liver through Phase I metabolic reactions mediated by cytochrome P450 enzymes such as CYP1A1 and CYP1B1 [52,62,63]. These reactions convert PAHs into highly reactive intermediates such as epoxides and diol epoxides, which can bind covalently to DNA, forming DNA adducts that interfere with normal replication processes. If these DNA lesions are not repaired, they may lead to mutations and ultimately initiate carcinogenesis [12,64].

Evidence Linking PAH Exposure to Human Malignancies

A large body of epidemiological and experimental evidence supports the carcinogenic potential of PAHs. Occupational exposure studies among coke oven workers, aluminum smelter workers, and chimney sweeps have demonstrated significantly elevated risks of cancers such as breast, lung, skin and bladder cancer (Figure 3) [52,65–69]. Several PAHs have been classified as carcinogenic by the International Agency for Research on Cancer, including benzo[a]pyrene, which is widely recognized as a prototypical PAH carcinogen [9]. Animal experiments further support these findings, showing that chronic exposure to PAHs can induce tumors in multiple organs, including the liver, lung, and skin (Table 1) [70].

Role of the Aryl Hydrocarbon Receptor Signaling Pathway in PAH Toxicity

The biological effects of PAHs are strongly influenced by activation of the Aryl Hydrocarbon Receptor signaling pathway. The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that regulates the expression of genes involved in xenobiotic metabolism [71]. Thus, AhR

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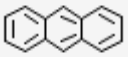
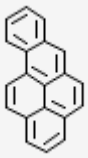
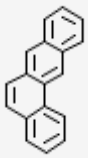
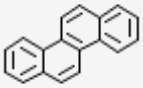
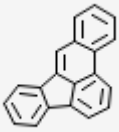
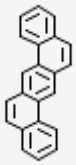
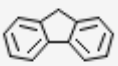
activation represents a key molecular mechanism linking environmental PAH exposure to cellular toxicity and carcinogenesis. Upon exposure to PAHs, these compounds bind to AhR in the cytoplasm, forming a ligand-receptor complex that translocates into the nucleus. The activated receptor subsequently binds to specific DNA response elements, promoting the transcription of detoxification enzymes such as CYP1A1 and CYP1BThese enzymes metabolize PAHs into reactive intermediates capable of generating oxidative stress and DNA damage [72–74].

Table Adapted from IARC [9] and Montano et al. [39], summarizing major environmental sources, exposure pathways, and carcinogenic classifications of selected PAHs compounds.

PAH Compound	Structure (PubChem)	Major Environmental Source	Main Exposure Pathway	Carcinogenic Classification
Anthracene	 [75]	Coal tar, wood combustion, industrial processes	Dermal, inhalation	IARC Group 2B
Benzo[a]pyrene	 [76]	Vehicle exhaust, tobacco smoke, grilled food	Inhalation, diet	IARC Group 1
Benz[a]anthracene	 [77]	Fossil fuel combination	Inhalation	IARC Group 2B
Chrysene	 [78]	Idustrial emissions, smoking	Inhalation, dermal	IARC Group 2B
Benzo[b]fluoranthene	 [79]	Diesel exhaust	Inhalation	IARC Group 2B
Dibenz[a,h]anthracene	 [80]	Coal tar, petroleum products	Dermal, inhalation	IARC Group 2A
Fluorene	 [81]	Fossil fuel combustion, oil spills	Inhalation, dermal	IARC Group 3

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Naphthalene	 [82]	Mothballs, tobacco smoke, fuel combustion	Inhalation	Group 2B
Pyrene	 [83]	Biomass burning, vehicle exhaust	Inhalation, dermal	Group 3

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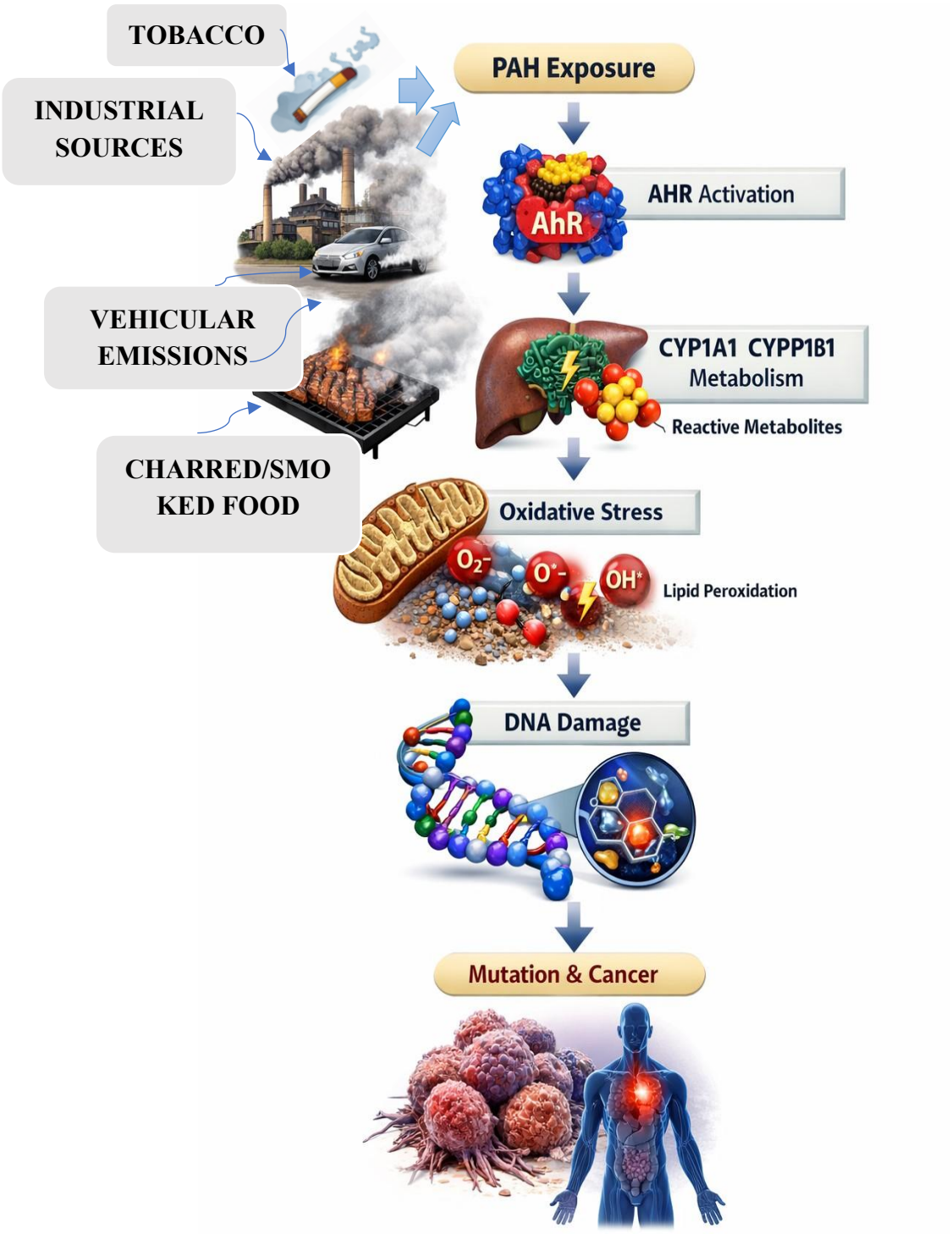

Figure Environmental sources of PAHs and major human exposure pathways [39].

Biotransformation of PAHs and the Emergence of Exposure Biomarkers

Polycyclic aromatic hydrocarbons (PAHs) are environmentally pervasive organic contaminants formed by incomplete combustion of organic matter, fossil fuels, and tobacco smoke [8,9]. Once PAHs enter the body via inhalation, ingestion, or dermal absorption, they undergo a series of enzymatic transformations collectively termed biotransformation. This process both attempts to detoxify hydrophobic PAHs and, paradoxically, can produce reactive metabolites with greater toxicity than

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the parent compound. Biotransformation comprises two broad phases: Phase I bioactivation and Phase II detoxification, culminating in metabolites that may serve as biomarkers of exposure [4,6,64].

3.Metabolic Activation of PAHs

In Phase I, PAHs undergo oxidative metabolism primarily catalyzed by cytochrome P450 (CYP) enzymes in the liver and extra-hepatic tissues. CYP1A1, CYP1A2, and CYP1B1 isoforms are particularly important in PAH metabolism, where they introduce oxygen into the hydrophobic compounds to form epoxides, dihydrodiols, and quinones (Figure 4) [64]. These intermediate products can have increased reactivity with cellular macromolecules, including DNA and proteins, raising the risk of mutagenesis and carcinogenesis if not further processed. For example, the bioactivation of benzo[a]pyrene to benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE) is well documented as a critical step in PAH-induced carcinogenicity [84]. Such reactive intermediates are central to understanding both toxic effects and the development of biomarkers that reflect internal dose and metabolic activity.

3.Phase II Detoxification and Conjugation Pathways

Following Phase I activation, PAH metabolites are subject to Phase II conjugation reactions, which enhance water solubility and facilitate excretion. Glucuronidation, catalyzed by UDP-glucuronosyltransferases (UGTs), attaches glucuronic acid to hydroxylated PAH metabolites, yielding glucuronides that are readily eliminated in urine and bile. Sulfation, mediated by sulfotransferases (SULTs), similarly conjugates sulfate groups, further increasing solubility. In addition, glutathione S-transferases (GSTs) catalyze the formation of glutathione conjugates, particularly with electrophilic epoxides, thereby reducing their potential to bind to DNA [85,86]. These Phase II pathways not only represent detoxification mechanisms but also generate metabolites that serve as measurable indicators of exposure and metabolic processing Figure Variations in enzyme expression due to genetic polymorphisms or co-exposures can influence the balance between detoxification and formation of harmful intermediates, underscoring the complexity of PAH biotransformation in different populations [86].

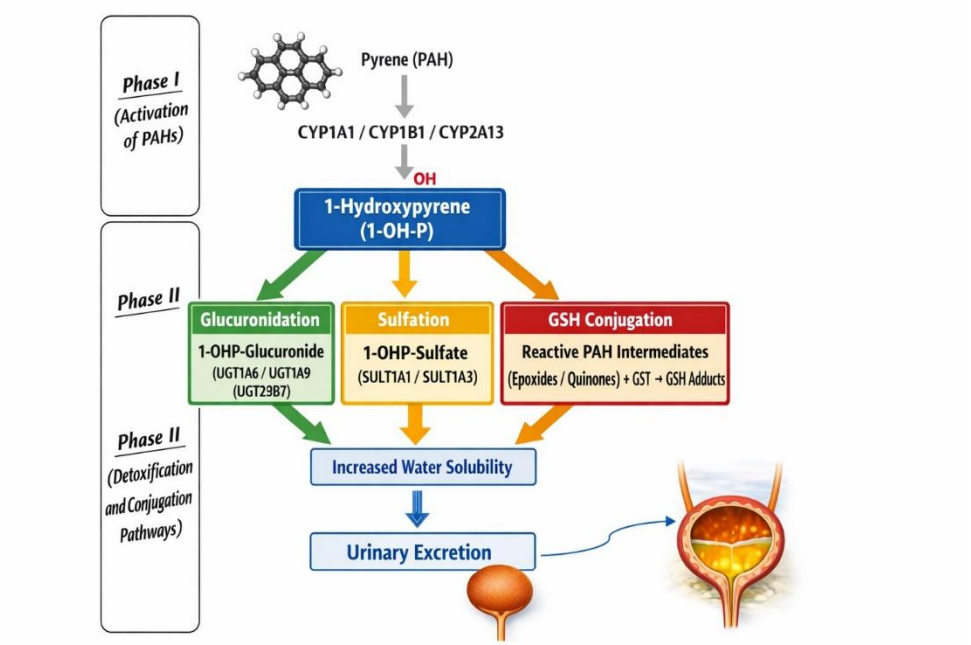

Figure Metabolic pathway of PAHs leading to the formation of Urinary 1-Hydoxypyrene Glucoronide [64,85–87].

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3.3. 1-Hydroxypyrene Glucuronide as a Biomarker of PAH Exposure

Among the array of PAH metabolites, 1-hydroxypyrene (1-OHP) and its glucuronide conjugate have emerged as robust biomarkers for assessing PAH exposure in occupational and environmental settings [27,88]. Pyrene is a four-ring PAH commonly present in combustion products, and its principal human metabolite, 1-OHP, is formed through CYP-mediated oxidation followed by Phase II glucuronidation [89]. Once conjugated with glucuronic acid, 1-hydroxypyrene glucuronide (1-OHPG) is excreted in urine and reflects recent exposure to PAHs, integrating multiple exposure routes over the preceding 24–48 hours. Because 1-OHPG levels correlate with external exposure metrics and internal dose, it has been widely used in biomonitoring studies of traffic-related air pollution, coke oven emissions, and charcoal workers [22,90]. Importantly, urinary creatinine adjustment is often applied to account for variations in urine concentration when interpreting 1-OHPG levels (Figure 5) [91].

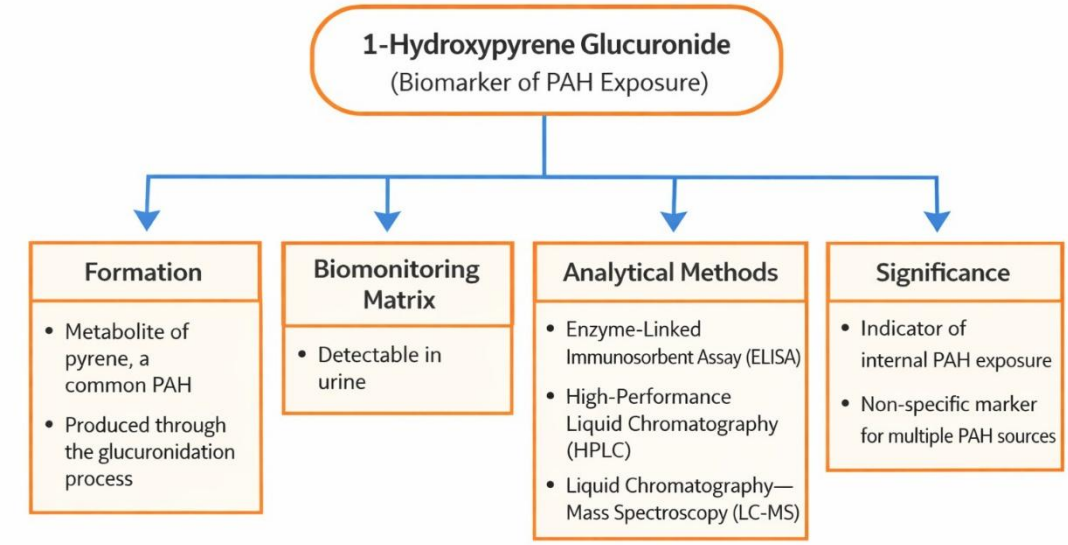

Figure 5. 1-Hydroxypyrene Glucuronide biomarker overview [92].

3.Analytical Detection and Biomonitoring Approaches

Accurate measurement of PAH metabolites like 1-OHPG depends on sensitive and specific analytical techniques. High-performance liquid chromatography (HPLC) with fluorescence detection has been a mainstay in biomonitoring because of its capacity to quantify low nanomolar concentrations of PAH metabolites in complex biological matrices [93]**.** Advances in liquid chromatography–mass spectrometry (LC-MS) have further enhanced analytical performance, offering improved selectivity, lower detection limits, and the ability to simultaneously quantify multiple metabolites, including glucuronides and sulfates, without the need for extensive sample clean-up. LC-MS methods also enable stable isotope dilution quantitation, reducing matrix effects and improving comparability across studies [94]. In addition, enzyme-linked immunosorbent assay (ELISA) techniques are widely employed as rapid, cost-effective immunochemical tools for screening PAH metabolites in urine and biological samples in large-scale exposure studies [27,95]. Together, these approaches provide powerful tools for biomonitoring exposure in epidemiological research and risk assessment, linking environmental sources of PAHs with internal doses and potential health outcomes (Table 2).

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Table Epidemiological studies assessing urinary 1-Hydroxypyrene Glucuronide in exposed populations.

Study (Author, Year)	*Population / Location*	*Exposure Source*	*Biomarker Measured*	*Analytical Method*	*Key Findings*
Anyakora et al. [96]	Petrol attendants & mechanics, Nigeria	Occupational PAHs	Urinary 1-OHPG / total pyro metabolites	HPLC-UV (1-OHP measurement includes 1-OHPG portion)	Indicated occupational PAH exposure in service workers.
Cho et al, [97]	Coke-oven workers, Korea	Workplace PAH exposures	Urinary 1-OHPG	Immunoaffinity + HPLC	Urinary 1-OHPG showed internal dose differences pre- and post-intervention.
Fagundes et al. [21]	Adults, Rio Grande do Sul, Brazil	Tobacco smoke, maté intake	Urinary 1-OHPG	Immunoaffinity chromatography followed by HPLC with fluorescence detection (HPLC-FLD)	Higher urinary 1-OHPG associated with smoking and maté drinking.
Hofmann et al. [98]	Women, Shanghai, China	PAH exposure sources	Urinary 1-OHPG	Immunoaffinity + fluorescence	Identified environmental/dietary determinants of 1-OHPG.
Hong [99]	Hospital workers, Korea	Smokers/non-smokers	Urinary 1-OHPG	Immunoaffinity + fluorescence	Smoking status modified 1-OHPG levels.
Adetunde, [100]	Smokers, Lagos, Nigeria	Tobacco smoke	Urinary 1-OHP / 1-OHPG	HPLC with UV detection (HPLC-UV))	Smokers & passive smokers had higher urinary 1-OHP supporting PAH exposure.
Kakimoto et al. [101]	Japan	Mixed environmental and occupational exposures	Urinary 1-OHPG	LC–MS/MS	Sensitive and direct quantification of 1-OHPG, improving specificity of exposure assessment in diverse populations.
Lai et al. [102]	Highway toll station workers	Traffic exhaust air pollution (PM2.5)	Urinary 1-OHPG	Immunoaffinity chromatography followed by HPLC-FLD	Significant elevation in urinary 1-OHPG associated with traffic exhaust exposure; correlated with lipid peroxidation and antioxidant biomarkers.
Lee et al., [103]	Incinerator workers, Korea	Occupational PAH	Urinary 1-OHPG	Synchronous fluorescence after immunoaffinity	GSTM1 genotype influenced urinary 1-OHPG.
Lee et al. [104]	Children, South Korea	Environmental smoke & diet	Urinary 1-OHPG	Immunoaffinity + fluorescence	ETS (parental smoking) and grilled food associated with higher 1-OHPG.
Lintelmann et al. [105]	Adults	Diet & ambient PAH	Urinary 1-OHPG	HPLC-fluorescence detection, LC/MS	Elevated 1-OHP with high-PAH exposures.
Kim & Hong., [106]	Elderly Koreans	Ambient and lifestyle PAH exposure	Urinary 1-OHP	-	Urinary 1-OHP levels associated with oxidative stress markers (MDA), supporting exposure-effect links in environmental studies.

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Olujimi et al., [107]	Charcoal workers, Nigeria	Occupational PAH	Urinary 1-OHP	HPLC (total including glucuronide)	Charcoal workers showed elevated urinary biomarkers.
Peters et al. [108]	Children, Baltimore, USA	ETS & outdoor air	Urinary 1-OHPG	Enzymatic hydrolysis + HPLC with fluorescence detection (HPLC-FLD)	Second-hand smoke linked to elevated 1-OHPG.
Raponi et al., [109]	Europe (adult population)	Environmental exposure (ambient air, diet)	Urinary 1-OHPG and other metabolites	HPLC-MS/MS	Sensitive measurement of 1-OHPG and other OH-PAHs in a mixed-exposure cohort, demonstrating utility of MS-based biomonitoring.
Sithisarankul et al., [110]	Mixed adult subjects (non-smokers and smokers)	Tobacco smoke and dietary grilled/broiled meats	Urinary 1-OHPG	Immunoaffinity chromatography + synchronous fluorescence spectroscopy	Significant positive associations between urinary 1-OHPG and number of cigarettes smoked and consumption of grilled/broiled meat; supports its use as a biomarker of inhalation and dietary PAH exposure.
Strickland & Kang [27]	Occupational groups (various)	Airborne PAH exposure	Urinary 1-OHPG	HPLC-fluorescence	1-OHPG shown as a sensitive biomarker of mixed PAH exposure.
Yoon et al, [111]	Korea	Traffic and urban exposures	Urinary 1-OHPG	HPLC / immunoaffinity fluorescence	Companion study validating 1-OHPG as indicator of combined ambient exposures across age groups; linked to oxidative stress biomarkers.

Oxidative Stress, DNA Damage, and the Biomarker 8-Hydroxy-2′-Deoxyguanosine

Oxidative stress is a pathological condition that arises when the generation of reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defenses, leading to damage to macromolecules such as lipids, proteins, and nucleic acids [112,113]. In the context of exposure to environmental toxicants, including polycyclic aromatic hydrocarbons (PAHs), oxidative stress is a central mechanistic pathway linking external pollutant exposure to cellular injury and disease susceptibility. One of the most prominent and widely measured manifestations of oxidative damage to DNA is the formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG), an oxidized derivative of guanine that serves as a biomarker for oxidative DNA lesions and, indirectly, for chronic exposure to environmental carcinogens (Figure 6) [32,33].

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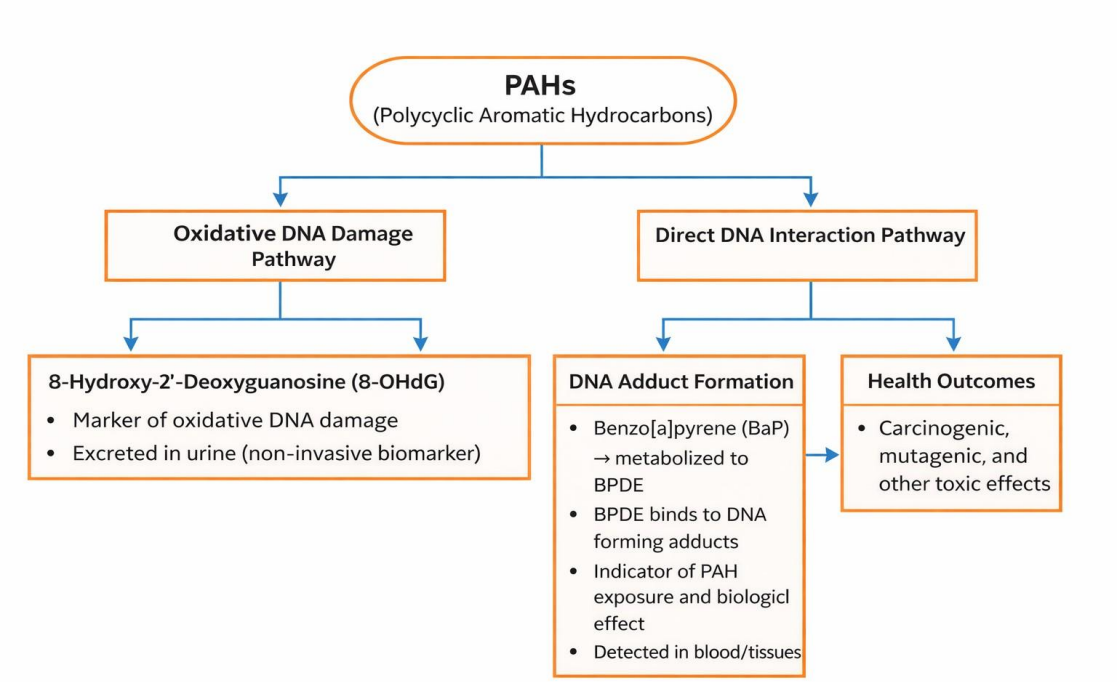

Figure PAHs biological pathways using 8-hydroxy-2′-deoxyguanosine (8-OHdG) as a biomarker and health outcomes [114].

4.Reactive Oxygen Species Generation During PAH Metabolism

Reactive oxygen species (ROS) are a group of highly reactive molecules that include free radicals such as superoxide (O_2^-), hydroxyl radical (•OH), and non-radical species such as hydrogen peroxide (H_2O_2) [115]. These species are normal by-products of cellular metabolism; however, during the metabolism of xenobiotics like polycyclic aromatic hydrocarbons (PAHs) the rate of ROS production increases significantly. When PAHs enter the body, they undergo enzymatic bioactivation primarily through the cytochrome P450 system in the liver and other tissues. During this process, intermediate metabolites of PAHs can undergo redox cycling, a process whereby electrons are transferred from reduced enzymatic intermediates to molecular oxygen, generating superoxide and other ROS [116]. These ROS are capable of damaging critical cellular components including lipids, proteins, and DNA. Mitochondria, as the central hub for energy production, also contribute to ROS generation during PAH exposure. Dysfunction of the mitochondrial electron transport chain caused by PAH interference leads to electron leakage and further ROS production. Excessive ROS overwhelm cellular antioxidant capacity and result in oxidative stress, a state characterized by an imbalance between pro-oxidants and antioxidant defenses [117]. This oxidative stress has been implicated as a central mechanistic link between PAH exposure and subsequent cellular damage that predisposes tissues to carcinogenesis. Evidence from experimental and epidemiological studies indicates that elevated ROS levels correlate with environmental exposures to PAHs and other carcinogenic agents, underscoring ROS's role in mediating PAH-induced toxicity [32,118,119].

ROS generated during PAH metabolism also act as intracellular signaling molecules [120]. Under normal conditions, ROS participate in physiological processes such as cell proliferation and immune responses. However, chronic exposure to elevated ROS levels triggers stress-activated signaling cascades, including the activation of transcription factors like NF-κB and AP-1, which regulate genes involved in inflammation and cell survival [121]. Persistent activation of these pathways can lead to chronic inflammation, genomic instability, and apoptosis evasion, all of which are hallmarks of carcinogenesis. The interplay between ROS generation and cellular signaling

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highlights how oxidative stress not only causes direct molecular damage but also disrupts normal regulatory networks, promoting maladaptive responses that contribute to disease progression.

4.Antioxidant Defense and Cellular Response

To protect against the harmful effects of ROS, cells possess intricate antioxidant defense systems that include enzymatic and non-enzymatic components. The Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a central regulator of the antioxidant response. Under basal conditions, Nrf2 is bound to its inhibitor Keap1 in the cytoplasm, where it undergoes ubiquitination and proteasomal degradation. Upon oxidative stress, specific cysteine residues on Keap1 are modified by ROS, leading to stabilization and release of NrfFree Nrf2 translocates into the nucleus where it binds to antioxidant response elements (AREs) in the promoter regions of target genes [122]. In the nucleus, Nrf2 induces the expression of a wide range of cytoprotective enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione S-transferase (GST), and other phase II detoxification enzymes that collectively restore redox homeostasis. These enzymatic systems work synergistically to eliminate ROS, detoxify reactive intermediates, and maintain redox equilibrium. Non-enzymatic antioxidants such as reduced glutathione (GSH), vitamins C and E, and thiol-containing molecules also contribute by directly scavenging free radicals and supporting enzymatic detoxification pathways. Collectively, the antioxidant network represents a dynamic defense system that mitigates oxidative damage and maintains cellular integrity. Disruption of this defense, either through overwhelming ROS production or impaired regulatory pathways, enhances susceptibility to oxidative DNA damage and disease pathogenesis. [122–124].

4.Formation and Biological Significance of 8-Hydroxy-2′-Deoxyguanosine

Among the variety of oxidative DNA lesions that can form in response to excessive ROS, 8-hydroxy-2′-deoxyguanosine (8-OHdG), also known as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), is one of the most extensively studied and widely accepted biomarkers of oxidative DNA damage [125]. Oxidation of the guanine base within DNA sequences occurs because guanine has the lowest redox potential among the DNA bases, making it particularly susceptible to attack by hydroxyl radicals and other ROS. When guanine is oxidized at the C8 position, it forms 8-OHdG, which can be excised from DNA during base excision repair and released into the nucleotide pool. Once in the nucleotide pool, 8-OHdG can be excreted in urine, providing a non-invasive measure of systemic oxidative DNA damage [29,126,127]. Elevated levels of 8-OHdG have been observed in various tissues and biological fluids following exposure to environmental carcinogens such as PAHs, tobacco smoke, heavy metals, and other pro-oxidant stimuli, making it a valuable indicator of oxidative stress burden [33]. In addition to reflecting cumulative oxidative DNA damage, increased 8-OHdG levels correlate with increased risk of cancer and degenerative diseases in exposed populations, supporting its relevance in risk assessment and disease monitoring [32].

The presence of 8-OHdG in DNA is not merely a marker of damage but has mutagenic consequences. During DNA replication, 8-OHdG can base-pair incorrectly with adenine instead of cytosine, leading to G→T transversion mutations. These point mutations, if not properly repaired, accumulate in critical genomic regions and contribute to genomic instability, a defining feature of carcinogenesis [29]. The accumulation of such mutations in oncogenes or tumor suppressor genes can drive uncontrolled cell proliferation, resistance to apoptosis, and other transformative changes characteristic of cancer cells. Consequently, 8-OHdG serves both as a biomarker of oxidative insults and as a mechanistic link between oxidative stress and mutagenesis. [123].

4.Analytical Measurement and Interpretation

Accurate quantification of 8-OHdG is paramount for interpreting oxidative DNA damage in both clinical and environmental studies. Analytical methods for measuring 8-OHdG have evolved significantly, driven by the need for specificity, sensitivity, and throughput. Traditionally,

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chromatographic techniques such as high-performance liquid chromatography (HPLC) coupled with electrochemical detection (ECD) or tandem mass spectrometry (LC–MS/MS) have been considered the gold standard for quantification due to their high specificity and ability to distinguish 8-OHdG from structurally similar compounds. These methods allow precise quantification of 8-OHdG in urine, blood, tissue extracts, and cellular DNA, making them powerful tools for both research and biomonitoring [33]. HPLC–MS/MS methodologies have gained favor as they combine chromatographic separation with mass-based detection, enhancing discrimination against potential confounders and improving quantitative accuracy. Recently, integrated methods that simultaneously quantify 8-OHdG and PAH metabolites in urine have been developed to streamline exposure and effect assessment in epidemiological studies [114,123].

Aside from chromatographic approaches, immunological assays such as enzyme-linked immunosorbent assay (ELISA) are widely used due to their relative simplicity and suitability for large-scale population studies. ELISA methods employ specific antibodies to detect 8-OHdG in biological samples. While ELISA offers higher throughput and lower cost, it may have limitations in specificity and potential cross-reactivity compared with chromatographic methods, which can affect absolute quantification [33]. Corrections for urine dilution, such as normalization to creatinine concentration, are routinely applied when interpreting urinary 8-OHdG levels to account for variations in sample concentration. Overall, interpreting 8-OHdG data requires careful consideration of the analytical method, biological matrix, and population characteristics, but this biomarker remains an indispensable tool for linking oxidative DNA damage with environmental exposures such as PAHs and disease risk (Table 3) [32].

Table Studies reporting elevated 8-Hydroxy-2′-Deoxyguanosine in populations exposed to PAHs.

Study (Author, Year)	*Population / Location*	*Exposure Source*	*Biomarker Measured*	*Analytical Method*	*Key Findings*
Cao et al. [128]	Large general population	Ambient PAHs	8-OHdG	LC-MS/MS ELISA	Urinary 8-OHdG positively associated with high-MW PAH metabolites.
Chien & Yeh, [129]	Adult volunteers	Barbecued meat (dietary PAHs)	Urinary 8-OHdG	HPLC-ECD	Significant increase in urinary 8-OHdG correlating with PAH metabolites after intake.
Marczynski et al. [130]	Workers in coke-oven / graphite plant	Occupational PAH exposure	8-oxodGuo (in WBC)	HPLC-ECD	Exposed workers showed 1.38–2.15× higher 8-oxodGuo vs control, indicating PAH-linked DNA oxidative damage.
Nguyen et al. [131]	Coke-oven workers, Korea	Workplace PAH exposures	Urinary 8-OHdG & 1-OHPG	Immunoaffinity + HPLC	Urinary 1-OHdG showed internal dose differences pre / post-intervention as a sensitive PAH biomarker.
Ren et al. [132]	Older adults	Urban air pollution with PAHs	Urinary 8-OHdG	ELISA	Ambient PM and organic carbon associated with increased 8-OHdG.
Ryu & Hong [118]	Workers with mixed PAH exposures	Occupational/Environmental PAHs	Urinary 8-OHdG	LC-MS/MS ELISA	1-Hydroxypyrene significantly correlated with 8-OHdG in multiple exposed groups.

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Souza et al. [133]	Lactating women & infants, Brazil	Environmental PAHs + metals	Urinary 8-OHdG	LC-MS/MS ELISA	PAH metabolites linked to increased urinary 8-OHdG by ML analysis.
Sun et al. [134]	Adults, China	Ambient/background PAHs	Urinary 8-OHdG	GC-MS + HPLC-ECD	Dose-dependent relationship between urinary OH-PAHs and 8-OHdG.
Xiao et al. [135]	Workers & residents, South China	Occupational incineration PAHs	Urinary 8-OHdG	LC-MS/MS ELISA	Higher PAH exposure and 8-OHdG in incineration workers vs controls.
Zhang et al. [136]	Residents, Guangzhou, China	Indoor PAHs in dust	Urinary 8-OHdG	LC-MS/MS ELISA	Positive association between PAH metabolites and 8-OHdG

Integrative Biomarker Framework Linking PAH Exposure to Carcinogenesis

The growing complexity of environmental carcinogenesis necessitates the development of integrative frameworks that can effectively link external exposure to internal biological responses and ultimately to disease outcomes. In this context, the combined application of exposure and effect biomarkers has emerged as a powerful approach in molecular epidemiology. Polycyclic aromatic hydrocarbons (PAHs), as ubiquitous environmental pollutants, exert their carcinogenic effects through a sequence of biological events that begin with exposure, proceed through metabolic activation and oxidative stress, and culminate in DNA damage and mutagenesis. The integration of biomarkers such as 1-hydroxypyrene glucuronide (1-OHPG) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) provides a mechanistic continuum that bridges these stages, offering a comprehensive tool for assessing environmental cancer risk [22,37] **(Figure 7)**.

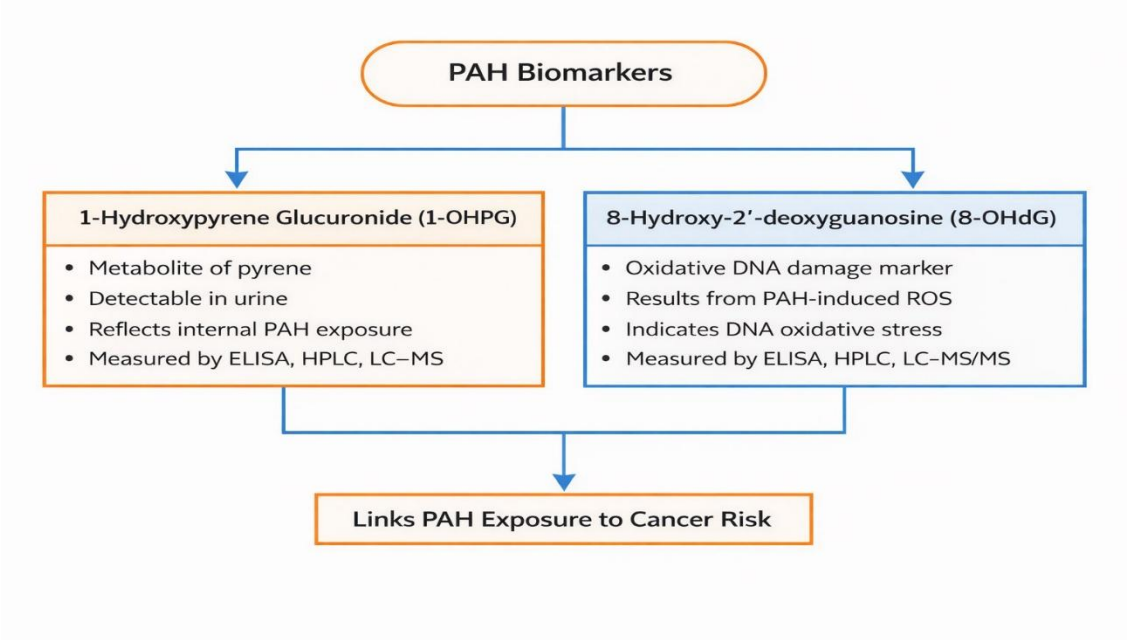

Figure Integrative framework of PAH biomarkers (1-OHPG and 8-OHdG) linking environmental PAH exposure to oxidative DNA damage and cancer risk [137].

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5.Complementary Roles of Exposure and Effect Biomarkers

Biomarkers can be broadly categorized into exposure biomarkers, which reflect the internal dose of a toxicant, and effect biomarkers, which indicate early biological responses to that exposure. The integration of these biomarker classes is essential for establishing causal relationships between environmental pollutants and disease outcomes [138].

1-Hydroxypyrene glucuronide (1-OHPG) is widely recognized as a robust biomarker of internal exposure to PAHs. As a Phase II conjugated metabolite of pyrene, 1-OHPG reflects the extent to which PAHs have been absorbed, metabolized, and processed within the body. Because pyrene is commonly present in PAH mixtures, urinary 1-OHPG serves as a reliable surrogate for total PAH exposure across multiple routes, including inhalation, ingestion, and dermal absorption. Numerous biomonitoring studies have demonstrated that urinary 1-OHPG levels correlate strongly with environmental and occupational exposure scenarios, including traffic-related air pollution, industrial emissions, and tobacco smoke [22,26]. Importantly, 1-OHPG integrates exposure over a short biological window typically between 24 to 48 hours, making it particularly useful for assessing recent exposure.

In contrast, 8-hydroxy-2′-deoxyguanosine (8-OHdG) represents a biomarker of biological effect, specifically oxidative DNA damage induced by reactive oxygen species (ROS). The formation of 8-OHdG occurs when ROS generated during PAH metabolism attack guanine bases in DNA, leading to oxidative lesions that can result in mutagenic base mispairing. Elevated levels of 8-OHdG in urine, blood, or tissue reflect increased oxidative stress and DNA damage, which are key events in the initiation of carcinogenesis [32]. Unlike 1-OHPG, which reflects exposure, 8-OHdG provides insight into the downstream biological consequences of that exposure.

The complementary use of 1-OHPG and 8-OHdG enables a more comprehensive assessment of the exposure–effect relationship. While 1-OHPG quantifies the internal burden of PAHs, 8-OHdG captures the resulting oxidative DNA damage, thereby linking external environmental exposure to molecular events that may lead to cancer. This integrative biomarker approach aligns with modern paradigms in environmental health, which emphasize the need to connect exposure metrics with biological endpoints to strengthen causal inference [19].

5.Evidence from Combined Biomarker Studies

A growing body of epidemiological studies has explored the simultaneous measurement of 1-OHPG and 8-OHdG to better understand the relationship between PAH exposure and oxidative DNA damage. These studies provide empirical support for the mechanistic link between exposure and biological effect, demonstrating that increased internal PAHs burden is often associated with elevated levels of oxidative DNA lesions.

Several occupational and environmental studies have reported positive correlations between urinary 1-OHPG and 8-OHdG levels. For instance, workers exposed to high levels of PAHs, such as coke oven workers, asphalt workers, and traffic police officers, often exhibit significantly elevated concentrations of both biomarkers compared to control populations (Table 4) [6,22,139,140]. These findings suggest that increased PAH exposure leads to enhanced ROS generation and subsequent oxidative DNA damage. Similarly, studies conducted in urban populations have demonstrated that individuals living in areas with high air pollution levels show concurrent increases in urinary 1-OHPG and 8-OHdG, further supporting the link between environmental exposure and oxidative stress [26].

The correlation between these biomarkers has important implications for environmental risk assessment. By combining exposure and effect biomarkers, researchers can better characterize the dose–response relationship and identify thresholds at which PAH exposure begins to exert harmful biological effects. This approach enhances the sensitivity and specificity of biomonitoring, allowing for more accurate identification of at-risk populations. Furthermore, the integration of 1-OHPG and 8-OHdG facilitates the evaluation of intervention strategies aimed at reducing exposure or mitigating oxidative damage, thereby contributing to public health protection (Table 4).

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Table Studies Simultaneously Evaluating Urinary 1-Hydroxypyrene Glucuronide and 8-Hydroxy-2′-Deoxyguanosine.

Study Population	Exposure Source	Key Findings	Authors and publication year
Coke oven workers	Industrial PAHs	Elevated 1-OHPG and 8-OHdG; positive correlation	Jongeneelen [22]; Li et al. [140]
Traffic police	Vehicular emissions	Increased levels of OH-pyrene and 8-OHdG in exposed and control group	Kamal et al. [139]; Li et al. [26]
Urban residents	Air pollution	Higher biomarker levels of 1-OHPyr and 8-OHdG	Wang et al. [137]; Kim et al. [6]
Smokers vs non-smokers	Tobacco smoke	Significantly higher 1-OHPG, Oxidative stress marker and 8-OHdG in smokers	Hecht, [46]; Leem et al. [141]

5.PAH Exposure, Biomarkers, and Cancer Risk

The integration of exposure and effect biomarkers provides a critical link between environmental PAH exposure and cancer risk. Epidemiological evidence has consistently demonstrated associations between PAH exposure and increased incidence of various cancers, including lung, skin, bladder, and breast cancers. These associations are supported by both occupational studies and general population analyses, highlighting the widespread impact of PAHs on human health [3,9].

Biomarkers such as 1-OHPG and 8-OHdG play a crucial role in elucidating the mechanistic pathways underlying these associations. Elevated levels of 1-OHPG indicate increased internal exposure to PAHs, while elevated 8-OHdG levels reflect oxidative DNA damage, a key step in carcinogenesis (Table 5). The presence of oxidative DNA lesions such as 8-OHdG is particularly significant because they can lead to G→T transversion mutations, which are commonly observed in oncogenes and tumor suppressor genes in various cancers [32]. Moreover, studies have shown that individuals with persistently high levels of oxidative DNA damage biomarkers are at greater risk of developing cancer, suggesting that 8-OHdG serve as a predictive marker for disease progression [32]. The combined assessment of 1-OHPG and 8-OHdG therefore provides a more comprehensive understanding of cancer risk, capturing both exposure and early molecular effects.

Table Cancer Types Associated with PAH Exposure and Biomarker Elevation.

Cancer Type	Associated PAH Exposure	Biomarker Evidence	Authors and publication year
Lung cancer	Air pollution, smoking	Elevated 1-OHPG & 8-OHdG	IARC [9]; Hecht [46]
Skin cancer	Occupational exposure	Increase 1-OHPG & 8-OHdG	Boström et al. [4]; Burke [142]; Lee et al. [143]
Bladder cancer	Industrial PAHs	Oxidative DNA damage observed	Loomis et al., [3]; Boström et al. [4]
Breast cancer	Environmental PAHs	Elevated 1-OHPG & 8-OHdG	Lee et al. [11]; Valavanidis et al. [32]

5.Limitations, Knowledge Gaps, and Future Directions

Despite the significant advances in biomarker research, several limitations and knowledge gaps remain in the application of integrated biomarker frameworks. One major challenge is inter-individual variability in PAH metabolism, which can significantly influence biomarker levels. Genetic polymorphisms in enzymes such as cytochrome P450s, glutathione S-transferases, and UDP-

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glucuronosyltransferases can alter the rate of PAH biotransformation, leading to differences in both 1-OHPG formation and ROS generation among individuals [85]. This variability complicates the interpretation of biomarker data and may obscure true exposure effect relationships. Another limitation is the presence of confounding environmental exposures. Individuals are often exposed to multiple pollutants simultaneously, including heavy metals, volatile organic compounds, and particulate matter, all of which can contribute to oxidative stress and DNA damage. As a result, elevated 8-OHdG levels may not be exclusively attributable to PAH exposure, reducing the specificity of this biomarker in complex environmental settings.

Furthermore, most studies rely on cross-sectional designs, which limit the ability to establish causal relationships between exposure, biomarker changes, and disease outcomes. Longitudinal studies are needed to better understand temporal relationships and to evaluate the predictive value of these biomarkers in cancer development. Future research should focus on the integration of biomarker data with advanced "omics" technologies, including genomics, transcriptomics, proteomics, and metabolomics. Such multi-omics approaches can provide a more comprehensive understanding of the molecular mechanisms underlying PAH-induced carcinogenesis and may identify novel biomarkers with improved sensitivity and specificity. Additionally, the development of standardized protocols for biomarker measurement and interpretation will enhance comparability across studies and facilitate the translation of research findings into public health practice [37].

Conclusions

Polycyclic aromatic hydrocarbons (PAHs) represent a significant class of environmental carcinogens whose adverse health effects are mediated through well-defined molecular mechanisms. Following exposure via inhalation, ingestion, or dermal contact, PAHs undergo metabolic activation that generates reactive intermediates and reactive oxygen species (ROS), leading to oxidative stress and DNA damage. The formation of oxidative DNA lesions, particularly 8-hydroxy-2′-deoxyguanosine (8-OHdG), plays a critical role in mutagenesis and genomic instability, thereby contributing to the initiation and progression of cancer. This mechanistic pathway highlights the continuum linking environmental exposure to molecular injury and ultimately carcinogenesis.

The simultaneous integration of 1-hydroxypyrene glucuronide (1-OHPG) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) provides a powerful biomonitoring framework that captures both internal exposure and early biological effects. While 1-OHPG reflects the internal burden of PAHs following metabolic processing, 8-OHdG serves as an indicator of oxidative DNA damage resulting from such exposure. The combined use of these complementary biomarkers enhances the ability to establish exposure–effect relationships, improves the accuracy of risk assessment, and strengthens causal inference in environmental health studies (Figure 8).

Overall, this integrative biomarker approach has important implications for environmental health surveillance and cancer risk prediction. By enabling early detection of both exposure and molecular damage, it offers valuable opportunities for identifying at-risk populations, guiding preventive interventions, and informing regulatory policies. Future advancements incorporating multi-omics technologies and longitudinal study designs will further refine this framework and enhance its applicability in precision environmental health and cancer epidemiology.

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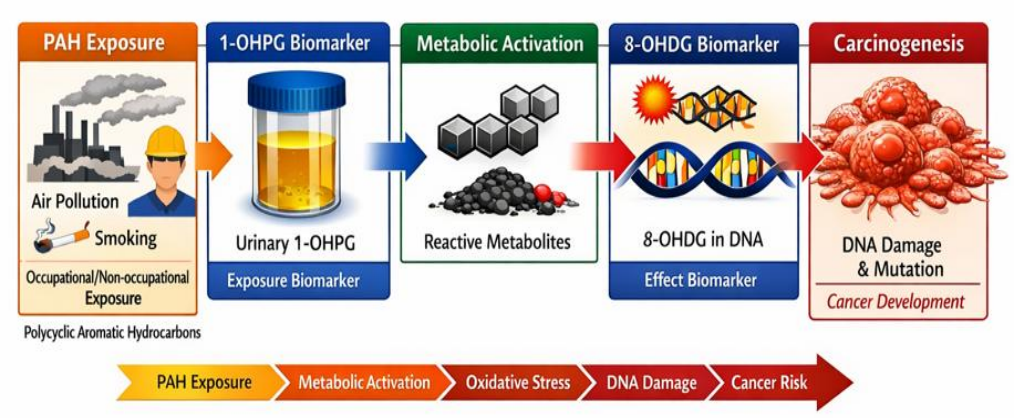

Figure Integrated mechanistic pathway linking PAH exposure, biomarker formation, oxidative DNA damage, and carcinogenesis [32,144].

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