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REVIEW ARTICLE

1-Hydroxypyrene glucuronide and 8-hydroxy-2′-deoxyguanosine as complementary biomarkers bridging polycyclic aromatic hydrocarbon exposure to carcinogenic risk: Mechanistic and epidemiological perspectives

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Abstract

Background: Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental carcinogens that contribute to cancer development through oxidative stress, DNA damage, and genomic instability. However, current biomonitoring approaches often assess exposure and biological effects independently, limiting risk assessment and mechanistic interpretation. **Aim:** This review evaluates the complementary roles of urinary 1-hydroxypyrene glucuronide (1-OHPG) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) as integrated biomarkers linking PAH exposure with early carcinogenic events. **Methods:** A narrative review of published literature was conducted, focusing on PAH metabolism, the biological significance of 1-OHPG and 8-OHdG, epidemiological evidence assessing both biomarkers, sources of heterogeneity, methodological limitations, and future directions for precision environmental carcinogenesis. **Results:** Urinary 1-OHPG is a validated biomarker of internal PAH exposure, whereas urinary 8-OHdG reflects oxidative DNA damage induced by reactive oxygen species generated during PAH metabolism. Epidemiological studies generally demonstrate positive associations between elevated 1-OHPG and 8-OHdG in occupationally and environmentally exposed populations. Nevertheless, biological variability, mixed exposures, analytical differences, and predominantly cross-sectional study designs contribute to heterogeneity. Integrating these biomarkers provides a more comprehensive exposure–effect framework for interpreting PAH-induced carcinogenic processes. **Conclusion:** The combined assessment of urinary 1-OHPG and 8-OHdG strengthens biomonitoring by simultaneously evaluating internal PAH exposure and early molecular damage. This integrated framework has the potential to improve environmental cancer risk assessment and support precision environmental health. **Relevance for patients:** Integrated biomonitoring of urinary 1-OHPG and 8-OHdG may facilitate earlier identification of individuals at increased risk from chronic PAH exposure, enabling targeted prevention, improved surveillance, and informed public health interventions.

Keywords: Polycyclic aromatic hydrocarbons; 1-hydroxypyrene glucuronide; 8-hydroxy-2′-deoxyguanosine; Biomarker integration; Oxidative DNA damage; Cancer risk

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with a substantial proportion of cases attributable to environmental and occupational exposures.[1] According to the World Health Organization[2], cancer accounted for nearly 10 million deaths globally in recent years, underscoring its enormous public health burden. Increasing epidemiological evidence indicates that environmental carcinogens constitute a diverse group of chemical (such as chemical contaminants in air, water, and food), physical, and biological agents capable of initiating or promoting malignant transformation through sustained interactions with cellular and molecular pathways.[3,4] These carcinogens include heavy metals (such as arsenic and cadmium), asbestos, crystalline silica, ultraviolet and ionizing radiation, persistent organic pollutants, endocrine-disrupting chemicals, pesticides, volatile organic compounds, per- and polyfluoroalkyl substances, diesel exhaust, tobacco smoke, aflatoxins, certain oncogenic viruses, and polycyclic aromatic hydrocarbons (PAHs).[2,5–7] Human exposure to these agents has increased substantially as a result of rapid industrialization, urbanization, fossil fuel combustion, occupational activities, and modern agricultural practices, making environmental pollution a major contributor to the global cancer burden.[8] Approximately 19%–20% of cancers worldwide have been attributed to environmental and occupational risk factors, many of which are preventable through effective exposure reduction and public health interventions.[2,9] Because these exposures are often chronic, occur at low doses, and involve complex mixtures rather than individual chemicals, identifying reliable biomarkers capable of linking internal exposure with early biological responses has become a major priority in environmental cancer research and precision environmental health.[8,10]

Among these environmental carcinogens, PAHs have attracted considerable scientific attention due to their widespread distribution and well-established toxicological properties.[4] PAHs constitute a large class of organic compounds formed primarily through the incomplete combustion of organic materials such as fossil fuels, biomass, tobacco, and industrial emissions.[11,12] 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.[13] Human exposure to PAHs occurs predominantly through inhalation of polluted air, ingestion of contaminated food or water, and dermal contact with contaminated materials.[14]

Several PAHs are well-established as potent carcinogens, mutagens, and teratogens.[15] Among them, benzo[a]pyrene 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.[7,11] 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.[4,16,17] 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.[18] This metabolic process is often mediated through signaling pathways such as the aryl hydrocarbon receptor (AhR) signaling pathway, which induces cytochrome P450 (CYP) enzymes that metabolize PAHs to reactive intermediates.[19,20] These metabolites can generate reactive oxygen species (ROS), resulting in oxidative stress, DNA damage, and mutagenesis, all of which are key events in the multistep process of carcinogenesis.[21,22]

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.[23] 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.[24,25] 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.[26]

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.[27–29] 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.[27,30–33] The measurement of 1-OHPG therefore provides valuable insight into the internal dose

or concentration of PAHs that have 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.[25,29] 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 ROS generated during cellular metabolism or toxicant exposure attack DNA molecules, leading to oxidative damage.[34] 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.[35–38] 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.[39–41]

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 environmental health studies.[42] 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 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.[43]

The integration of 1-OHPG and 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

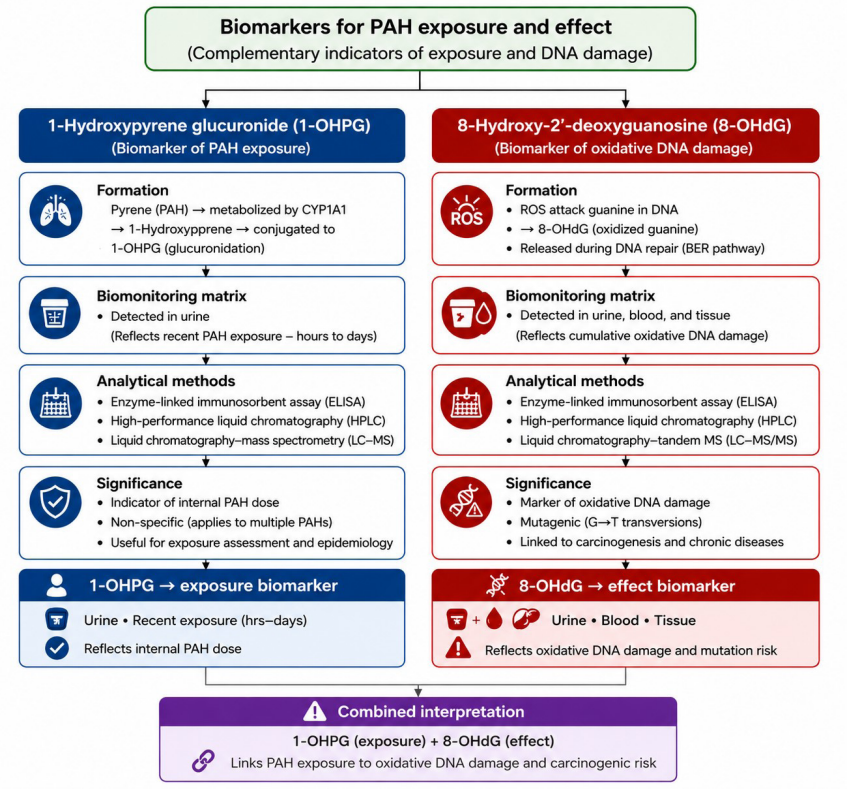


Figure 1. Association between polycyclic aromatic hydrocarbon (PAH) biomarkers and cancer risk. Created by the author based on information from Refs.[39,44]

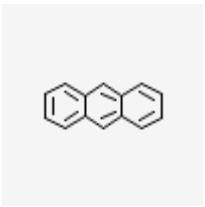
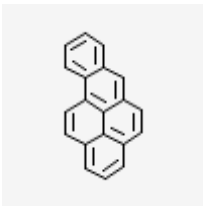
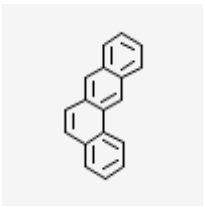
as 8-OHdG, the combined assessment of exposure and effect biomarkers provides a clearer understanding of the mechanistic pathway leading to carcinogenic outcomes. This review therefore synthesizes current evidence on PAH sources, exposure pathways, metabolic processes, and oxidative damage, emphasizing 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.

2. Environmental sources, human exposure pathways, and toxicological significance of polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons 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.[45] 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.[46] Consequently, humans are continuously exposed to PAHs through multiple environmental pathways, raising significant concerns regarding their potential health effects, including carcinogenesis (Figure 2; Table 1).[7,13]

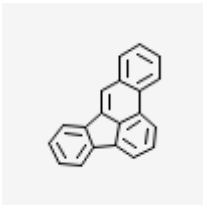
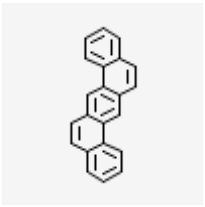
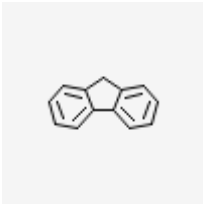
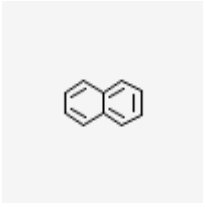
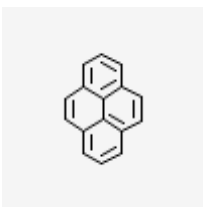
Pyrene is metabolized primarily to 1-hydroxypyrene (1-OHP), which subsequently undergoes glucuronidation by hepatic UDP-glucuronosyltransferases (UGTs) to form 1-OHPG, the predominant urinary metabolite in humans.

Table 1. Major environmental sources, exposure pathways, and IARC carcinogenicity classifications of selected PAHs

PAH	Chemical structure	Major environmental source	Main exposure pathways	IARC carcinogenicity classification	Reference
Anthracene		Coal tar, wood combustion, industrial processes	Dermal, inhalation	IARC Group 2B	47
Benzo[a]pyrene		Vehicle exhaust, tobacco smoke, grilled food	Inhalation, diet	IARC Group 1	48
Benz[a]anthracene		Fossil-fuel combination	Inhalation	IARC Group 2B	49

(*Cont'd...*)

Table 1. (*Continued*)

PAH	Chemical structure; reference	Major environmental source	Main exposure pathways	IARC carcinogenicity classification	Reference
Chrysene		Industrial emissions, smoking	Inhalation, dermal	IARC Group 2B	50
Benzo[b] fluoranthene		Diesel exhaust	Inhalation	IARC Group 2B	51
Dibenz[a,h] anthracene		Coal tar, petroleum products	Dermal, inhalation	IARC Group 2A	52
Fluorene		Fossil fuel combustion, oil spills	Inhalation, dermal	IARC Group 3	53
Naphthalene		Mothballs, tobacco smoke, fuel combustion	Inhalation	Group 2B	54
Pyrene		Biomass burning, vehicle exhaust	Inhalation, dermal	Group 3	55

Notes: Compiled by the author based on information from IARC[7] and Montano *et al.*[45] Chemical structures were obtained from PubChem.
Abbreviations: IARC: International Agency for Research on Cancer; PAH: Polycyclic aromatic hydrocarbon.

Consequently, both urinary 1-OHP and 1-OHPG are established biomarkers of internal PAH exposure; however, they represent different analytical endpoints. Some studies quantify total urinary 1-OHP following enzymatic hydrolysis of conjugated metabolites, whereas others directly measure urinary 1-OHPG. Direct quantification of 1-OHPG offers several analytical advantages, including greater chemical stability, higher fluorescence intensity, and reduced variability associated with enzymatic hydrolysis. Accordingly, the present review adopts urinary 1-OHPG as the principal biomarker of PAH exposure. Nevertheless, studies reporting urinary 1-OHP or total urinary hydroxylated PAH (OH-PAH) metabolites are discussed using their original terminology to accurately reflect the analytical methodologies employed.[13,28,33,56]

2.1. Environmental and anthropogenic sources of polycyclic aromatic hydrocarbons

2.1.1. 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.[57] 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.[7,57]

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.[15]

2.1.2. 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.[58,59] 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.[31]

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.[60]

2.1.3. 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.[61–63]

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.[64] 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.[61] 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.[62]

2.1.4. Dietary sources (charred and smoked foods)

Dietary intake represents a major route of 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.[65,66] 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.[7]

2.2. 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.

2.2.1. 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.[67] 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.[68]

2.2.2. Dietary ingestion

Dietary ingestion represents one of the most significant exposure routes for PAHs in the general population.[65] 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.[69] 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.[70,71]

2.2.3. 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.[72,73] Environmental exposure can also occur through contact with contaminated sediments, soils, or industrial products containing PAHs.[74,75]

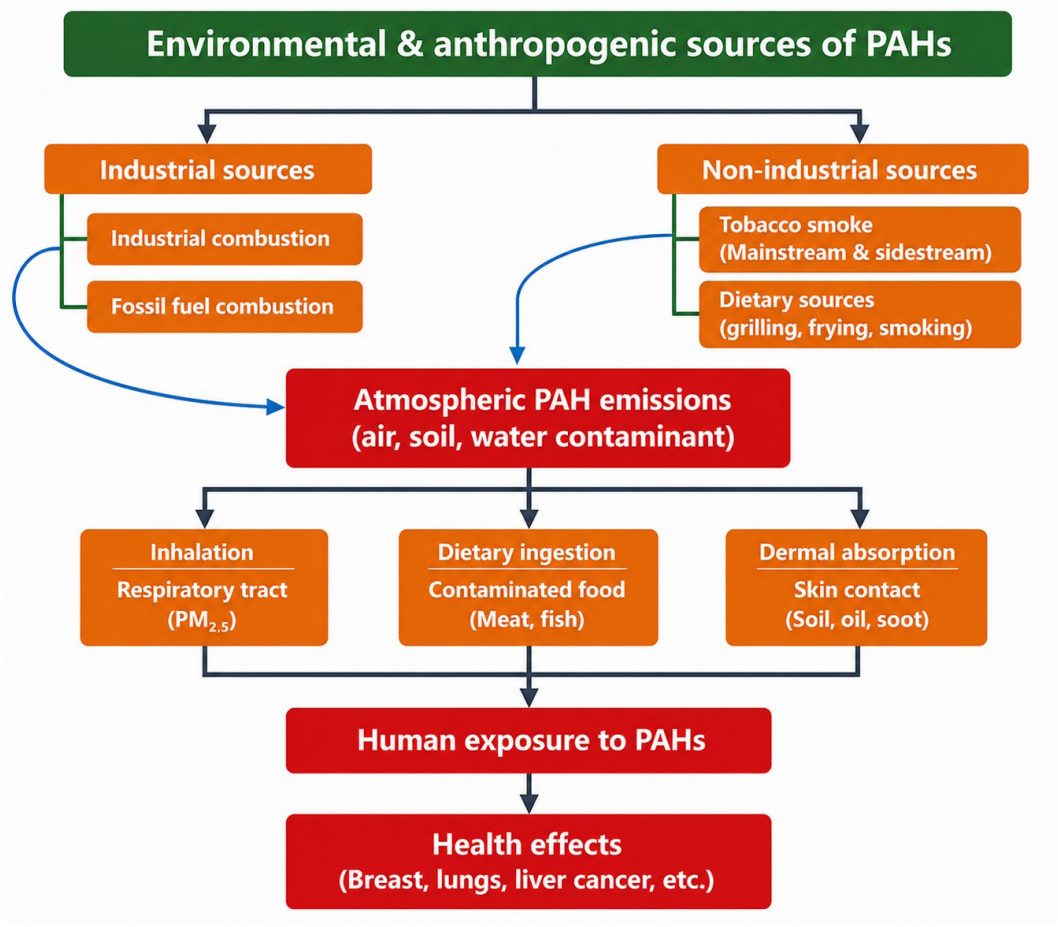


Figure 2. Pathways of environmental and anthropogenic polycyclic aromatic hydrocarbon (PAH) exposure and health effects. Figure created by the author based on information from Refs.[45,76,77]

2.3. 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.

2.3.1. Metabolic activation of polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons 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 CYP enzymes such as CYP1A1 and CYP1B1.[68,78,79] 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.[18,80]

2.3.2. Evidence linking polycyclic aromatic hydrocarbon 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).[68,81–85] 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.[7] Animal experiments further support these findings, showing that chronic exposure to PAHs can induce tumors in multiple organs, including the liver, lung, and skin.[86]

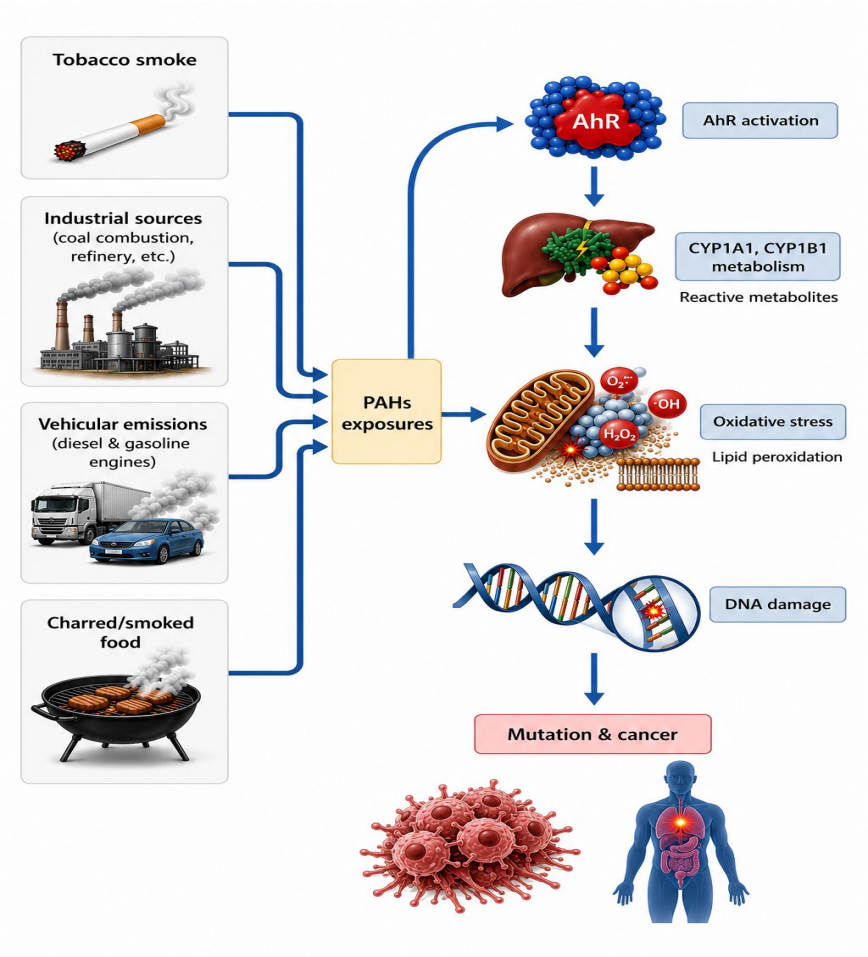


Figure 3. Environmental sources of PAHs and major human exposure pathways. Figure created by the author based on information from Ref.[45]

2.3.3. Role of the aryl hydrocarbon receptor signaling pathway in polycyclic aromatic hydrocarbon toxicity

The biological effects of PAHs are strongly influenced by activation of the AhR signaling pathway. The AhR is a ligand-activated transcription factor that regulates the expression of genes involved in xenobiotic metabolism.[87] Thus, AhR 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 CYP1B1. These enzymes metabolize PAHs into reactive intermediates capable of generating oxidative stress and DNA damage.[88–90]

3. Biotransformation of polycyclic aromatic hydrocarbons and the emergence of exposure biomarkers

Polycyclic aromatic hydrocarbons are environmentally pervasive organic contaminants formed by incomplete combustion of organic matter, fossil fuels, and tobacco smoke.[7,15] Once PAHs enter the body via inhalation, ingestion, or dermal absorption, they undergo a series of enzymatic transformations collectively termed biotransformation. Biotransformation can detoxify hydrophobic PAHs but can also generate metabolites that are more reactive than the parent compounds. Biotransformation comprises two broad phases—phase I bioactivation and phase II detoxification—culminating in metabolites that may serve as biomarkers of exposure.[11,13,80]

3.1. Metabolic activation of polycyclic aromatic hydrocarbons

In phase I, PAHs undergo oxidative metabolism primarily catalyzed by CYP enzymes in the liver and extrahepatic 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).[80] These intermediate products can be more reactive toward 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 is well documented as a critical step in PAH-induced carcinogenicity.[91] Such reactive intermediates are central to understanding both toxic effects and the development of biomarkers that reflect internal dose and metabolic activity.

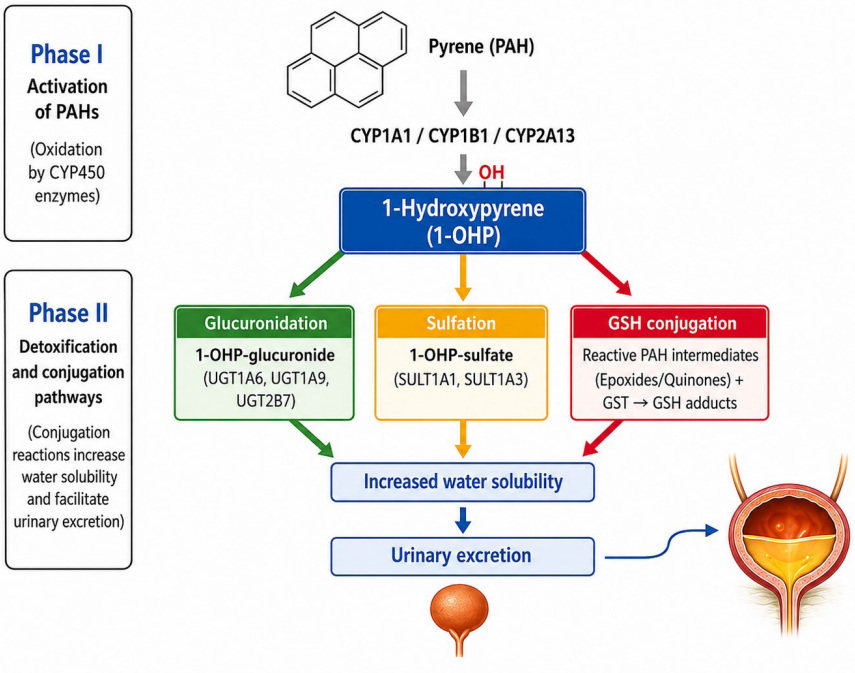


Figure 4. Metabolic pathway of PAHs leading to the formation of urinary 1-hydoxypyrene glucuronide. Figure created by the author based on information from Refs.[80,92–94]

Abbreviations: GSH: Glutathione; GST: Glutathione S-transferase; PAH: Polycyclic aromatic hydrocarbon.

3.2. 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 UGTs, attaches glucuronic acid to OH-PAH metabolites, yielding glucuronides that are readily eliminated in urine and bile. Sulfation, mediated by sulfotransferases, 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.[92,93] These phase II pathways not only represent detoxification mechanisms but also generate metabolites that serve as measurable indicators of exposure and metabolic processing (Figure 4). 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.[93]

3.3. 1 Hydroxypyrene glucuronide as a biomarker of polycyclic aromatic hydrocarbon exposure

Among the array of PAH metabolites, 1-OHP and its glucuronide conjugate have emerged as robust biomarkers for assessing PAH exposure in occupational and environmental settings.[33,95] 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.[96] Once conjugated with glucuronic acid, 1OHPG is excreted in urine and reflects recent exposure to PAHs, integrating multiple exposure routes over the preceding 24–48 h. 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.[28,97] Importantly, urinary creatinine adjustment is often applied to account for variations in urine concentration when interpreting 1-OHPG levels (Figure 5).[98]

3.4. Analytical detection and biomonitoring approaches

Accurate measurement of PAH metabolites such as 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

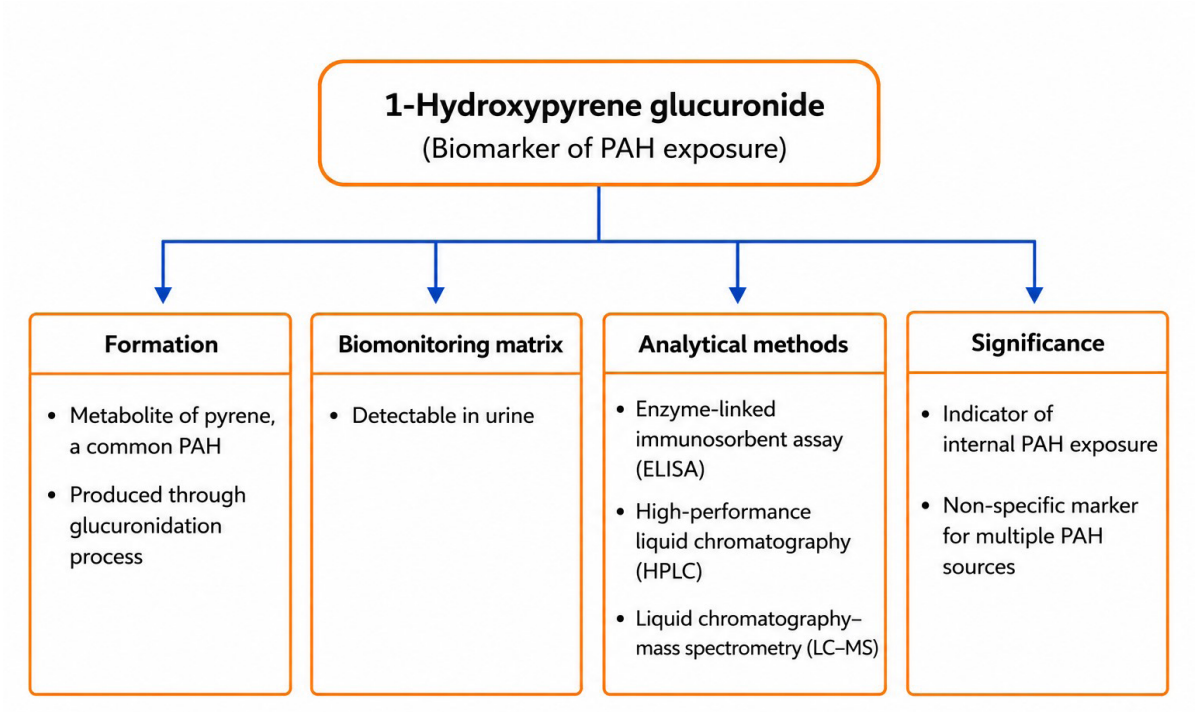


Figure 5. Overview of 1-hydroxypyrene glucuronide as a biomarker of PAH exposure. Figure created by the author based on information from Ref.[99]
Abbreviation: PAH: Polycyclic aromatic hydrocarbon.

biological matrices.[100] 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.[101] 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.[33,102] 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).

Table 2. Epidemiological studies assessing urinary 1-OHPG in exposed populations

Study	Population/ location	Exposure source	Biomarker measured	Analytical method	Key findings
Anyakora *et al.*[103]	Petrol attendants & mechanics, Nigeria	Occupational PAHs	Urinary 1OHPG/total pyro metabolites	HPLC–UV (1OHP measurement includes 1OHPG portion)	Indicated occupational PAH exposure in service workers.
Cho *et al.*[104]	Cokeoven workers, Korea	Workplace PAH exposures	Urinary 1OHPG	Immunoaffinity + HPLC	Urinary 1OHPG showed internal dose differences pre and postintervention.
Fagundes *et al.*[27]	Adults, Rio Grande do Sul, Brazil	Tobacco smoke, maté intake	Urinary 1OHPG	Immunoaffinity chromatography followed by HPLC–FLD	Higher urinary 1OHPG associated with smoking and maté drinking.
Hofmann *et al.*[105]	Women, Shanghai, China	PAH exposure sources	Urinary 1OHPG	Immunoaffinity + fluorescence	Identified environmental/ dietary determinants of 1OHPG.
Hong[106]	Hospital workers, Korea	Smokers/ nonsmokers	Urinary 1OHPG	Immunoaffinity + fluorescence	Smoking status modified 1OHPG levels.
Adetunde[107]	Smokers, Lagos, Nigeria	Tobacco smoke	Urinary 1OHP/1OHPG	HPLC–UV	Smokers & passive smokers had higher urinary 1-OHP, supporting PAH exposure.
Kakimoto *et al.*[108]	Japan	Mixed environmental and occupational exposures	Urinary 1OHPG	LC–MS/MS	Sensitive and direct quantification of 1OHPG, improving specificity of exposure assessment in diverse populations.
Lai *et al.*[109]	Highway toll station workers	Traffic exhaust air pollution ($PM_{2.5}$)	Urinary 1OHPG	Immunoaffinity chromatography followed by HPLC–FLD	Significant elevation in urinary 1OHPG associated with traffic exhaust exposure; correlated with lipid peroxidation and antioxidant biomarkers.

(*Cont'd...*)

Table 2. (*Continued*)

Study	Population/ location	Exposure source	Biomarker measured	Analytical method	Key findings
Lee *et al.*[110]	Incinerator workers, Korea	Occupational PAH	Urinary 1OHPG	Synchronous fluorescence after immunoaffinity	GSTM1 genotype influenced urinary 1OHPG.
Lee *et al.*[111]	Children, South Korea	Environmental smoke & diet	Urinary 1OHPG	Immunoaffinity + fluorescence	ETS (parental smoking) and grilled food associated with higher 1OHPG.
Lintelmann *et al.*[112]	Adults	Diet & ambient PAH	Urinary 1OHPG	HPLC–FLD, LC–MS	Elevated 1OHP with highPAH exposures.
Kim & Hong[113]	Elderly Koreans	Ambient and lifestyle PAH exposure	Urinary 1OHP	Not reported	Urinary 1OHP levels associated with oxidative stress markers (MDA), supporting exposure–effect links in environmental studies.
Olujimi *et al.*[114]	Charcoal workers, Nigeria	Occupational PAH	Urinary 1OHP	HPLC (total including glucuronide)	Charcoal workers showed elevated urinary biomarkers.
Peters *et al.*[115]	Children, Baltimore, USA	ETS & outdoor air	Urinary 1OHPG	Enzymatic hydrolysis + HPLC–FLD	Secondhand smoke linked to elevated 1OHPG.
Raponi *et al.*[116]	Europe (adult population)	Environmental exposure (ambient air, diet)	Urinary 1OHPG and other metabolites	LC–MS/MS	Sensitive measurement of 1OHPG and other OHPAHs in a mixed-exposure cohort, demonstrating utility of MS-based biomonitoring.
Sithisarankul *et al.*[117]	Mixed adult subjects (nonsmokers and smokers)	Tobacco smoke and dietary grilled/broiled meats	Urinary 1OHPG	Immunoaffinity chromatography + synchronous fluorescence spectroscopy	Significant positive associations between urinary 1OHPG 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[33]	Occupational groups (various)	Airborne PAH exposure	Urinary 1OHPG	HPLCFLD	1OHPG shown as a sensitive biomarker of mixed PAH exposure.
Yoon *et al.*[118]	Korea	Traffic and urban exposures	Urinary 1OHPG	HPLC/immunoaffinity fluorescence	Companion study validating 1OHPG as indicator of combined ambient exposures across age groups; linked to oxidative stress biomarkers.

Abbreviations: 1-OHP: 1-Hydroxypyrene; 1-OHPG: 1-Hydroxypyrene glucuronide; ETS: Environmental tobacco smoke; GSTM1: Glutathione S-transferase mu 1; HPLC: High-performance liquid chromatography; HPLC–FLD: High-performance liquid chromatography with fluorescence detection; HPLC–UV: High-performance liquid chromatography with ultraviolet detection; LC–MS: Liquid chromatography–mass spectrometry; LC–MS/MS: Liquid chromatography–tandem mass spectrometry; MDA: Malondialdehyde; OH-PAHs: Hydroxylated polycyclic aromatic hydrocarbons; PAH: Polycyclic aromatic hydrocarbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter of ≤2.5 μm; UV: ultraviolet.

4. Oxidative stress, DNA damage, and the biomarker 8-hydroxy-2′-deoxyguanosine

Oxidative stress is a pathological condition that arises when the generation of ROS exceeds the capacity of cellular antioxidant defenses, leading to damage to macromolecules such as lipids, proteins, and nucleic acids.[119,120] In the context of exposure to environmental toxicants, including 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-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).[38,39]

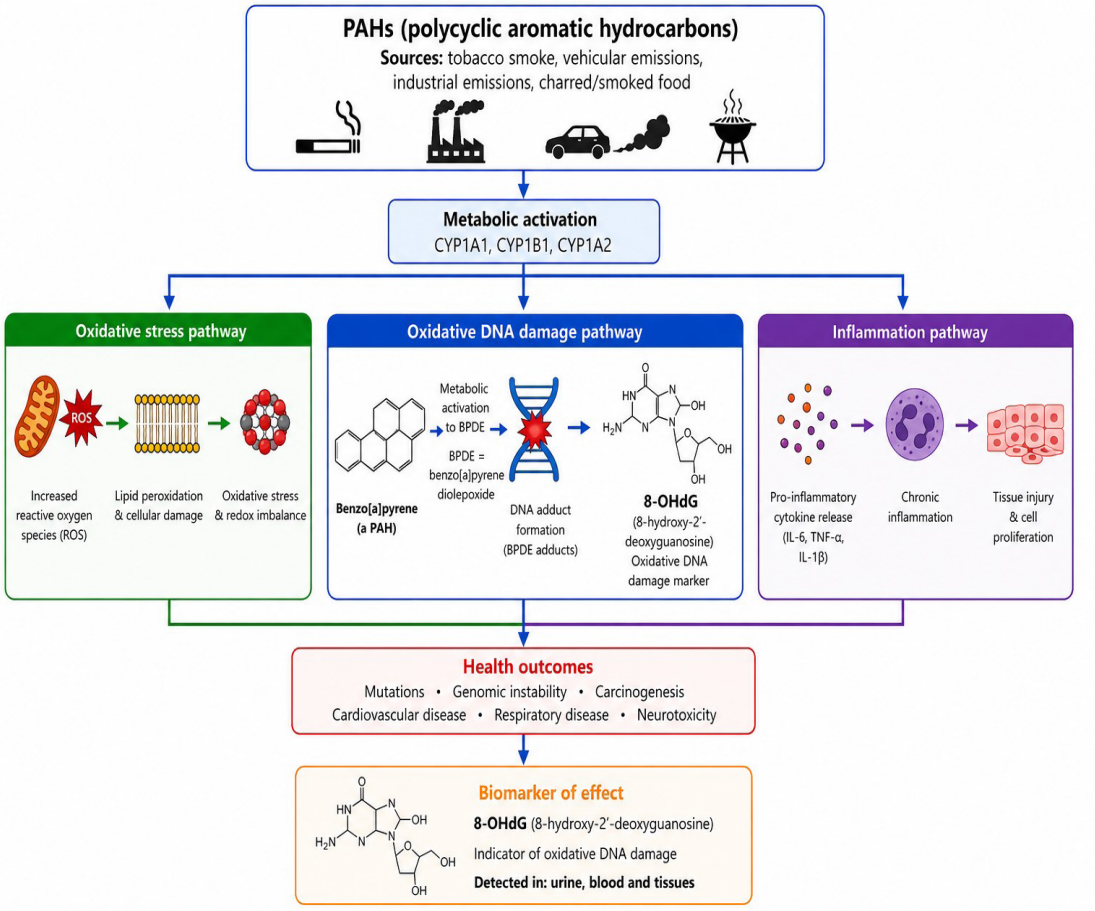


Figure 6. Biological pathways linking PAH exposure to health outcomes, with 8OHdG as a biomarker of oxidative DNA damage. Figure created by the author based on information from Ref.[121]

4.1. Reactive oxygen species generation during polycyclic aromatic hydrocarbon metabolism

Reactive oxygen species 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).[122] These species are normal by-products of cellular metabolism; however, during the metabolism of xenobiotics such as PAHs, the rate of ROS production increases significantly. When PAHs enter the body, they undergo enzymatic bioactivation primarily through the CYP 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.[123] 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.[124] 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 the role of ROS in mediating PAH-induced toxicity.[38,125,126]

Reactive oxygen species generated during PAH metabolism also act as intracellular signaling molecules.[127] 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 such as nuclear factor kappa B and activator protein 1, which regulate genes involved in inflammation and cell survival.[128] Persistent activation of these pathways can lead to chronic inflammation, genomic instability, and evasion of apoptosis, all of which are hallmarks of carcinogenesis. The interplay between ROS generation and cellular signaling highlights how oxidative stress not only causes direct molecular damage but also disrupts normal regulatory networks, promoting maladaptive responses that contribute to disease progression.

4.2. 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 Kelch-like ECH-associated protein 1 (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 Nrf2. Free Nrf2 translocates into the nucleus, where it binds to antioxidant response elements in the promoter regions of target genes.[129] In the nucleus, Nrf2 induces the expression of a wide range of cytoprotective enzymes, including superoxide dismutase, catalase, glutathione peroxidase, 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, 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.[129–131]

4.3. 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-OHdG, also known as 8-oxo-7,8-dihydro-2'-deoxyguanosine, is one of the most extensively studied and widely accepted biomarkers of oxidative DNA damage.[132] 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.[35,133,134] 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.[39] 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.[38]

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.[35] 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.[130]

4.4. 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, chromatographic techniques such as HPLC coupled with electrochemical detection 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.[39] LC–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.[121,130]

Aside from chromatographic approaches, immunological assays such as 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.[39] 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).[38]

Table 3. Studies reporting elevated 8-OHdG levels in populations exposed to PAHs

Study	Population/ *l*ocation	Exposure *s*ource	Biomarker measured	Analytical method	Key findings
Cao *et al.*[135]	Large general population	Ambient PAHs	8OHdG	LC–MS/MS ELISA	Urinary 8OHdG positively associated with highmolecular weight PAH metabolites.
Chien & Yeh,[136]	Adult volunteers	Barbecued meat (dietary PAHs)	Urinary 8OHdG	HPLC–ECD	Significant increase in urinary 8OHdG correlating with PAH metabolites after intake.
Marczynski *et al.*[137]	Workers in cokeoven/ graphite plant	Occupational PAH exposure	8oxodGuo (in white blood cells)	HPLC–ECD	Exposed workers showed 1.38-to- 2.15-fold higher 8oxodGuo vs control, indicating PAHlinked DNA oxidative damage.
Nguyen *et al.*[138]	Cokeoven workers, Korea	Workplace PAH exposures	Urinary 8OHdG & 1OHPG	Immunoaffinity + HPLC	Urinary 1OHdG showed internal dose differences pre-/ postintervention as a sensitive PAH biomarker.
Ren *et al.*[139]	Older adults	Urban air pollution with PAHs	Urinary 8OHdG	ELISA	Ambient particulate matter and organic carbon associated with increased 8OHdG.
Ryu & Hong[125]	Workers with mixed PAH exposures	Occupational/ Environmental PAHs	Urinary 8OHdG	LC–MS/MS ELISA	1OHP significantly correlated with 8OHdG in multiple exposed groups.

(*Cont'd...*)

Table 3. (***Continued***)

Study	Population/ *l*ocation	Exposure *s*ource	Biomarker measured	Analytical method	Key findings
Souza *et al.*[140]	Lactating women & infants, Brazil	Environmental PAHs + metals	Urinary 8OHdG	LC–MS/MS ELISA	PAH metabolites linked to increased urinary 8OHdG by machine learning analysis.
Sun *et al.*[141]	Adults, China	Ambient/ background PAHs	Urinary 8OHdG	GC–MS + HPLC–ECD	Dosedependent relationship between urinary OHPAHs and 8OHdG.
Xiao *et al.*[142]	Workers & residents, South China	Occupational incineration PAHs	Urinary 8OHdG	LC–MS/MS ELISA	Higher PAH exposure and 8OHdG in incineration workers vs. controls.
Zhang *et al.*[143]	Residents, Guangzhou, China	Indoor PAHs in dust	Urinary 8OHdG	LC–MS/MS ELISA	Positive association between PAH metabolites and 8OhdG.

Abbreviations: 1-OHP: 1-Hydroxypyrene; 1-OHPG: 1-Hydroxypyrene glucuronide; 8-OHdG: 8-Hydroxy-2'-deoxyguanosine; 8-oxodGuo: 8-Oxo-7,8-dihydro-2'-deoxyguanosine; ELISA: Enzyme-linked immunosorbent assay; GC–MS: Gas chromatography–mass spectrometry; HPLC: High-performance liquid chromatography; HPLC–ECD: High-performance liquid chromatography with electrochemical detection; LC–MS/MS: Liquid chromatography–tandem mass spectrometry; OH-PAHs: Hydroxylated polycyclic aromatic hydrocarbons; PAH: Polycyclic aromatic hydrocarbon.

5. Integrative biomarker framework linking polycyclic aromatic hydrocarbon exposure to carcinogenesis

Environmental carcinogenesis is a dynamic, multistage process that extends from toxicant exposure and internal dose to molecular perturbations, genomic instability, and ultimately malignant transformation.[4] Although considerable progress has been made in identifying biomarkers that characterize individual stages of this continuum, reliance on a single biomarker often provides only a partial representation of the biological processes linking environmental exposure to disease development. Consequently, contemporary molecular epidemiology increasingly advocates for integrated biomarker frameworks that combine complementary indicators of exposure and biological effect to improve mechanistic understanding, exposure assessment, and cancer risk prediction.[25,144] Such integrative approaches align with the broader shift toward precision environmental health, where multiple biomarkers are employed to characterize the complex interactions between environmental toxicants and host biological responses.

Among environmental carcinogens, PAHs represent an ideal model for developing integrated biomarker strategies because their carcinogenicity is mediated through a well-defined sequence of biological events. Following inhalation, ingestion, or dermal absorption, PAHs undergo metabolic activation primarily by CYP enzymes to form reactive electrophilic intermediates and ROS. These metabolites not only generate DNA adducts but also induce oxidative DNA lesions, chronic inflammation, and genomic instability, all of which contribute to carcinogenesis.[11,20,22] Capturing these sequential events therefore requires biomarkers that reflect both the magnitude of internal exposure and the ensuing biological consequences.

5.1. Rationale for integrating exposure and effect biomarkers

An effective biomonitoring strategy for PAH-associated carcinogenesis should establish a biologically coherent link between external exposure, internal dose, and early molecular alterations preceding clinical disease. This objective cannot be adequately achieved using either exposure biomarkers or effect biomarkers in isolation, as each reflects only one component of the exposure–disease continuum. Instead, integrating biomarkers that represent distinct but complementary stages of PAH toxicokinetics and toxicodynamics provides a more comprehensive framework for understanding environmental carcinogenesis and strengthening causal interpretation in molecular epidemiology.[25,144]

Urinary 1-OHPG is widely regarded as one of the most reliable biomarkers of internal PAH exposure

because it reflects the absorption, metabolism, and urinary excretion of pyrene, a representative constituent of most environmental PAH mixtures.[28,32] Owing to its relatively short biological half-life, urinary 1-OHPG is particularly valuable for assessing recent exposure across occupational and environmental settings, including industrial emissions, traffic-related air pollution, biomass combustion, tobacco smoke, and dietary intake of PAH-contaminated foods.[28,29,31] However, despite its utility in confirming internal exposure, 1-OHPG alone provides limited information regarding whether the absorbed PAHs have initiated biologically significant molecular injury or activated carcinogenic pathways.

Conversely, 8-OHdG is a well-established biomarker of oxidative DNA damage generated following ROS-mediated oxidation of guanine residues. Elevated urinary, plasma, or tissue concentrations of 8-OHdG reflect cumulative oxidative stress and have been associated with genomic instability, mutagenesis, accelerated cellular aging, and increased susceptibility to several chronic diseases, including cancer.[22,38] Nevertheless, although 8-OHdG serves as a sensitive indicator of oxidative DNA injury, it lacks specificity for PAH exposure because elevated concentrations may also arise from other environmental pollutants, cigarette smoking, chronic inflammation, metabolic disorders, neurodegenerative diseases, and physiological aging.[38] Consequently, interpretation of 8-OHdG in isolation cannot reliably distinguish PAH-induced oxidative damage from oxidative stress arising through unrelated pathological processes.

The complementary biological characteristics of these biomarkers provide the principal rationale for their integration. Whereas urinary 1-OHPG indicates internal exposure to PAHs, 8-OHdG provides evidence of a biologically meaningful downstream effect—oxidative DNA damage—which represents one of the earliest molecular hallmarks of carcinogenesis.[28,38] Simultaneous assessment therefore bridges two critical stages of the toxicological continuum by connecting exposure confirmation with molecular effect, thereby offering stronger biological plausibility than either biomarker alone. Rather than functioning as independent indicators, 1-OHPG and 8-OHdG collectively establish an exposure–effect continuum that enhances interpretation of toxicological mechanisms, facilitates identification of susceptible populations, and strengthens environmental cancer risk assessment.

Importantly, relatively few epidemiological investigations have simultaneously evaluated urinary 1-OHPG and 8-OHdG within a unified mechanistic framework, despite increasing recognition that integrated biomarker approaches provide greater biological insight than single-marker strategies. Most PAH biomonitoring studies have emphasized either confirmation of exposure through urinary OH-PAH metabolites or assessment of oxidative stress using DNA damage biomarkers independently, limiting the ability to directly connect internal exposure with downstream molecular injury. This fragmented approach may underestimate the complexity of PAH-induced carcinogenesis and reduce the predictive utility of biomonitoring data. By integrating 1-OHPG and 8-OHdG, the present review proposes a biologically coherent exposure–effect framework capable of linking environmental PAH exposure with early carcinogenic events, thereby providing a stronger foundation for mechanistic interpretation, biomonitoring, and precision environmental risk assessment (Figure 7).

5.2. Evidence supporting the integrated biomarker framework

The rationale for integrating urinary 1-OHPG and 8-OHdG is increasingly supported by epidemiological evidence demonstrating that these biomarkers capture complementary yet biologically interconnected stages of PAH-induced toxicity. Although studies simultaneously measuring urinary 1-OHPG and 8-OHdG remain comparatively limited, available evidence consistently supports a positive relationship between increasing PAH exposure and oxidative DNA damage across diverse occupational and environmental settings (Table 4). Occupational investigations among coke oven workers, asphalt workers, aluminum production workers, traffic police officers, and other industrially exposed populations generally report significantly elevated urinary concentrations of both biomarkers compared with non-exposed controls, indicating that higher internal PAH burdens are accompanied by increased oxidative DNA damage.[13,28,145,146]

These findings are biologically plausible because metabolic activation of PAHs by CYP enzymes generates reactive electrophilic intermediates and ROS, which subsequently oxidize guanine residues to form 8-OHdG while simultaneously increasing urinary PAH metabolites such as 1-OHPG.[80,94]

Evidence from environmentally exposed populations further supports this integrated framework. Individuals residing in urban areas characterized by heavy vehicular traffic, industrial emissions, biomass combustion, or elevated ambient particulate matter frequently exhibit concurrent increases in urinary PAH metabolites and oxidative DNA damage biomarkers, although biomarker

concentrations are generally lower than those observed in highly exposed occupational cohorts.[13,32,147] Similarly, cigarette smokers consistently demonstrate higher urinary concentrations of both 1-OHPG and 8-OHdG than non-smokers, reflecting the substantial contribution of tobacco smoke to internal PAH exposure and oxidative stress.[62,148] Collectively, these observations indicate that the integrated biomarker approach is applicable across a broad spectrum of exposure scenarios, ranging from intense occupational exposure to chronic low-level environmental exposure as shown in Table 4.

Importantly, simultaneous biomarker assessment provides greater biological insight than either marker alone. Elevated urinary 1-OHPG confirms recent internal PAH exposure but cannot determine whether biologically significant molecular injury has occurred. Conversely, elevated 8-OHdG demonstrates oxidative DNA damage but lacks specificity because numerous environmental and pathological conditions generate oxidative stress independently of PAH exposure. When interpreted together, however, the biomarkers establish a biologically coherent exposure–effect relationship in which confirmed internal PAH exposure is directly linked to one of the earliest molecular events involved in carcinogenesis. This complementary relationship substantially improves mechanistic interpretation, reduces uncertainty associated with individual biomarkers, and enhances confidence in exposure assessment within molecular epidemiological investigations.[25,144]

Table 4. Summary of epidemiological and review evidence supporting the integrated assessment of urinary 1-OHP/1-OHPG and 8-OHdG in PAH-exposed populations

Study population	Major PAH exposure source	Biomarker findings	Interpretation supporting the integrated biomarker framework	References
Traffic conductors (n = 91) vs. office workers (n = 53), Taipei, Taiwan	Traffic exhaust ($PM_{2.5}$ and PAHs)	Urinary 1-OHPG positively correlated with urinary 8-OHdG; traffic conductors showed higher 8-OHdG and DNA strand breaks than office workers	Demonstrates that traffic-related PAH exposure elevates oxidative DNA damage, validating 1-OHPG as exposure biomarker and 8-OHdG as effect biomarker	Huang *et al.*[149]
Highway toll station workers (n = 47, female) vs. office workers (n = 27, female reference group), Taipei, Taiwan	Traffic exhaust (vehicle emissions, PAHs)	Urinary 1-OHPG (PAH exposure biomarker) positively correlated with urinary 8-OHdG (oxidative DNA damage biomarker)	Demonstrates that traffic exhaust exposure increases oxidative DNA damage, validating 1-OHPG as an exposure biomarker and 8-OHdG as an effect biomarker	Lai *et al.*[150]
Review of occupational/ environmental exposures (various populations)	Workplaces, environment, tobacco smoke	1-OHP/1-OHPG validated as exposure biomarkers; 8-OHdG suggested as effect biomarker	Supports integrated biomarker framework across diverse PAH sources	Kim *et al.*[13]
Chinese postgraduates (n = 20, seasonal study)	Ambient PAHs (cold vs. warm season)	Seasonal variation in OH-PAHs such urinary 1-OHPG, 1-OHP, and 8-OHdG, positive but non-linear correlation	Suggests susceptibility to PAH-induced oxidative stress varies with season	Huang *et al.*[151]
Brazilian Wildland firefighters (n = 84)	Biomass combustion (forest fires)	Urinary OH-PAH (such as 1-OHPG) and 8-OHdG were quantified. Elevated urinary OH-PAH and 8-OhdG; correlation observed	Highlights acute PAH exposure during firefighting as a driver of oxidative DNA damage	Silva *et al.*[152]
Engine room personnel (n = 36) vs. controls (n = 34), Sweden & Norway	Oil products and engine exhaust (dermal uptake)	Urinary 1-OHP positively correlated with urinary 8-OHdG; personnel with skin contact to oils had significantly higher 8-OHdG than controls	Demonstrates that dermal PAH exposure in engine rooms contributes to oxidative DNA damage, validating 1-OHP as exposure biomarker and 8-OHdG as effect biomarker	Nilsson *et al.*[153]

(*Cont'd...*)

Table 4. (*Continued*)

Study population	Major PAH exposure source	Biomarker findings	Interpretation supporting the integrated biomarker framework	References
Coke oven workers (n = 36) vs. controls (n = 78, medical staff)	Coke production and industrial combustion	Urinary 1-OHP significantly higher in exposed workers; urinary 8-OHdG also elevated in top- and side-oven workers; tendency for positive correlation between 1-OHP and 8-OHdG	Strong occupational evidence linking internal PAH dose to oxidative DNA damage in coke oven workers	Nguyen *et al.*[138]
Traffic police officers (n = 45), drivers (n = 50), controls (n = 34) in Rawalpindi, Pakistan	Vehicular exhaust emissions	Higher urinary 1-OHPyr and 8-OHdG in exposed groups vs. controls, positive correlation	Demonstrates traffic-related PAH exposure contributes to oxidative DNA damage	Kamal *et al.*[145]
Chinese general population (n = 3,053)	Mixed environmental PAHs (diet, air pollution)	Dose–response relationship between urinary OH-PAH metabolites (including 1-OHPG) and 8-OHdG	Provides large-scale evidence linking PAH internal dose to oxidative DNA damage	Sun *et al.*[141]
School children age 8–11 years, Shenzhen, China	Ambient PAHs (urban/suburban air pollution) and phthalates (dietary/environmental sources)	Urinary OH-PAHs were positively correlated with urinary 8-OHdG (r = 0.160–0.365, $p < 0.05$)	Demonstrates that co-exposure to PAHs and phthalates induces oxidative DNA damage in children, with PAHs being the stronger driver of 8-OHdG elevation. Highlights environmental risk in urban/suburban settings	Yu *et al.*[154]
Kindergarten children (n = 453), Taiwan	Ambient PAHs	Urinary 1-OHP positively correlated with urinary 8-OHdG; 1-OHP also associated with higher immunoglobulin E levels and asthma risk; ~35% of PAH–asthma effect mediated by 8-OHdG	Demonstrates that PAH exposure enhances oxidative stress and contributes to asthma development in children	Wang *et al.*[44]
Healthy young adults (n = 36), Taiyuan, China	Ambient PAHs (urban vs. suburban air pollution)	Urinary OH-PAHs positively correlated with 8-OHdG and inflammatory markers (interleukin-8, fractional exhaled nitric oxide); specific OH-Phe showed consistent positive association with oxidative DNA damage	Short-term fluctuations in PAH exposure linked to oxidative stress and DNA damage, supporting 1-OHPG/OH-PAHs as exposure biomarkers and 8-OHdG as effect biomarker	Zhang *et al.*[155]
Elderly volunteers (n = 109), Tianjin, China	Ambient PAHs (winter exposure)	Urinary PAH metabolites correlated with 8-OHdG and altered lipid profiles	Suggests PAH exposure elevates oxidative DNA damage and influences lipid metabolism, though lipid changes may occur via pathways beyond oxidative stress	Wang *et al.*[147]
College students in Guangzhou, China (smokers vs. non-smokers, n = 53)	Tobacco smoke + ambient PAHs	Urinary OH-PAHs (including 1-OHPG) positively associated with 8-OHdG, stronger in smokers	Confirms smoking and environmental PAHs jointly drive oxidative DNA damage	Li *et al.*[146]

Note: The studies included in this review assessed urinary biomarkers of PAH exposure using different analytical approaches. Some studies directly quantified 1-OHPG, whereas others measured 1-OHP following enzymatic deconjugation or reported total urinary OH-PAHs. Because these biomarkers represent related but analytically distinct endpoints, the terminology used in the original studies has been retained. This review emphasizes 1-OHPG because it represents the predominant urinary conjugate of pyrene and offers greater analytical specificity and stability as an exposure biomarker.[33,56]
Abbreviations: 1-OHP: 1-Hydroxypyrene; 1-OHPG: 1-Hydroxypyrene glucuronide; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; OH-PAHs: Hydroxylated polycyclic aromatic hydrocarbons; PAHs: Polycyclic aromatic hydrocarbons; $PM_{2.5}$: Particulate matter with an aerodynamic diameter of ≤2.5 μm.

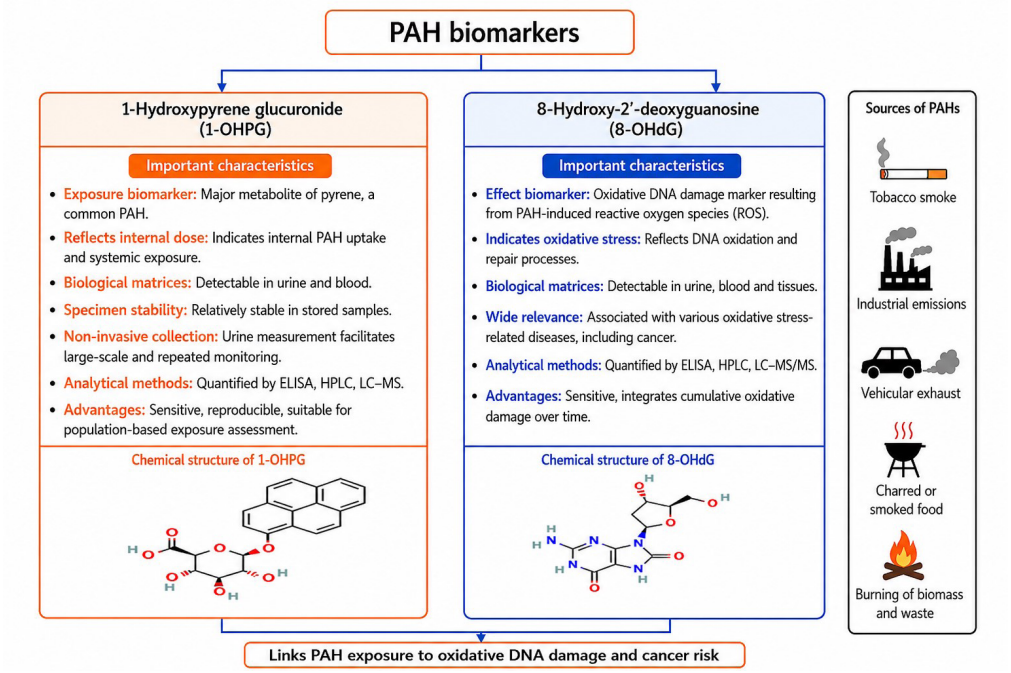


Figure 7. Proposed exposure–effect framework illustrating the complementary roles of urinary 1-OHPG and 8-OHdG in linking PAH exposure to oxidative DNA damage and cancer risk. Figure created by the author based on information from Ref.[13]
Abbreviations: ELISA: Enzyme-linked immunosorbent assay; HPLC: High-performance liquid chromatography; LC–MS: Liquid chromatography–mass spectrometry; LC–MS/MS: Liquid chromatography–tandem mass spectrometry; PAH: Polycyclic aromatic hydrocarbon; ROS: Reactive oxygen species.

Nevertheless, the current body of evidence remains relatively modest and is characterized by considerable methodological diversity. Existing studies differ in exposure source, biological matrices, analytical techniques, study design, and methods of biomarker normalization, making direct quantitative comparisons challenging. Furthermore, many investigations were designed primarily to evaluate occupational exposure rather than to examine mechanistic relationships between exposure biomarkers and oxidative DNA damage. Consequently, although available studies collectively support the biological plausibility of the integrated biomarker framework, additional well-designed prospective investigations employing standardized analytical protocols and simultaneous biomarker assessment are required to establish stronger exposure–response relationships and improve risk prediction (Table 4).[13]

5.3. Sources of heterogeneity and inconsistent findings

Although the majority of epidemiological studies support a positive association between urinary PAH metabolites and 8-OHdG, the magnitude and statistical significance of these relationships vary considerably across populations. Several investigations have reported weak, non-significant, or nonlinear associations between urinary 1-OHP, 1-OHPG, or other OH-PAH metabolites and oxidative DNA damage biomarkers, suggesting that the relationship between internal PAH exposure and molecular injury is influenced by multiple biological, environmental, and methodological factors rather than a simple linear dose–response relationship.[13,151,155] Such variability should not be interpreted as evidence against the integrated biomarker framework but rather as an indication of the complexity of PAH toxicokinetics, toxicodynamics, and inter-individual susceptibility.

One of the principal sources of heterogeneity is variation in exposure characteristics and differences in genetic mechanisms in different individuals. Occupational cohorts, such as coke oven workers, traffic police officers, firefighters, and asphalt workers, generally experience higher and more sustained PAH exposure than environmentally exposed populations, resulting in stronger correlations between urinary PAH metabolites and 8-OHdG.[138,145,152,156,157] Conversely, individuals exposed to lower ambient PAH concentrations through urban air pollution or dietary sources often exhibit weaker associations because biomarker concentrations remain

within narrower exposure ranges and are more susceptible to confounding by other oxidative stressors.[141,147] Seasonal fluctuations in ambient PAH concentrations further contribute to variability, with higher urinary OH-PAH metabolite and 8-OHdG levels frequently observed during colder months when domestic heating, biomass combustion, and atmospheric inversion increase PAH accumulation.[151]

Host-related characteristics also substantially influence biomarker responses. Age, sex, nutritional status, smoking habits, alcohol consumption, obesity, pre-existing inflammatory conditions, and antioxidant capacity all modulate oxidative stress independently of PAH exposure, thereby affecting urinary 8-OHdG concentrations.[22,38] In particular, cigarette smoking represents one of the strongest confounding factors because tobacco smoke is a major source of PAHs and ROS, simultaneously elevating urinary PAH metabolites and oxidative DNA damage biomarkers.[62,146] Furthermore, genetic polymorphisms in xenobiotic-metabolizing enzymes, including CYP (CYP1A1), GSTs (GSTM1 and GSTT1), and UGTs, influence PAH metabolism, detoxification, and glucuronidation efficiency, thereby contributing to considerable inter-individual variability in urinary 1-OHP/1-OHPG and subsequent oxidative DNA damage.[11,13]

Methodological differences among studies represent another important source of inconsistency. Analytical protocols vary considerably, with some investigations quantifying free urinary 1-OHP following enzymatic deconjugation, others directly measuring urinary 1-OHPG, and several reporting total urinary OH-PAH metabolites. Although these biomarkers are closely related indicators of internal PAH exposure, differences in analytical methodology, sample preparation, chromatographic techniques, and detection platforms may influence measured concentrations and complicate direct comparison across studies.[13,28,33,56] Likewise, differences in urine normalization methods (in creatinine adjustment and specific gravity correction), biological matrices, timing of sample collection relative to exposure, and study design further contribute to observed variability.[158–160] Because urinary 1-OHPG primarily reflects recent exposure, whereas 8-OHdG may represent cumulative oxidative damage over a longer biological timescale, failure to synchronize exposure assessment with biological response may attenuate observed associations.

Co-exposure to multiple environmental contaminants also complicates interpretation of integrated biomarker studies. Individuals exposed to airborne particulate matter, heavy metals, volatile organic compounds, phthalates, or persistent organic pollutants may exhibit elevated oxidative DNA damage independently of PAHs, thereby reducing the specificity of 8-OHdG as an isolated biomarker.[147,154] Consequently, observed increases in oxidative DNA damage cannot always be attributed exclusively to PAHs without concurrent evidence confirming internal exposure.

Despite these sources of heterogeneity, the collective evidence consistently supports the biological plausibility of integrating exposure and effect biomarkers in PAH biomonitoring. Rather than undermining the proposed framework, these modifying factors highlight the importance of considering exposure characteristics, host susceptibility, and methodological standardization when interpreting biomarker data. Future investigations employing harmonized analytical protocols, repeated biomarker measurements, and comprehensive adjustment for confounding variables will further strengthen the utility of integrated biomarker strategies for environmental carcinogenesis research (Figure 8).

5.4. Implications for cancer risk assessment

The ultimate objective of biomonitoring is not merely to confirm environmental exposure but to determine whether such exposure has progressed to biologically meaningful events that increase disease risk. In the context of PAH-induced carcinogenesis, this requires biomarkers capable of linking internal exposure with early molecular alterations preceding clinical malignancy. The combined assessment of urinary 1-OHPG and 8-OHdG addresses this need by integrating complementary information on toxicant exposure and oxidative DNA damage within a unified exposure–effect framework. Such integration provides greater biological relevance than reliance on either biomarker independently and represents an important advancement in environmental cancer risk assessment.[25,144]

Exposure biomarkers alone, including urinary 1-OHP or 1-OHPG, provide objective evidence that PAHs have entered the body but do not indicate whether sufficient molecular injury has occurred to initiate carcinogenic processes. Conversely, elevated 8-OHdG reflects oxidative DNA damage but lacks specificity because oxidative stress arises from numerous environmental, metabolic, and inflammatory conditions unrelated to PAH exposure.[22,38] Integrating these biomarkers substantially improves interpretability by demonstrating that confirmed internal PAH exposure is accompanied by one of the earliest molecular events implicated in genomic instability and malignant transformation. Consequently, simultaneous biomarker assessment enhances confidence in identifying biologically relevant exposures while reducing uncertainty associated with isolated biomarker interpretation.

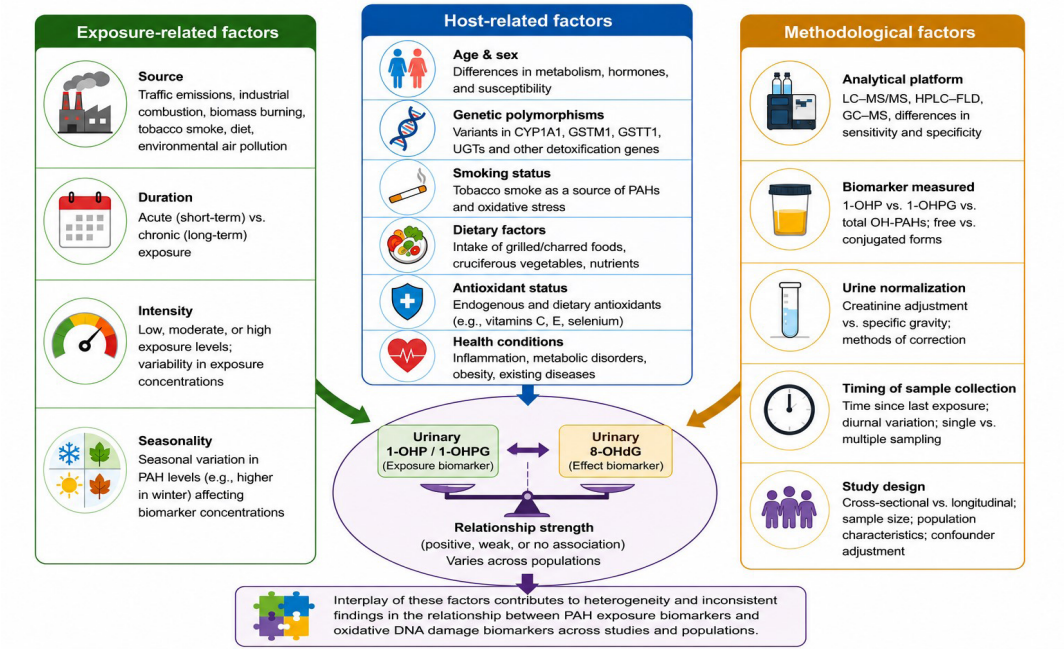


Figure 8. Factors contributing to heterogeneity in the relationship between urinary 1-OHPG and 8-OHdG in PAH-exposed populations. Figure created by the author based on information from Refs.[13,98,149]
Abbreviations: 1-OHPG: 1-Hydroxypyrene glucuronide; 8-OHdG: 8-Hydroxy-2'-deoxyguanosine; GC–MS: Gas chromatography–mass spectrometry; HPLC–FLD: High-performance liquid chromatography with fluorescence detection; LC–MS/MS: Liquid chromatography–tandem mass spectrometry; OH-PAHs: Hydroxylated polycyclic aromatic hydrocarbons; PAHs: Polycyclic aromatic hydrocarbons; UGTs: UDP-glucuronosyltransferases.

From a mechanistic perspective, the integrated biomarker framework closely reflects the established sequence of PAH-induced carcinogenesis. Following absorption, PAHs undergo CYP-mediated metabolic activation, generating electrophilic intermediates and ROS capable of inducing oxidative DNA lesions, DNA adduct formation, mutagenesis, chronic inflammation, and genomic instability.[11,20] Urinary 1-OHPG captures the internal dose resulting from PAH metabolism, whereas 8-OHdG reflects oxidative damage arising from these downstream biochemical processes. Simultaneous elevation of both biomarkers therefore provides stronger mechanistic evidence that environmental exposure has progressed beyond toxicant uptake to molecular injury associated with carcinogenic risk.

The integrated biomarker approach also has important applications in occupational and environmental health surveillance. Workers employed in coke production, petroleum refining, aluminum smelting, asphalt paving, firefighting, and transportation industries frequently experience chronic PAH exposure and may benefit from routine biomonitoring capable of identifying early biological responses before irreversible pathological changes occur.[138,145,152] Likewise, environmentally exposed populations residing near industrial complexes, high-traffic urban areas, or regions affected by biomass combustion could be monitored using combined biomarker strategies to identify susceptible individuals and evaluate the effectiveness of exposure-reduction interventions. Such applications align with preventive public health strategies emphasizing early detection rather than diagnosis following disease onset.

Beyond individual risk assessment, integrated biomarker frameworks may strengthen environmental epidemiology by improving exposure classification and reducing exposure misclassification, a persistent limitation in studies relying exclusively on environmental monitoring data and reviews. Biomarker-based approaches account for differences in absorption, metabolism, and individual susceptibility that cannot be captured through environmental measurements alone, thereby providing more accurate estimates of biologically effective exposure.[25] Furthermore, combining exposure and effect biomarkers facilitates investigation of dose–response relationships, identification of vulnerable subpopulations, and evaluation of intervention strategies aimed at reducing oxidative DNA damage associated with PAH exposure.

Nevertheless, it is important to recognize that simultaneous elevation of urinary 1-OHPG and 8-OHdG should not be interpreted as direct evidence of carcinogenesis. Instead, these biomarkers represent complementary indicators of exposure and early molecular injury that contribute to biological plausibility within established carcinogenic pathways. Cancer development is a multifactorial and prolonged process influenced by genetic susceptibility, DNA repair capacity, immune surveillance, lifestyle factors, and co-exposure to other environmental carcinogens. Consequently, integrated biomarker assessment should be regarded as an important component of a broader risk assessment framework rather than a standalone predictor of cancer (Table 5).

5.5. Current limitations and future research priorities

Despite growing evidence supporting the combined use of urinary 1-OHPG and 8-OHdG as complementary biomarkers of PAH exposure and oxidative DNA damage, several methodological, biological, and epidemiological challenges continue to limit their widespread application in cancer risk assessment. These limitations highlight the need for improved study designs, standardized analytical protocols, and advanced molecular epidemiological approaches capable of strengthening causal inference between environmental PAH exposure and carcinogenesis. Addressing these gaps will be critical for translating integrated biomarker frameworks into reliable tools for precision environmental health and preventive oncology.[13]

Table 5. Mechanistic evidence supporting the combined assessment of urinary 1-OHP/1-OHPG and 8-OHdG in relation to PAH-associated cancer risk

Cancer type	Predominant PAH exposure source	Mechanistic biomarker evidence	Implication for integrated cancer risk assessment	Reference
Lung cancer	Tobacco smoke, ambient air pollution, occupational combustion emissions	Elevated urinary 1-OHP/1-OHPG indicates increased internal PAH exposure, while elevated 8-OHdG reflects oxidative DNA damage associated with pulmonary carcinogenesis.	Supports the use of combined exposure and effect biomarkers for identifying individuals at increased risk following chronic inhalational PAH exposure.	7,11,62
Skin cancer	Coal tar, creosote, asphalt, coke oven emissions, occupational dermal exposure	Chronic dermal PAH exposure increases internal PAH burden and oxidative DNA damage, contributing to mutagenesis in epidermal cells. Such exposure may be accompanied by elevated urinary 1-OHPG & 8-OHdG.	Suggests integrated biomarker assessment may improve monitoring of workers with prolonged dermal PAH exposure.	11,13,161,162
Breast cancer	Urban air pollution, dietary PAHs, tobacco smoke	Increased PAH exposure has been associated with oxidative DNA damage and endocrine-related molecular alterations implicated in breast carcinogenesis.	Highlights the potential utility of integrated biomarkers for evaluating environmentally mediated breast cancer risk.	17,38
Bladder cancer	Coke production, aluminum smelting, diesel emissions, industrial PAHs	PAH metabolism generates reactive intermediates capable of inducing oxidative DNA damage in the urinary tract, reflected by elevated oxidative stress biomarkers.	Indicates combined exposure and oxidative DNA damage biomarkers may strengthen occupational surveillance among high-risk industrial workers.	4,11
Gastrointestinal cancers	Charred foods, biomass smoke, occupational combustion products	Dietary and inhalational PAH exposure contributes to oxidative DNA damage and chronic inflammation within the gastrointestinal tract.	Supports investigation of integrated biomarkers in populations chronically exposed to dietary PAHs.	7,11

Note: Some cited studies quantified urinary 1-OHP following enzymatic deconjugation, whereas others directly measured urinary 1-OHPG. These biomarkers are therefore presented according to the terminology used in the original publications. This table summarizes mechanistic evidence linking PAH exposure, oxidative DNA damage, and cancer risk; it does not imply that these biomarkers are cancer-specific diagnostic markers.
Abbreviations: 1-OHP: 1-Hydroxypyrene; 1-OHPG: 1-Hydroxypyrene glucuronide; 8-OHdG: 8-Hydroxy-2'-deoxyguanosine; PAHs: Polycyclic aromatic hydrocarbons.

5.5.1. Current limitations

One of the major limitations of current biomonitoring studies is the considerable inter-individual variability in PAH metabolism and detoxification. Following absorption, PAHs undergo phase I metabolism primarily through CYP enzymes, followed by glucuronidation and other phase II conjugation reactions before urinary excretion. Variations in genes encoding xenobiotic-metabolizing enzymes, including CYP1A1, CYP1B1, GSTM1, GSTT1, GSTP1, and UGTs, may substantially influence urinary 1-OHPG concentrations despite comparable exposure levels.[11,13] Similarly, polymorphisms in DNA repair genes and differences in endogenous antioxidant capacity may modify oxidative DNA damage, thereby affecting urinary 8-OHdG concentrations independently of PAH exposure.[38] Consequently, biomarker concentrations may reflect both exposure burden and individual susceptibility, complicating direct comparisons across populations.

Another important challenge arises from mixed environmental exposures and the non-specific nature of oxidative stress biomarkers. Human populations are rarely exposed exclusively to PAHs but instead encounter complex mixtures of airborne particulate matter, heavy metals, volatile organic compounds, pesticides, tobacco smoke, and other environmental contaminants capable of inducing oxidative stress. Under these conditions, elevated urinary 8-OHdG may not be attributable solely to PAH exposure, thereby limiting its specificity as an isolated biomarker of PAH-induced molecular damage.[147,154] Moreover, increased urinary 8-OHdG has been reported in several non-malignant conditions associated with oxidative stress, including neurodegenerative disorders such as Friedreich ataxia, diabetes mellitus, cardiovascular disease, chronic inflammatory disorders, obesity, and other metabolic diseases.[40] These factors may confound biomarker interpretation, underscoring the importance of integrating 8-OHdG with a PAH-specific exposure biomarker such as urinary 1-OHPG to improve the specificity and biological interpretation of PAH-related biomonitoring.

Methodological inconsistency further limits comparisons across studies. Although this review emphasizes urinary 1-OHPG as the preferred exposure biomarker, previous investigations have employed diverse analytical approaches, including direct measurement of urinary 1-OHPG, quantification of free 1-OHP following enzymatic deconjugation, or determination of total urinary OH-PAH metabolites. While these analytical endpoints are biologically related, they are not identical and should not be interpreted interchangeably when comparing epidemiological findings. Additional variability arises from differences in chromatographic platforms, sample preparation procedures, urine normalization methods (creatinine adjustment versus specific gravity correction), and quality-control protocols, thereby limiting harmonization and quantitative synthesis across studies.[13,28,33,56,158–160]

A further limitation concerns the predominance of cross-sectional study designs, which account for the majority of epidemiological investigations evaluating urinary PAH metabolites and oxidative DNA damage biomarkers. Although these studies consistently demonstrate significant associations between internal PAH exposure and urinary 8-OHdG, they cannot establish temporal relationships or distinguish transient oxidative responses from cumulative molecular injury. Because urinary 1-OHPG primarily reflects recent internal exposure, while oxidative DNA damage may accumulate over longer periods depending on DNA repair capacity and repeated exposure, single-point biomarker measurements provide only a limited representation of the dynamic processes underlying PAH-induced carcinogenesis.[13,141] The continued use of different analytical endpoints (1-OHPG, free 1-OHP, or total OH-PAHs) contributes to methodological heterogeneity across epidemiological studies. Greater adoption of direct urinary 1-OHPG quantification may improve analytical consistency because it represents the predominant urinary conjugate of pyrene and minimizes variability associated with enzymatic hydrolysis.[33,56]

Finally, current evidence largely remains associational rather than causal. Simultaneous elevation of urinary 1-OHPG and 8-OHdG provides compelling evidence that internal PAH exposure is accompanied by oxidative DNA damage. Although oxidative DNA damage is strongly associated with genomic instability, it does not by itself establish a direct causal pathway to carcinogenesis. Instead, such damage can introduce replication errors, leading to the accumulation of mutations that promote malignant transformation.[163–166] Cancer development is a multifactorial process involving DNA repair mechanisms, epigenetic modifications, chronic inflammation, immune dysregulation, cellular senescence, and interactions with numerous environmental and genetic determinants.[3,167]

5.5.2. Future research priorities

Future research should prioritize well-designed prospective longitudinal cohort studies incorporating repeated measurements of urinary 1-OHPG and 8-OHdG over extended follow-up periods. Such studies would improve characterization of chronic PAH exposure, capture temporal fluctuations in biomarker concentrations, and

facilitate evaluation of exposure trajectories preceding cancer development. Repeated biomarker assessment would also minimize exposure misclassification associated with single urine samples and provide stronger evidence for temporal relationships between environmental exposure, oxidative DNA damage, and disease progression.

To better account for biological variability, future investigations should integrate metabolic and genetic susceptibility profiling into biomonitoring studies. Simultaneous evaluation of polymorphisms in genes encoding xenobiotic-metabolizing enzymes such as CYP1A1, CYP1B1, GSTM1, GSTT1, GSTP1, and UGTs together with DNA repair genes and antioxidant defense pathways would facilitate identification of susceptible individuals and improve interpretation of inter-individual differences in biomarker responses. Incorporating metabolic genotyping into epidemiological studies represents an important step toward personalized environmental risk assessment and precision prevention strategies.[168]

Given the complexity of real-world environmental exposures, future studies should also employ multi-pollutant exposure models rather than evaluating PAHs in isolation. Statistical approaches capable of simultaneously accounting for particulate matter, heavy metals, volatile organic compounds, tobacco smoke, dietary contaminants, and other environmental toxicants would improve attribution of oxidative DNA damage specifically to PAHs while reducing residual confounding.[169] The application of exposomic approaches, integrating comprehensive lifetime exposure assessment with biological response biomarkers, provides a promising framework for understanding cumulative environmental influences on carcinogenesis.[8,170]

Greater emphasis should likewise be placed on methodological standardization. International harmonization of analytical protocols, urine normalization procedures, quality assurance measures, and biomarker nomenclature would substantially improve reproducibility across laboratories. Importantly, future studies should clearly distinguish between urinary 1-OHPG, urinary 1-OHP, and total urinary OH-PAH metabolites, reporting analytical methods in sufficient detail to facilitate comparison among studies and future quantitative meta-analyses. Such standardization will enhance the reliability of integrated biomarker frameworks for occupational and environmental health surveillance.[28,33,56]

Perhaps the most important future direction involves strengthening causal inference. Advanced analytical approaches, including mediation analysis, Mendelian randomization, Bayesian causal network modeling, and repeated longitudinal biomarker measurements, offer powerful opportunities to determine whether oxidative DNA damage mediates the relationship between internal PAH exposure and subsequent carcinogenesis.[25,171–175] Integration of urinary 1-OHPG and 8-OHdG with complementary molecular biomarkers derived from genomics, epigenomics, transcriptomics, metabolomics, adductomics, and spatial multi-omics technologies may further elucidate the biological pathways linking environmental exposure to malignant transformation.[176,177] Such multidisciplinary strategies have the potential to shift environmental biomonitoring beyond exposure assessment toward mechanistic prediction, individualized risk stratification, and precision environmental carcinogenesis (Figure 9).

5.6. An integrated exposure–effect paradigm for precision environmental carcinogenesis

The increasing complexity of environmental exposures and the multifactorial nature of cancer necessitate a transition from conventional single-biomarker approaches toward integrated biomonitoring strategies capable of capturing multiple stages of the carcinogenic process. Traditionally, biomonitoring studies have relied on either biomarkers of exposure or biomarkers of biological effect independently, thereby providing only a partial understanding of the continuum linking environmental contaminants to disease outcomes. While urinary 1-OHPG provides robust evidence of internal PAH exposure, it does not directly reflect the biological consequences of exposure. Conversely, 8-OHdG is a sensitive indicator of oxidative DNA damage but lacks specificity regarding the environmental source responsible for its formation. Integrating these complementary biomarkers provides a biologically coherent framework that simultaneously captures the internal dose of PAHs and one of their earliest molecular consequences, thereby strengthening mechanistic interpretation of PAH-induced carcinogenesis.[13,38]

This integrated exposure–effect paradigm aligns with contemporary concepts in precision environmental health, which seek to characterize disease risk through the simultaneous assessment of environmental exposures, host susceptibility, and molecular responses. Rather than viewing exposure and disease as isolated events, precision environmental carcinogenesis recognizes cancer as the cumulative outcome of dynamic interactions between environmental toxicants, genetic predisposition, metabolic capacity, epigenetic regulation, oxidative stress, chronic inflammation, immune responses, and lifestyle factors.[3,8] Within this framework, urinary 1-OHPG serves as a quantitative measure of internal PAH exposure, whereas urinary 8-OHdG reflects oxidative genomic injury resulting from exposure-related ROS generation. Together, these

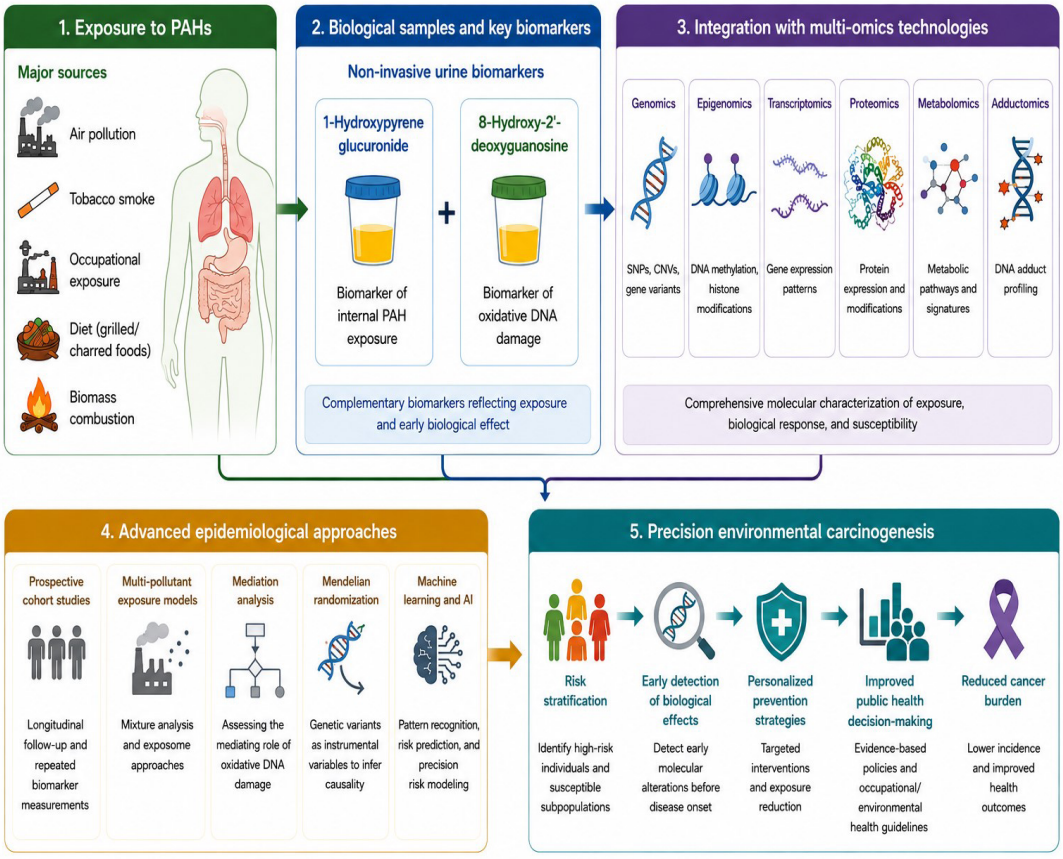


Figure 9. Future perspective on integrated biomonitoring of PAH exposure using 1-OHPG, 8-OhdG, multi-omics technologies, and advanced epidemiological approaches for precision environmental carcinogenesis. Figure created by the author based on information from Refs.[170,173,175–177]
Abbreviations: 1-OHP: 1-Hydroxypyrene; 1-OHPG: 1-Hydroxypyrene glucuronide; 8-OHdG: 8-Hydroxy-2'-deoxyguanosine; CNVs: Copy-number variations; PAHs: Polycyclic aromatic hydrocarbons; SNPs: Single-nucleotide polymorphisms.

biomarkers provide complementary evidence supporting the biological progression from environmental exposure to early molecular damage.

The integration of urinary 1-OHPG and 8-OHdG may also facilitate improved risk stratification across populations with varying environmental and occupational exposures. Individuals demonstrating persistently elevated concentrations of both biomarkers may represent subgroups experiencing sustained internal PAH exposure together with increased oxidative DNA damage, potentially identifying populations requiring intensified exposure mitigation, medical surveillance, or preventive interventions. Although these biomarkers should not be interpreted as diagnostic indicators of cancer, their combined application may substantially improve identification of individuals at increased biological risk before the onset of clinically detectable disease. Such an approach is particularly relevant for occupational settings involving coke production, asphalt paving, traffic-related air pollution, biomass combustion, petroleum industries, and other environments characterized by chronic PAH exposure.[4,7]

Beyond occupational biomonitoring, integrated exposure–effect assessment has important implications for population-level environmental health surveillance. Urbanization, industrialization, biomass fuel utilization, tobacco smoke, dietary PAHs, and traffic emissions continue to expose millions of individuals worldwide to complex PAH mixtures. Simultaneous monitoring of urinary 1-OHPG and 8-OHdG offers a practical strategy for evaluating both internal exposure burden and early oxidative DNA damage within susceptible populations, thereby providing valuable information for environmental risk assessment, regulatory decision-making, and

public health intervention programs. The adoption of standardized analytical protocols and harmonized reporting criteria would further facilitate comparisons across geographical regions and support international biomonitoring initiatives.

6. Conclusion

Polycyclic aromatic hydrocarbons remain among the most important environmental carcinogens because of their widespread occurrence and well-established capacity to induce oxidative stress, DNA damage, and malignant transformation. Following exposure through inhalation, ingestion, or dermal absorption, PAHs undergo metabolic activation to form reactive intermediates and ROS, which promote oxidative DNA lesions, genomic instability, and other molecular alterations associated with carcinogenesis. Among these lesions, 8-OHdG is one of the most extensively validated biomarkers of oxidative DNA damage, providing valuable insight into the early biological consequences of PAH exposure.

This review demonstrates that integrating urinary 1-OHPG, a biomarker of internal PAH exposure, with 8-OHdG, a biomarker of oxidative DNA damage, offers a more comprehensive biomonitoring strategy than the use of either biomarker alone (Figure 10). By simultaneously assessing exposure burden and early molecular effects, this integrated exposure–effect framework strengthens the biological interpretation of PAH-associated carcinogenesis, improves exposure–response assessment, and enhances the identification of populations at increased risk of adverse health outcomes. Importantly, this review also highlights current methodological challenges, including biological variability, mixed environmental exposures, analytical heterogeneity, and the predominance of cross-sectional evidence, all of which should be considered when interpreting biomarker data.

The transition toward precision environmental carcinogenesis will require harmonized biomonitoring protocols, well-designed longitudinal cohort studies, incorporation of metabolic and genetic susceptibility profiling, and the application of advanced epidemiological approaches capable of strengthening causal inference. Furthermore, integrating urinary 1-OHPG and 8-OHdG with emerging technologies including exposomics, adductomics, epigenomics, transcriptomics, proteomics, metabolomics, and artificial intelligence-assisted data analysis offers considerable potential for improving environmental risk prediction and elucidating the molecular pathways linking PAH exposure to cancer development.

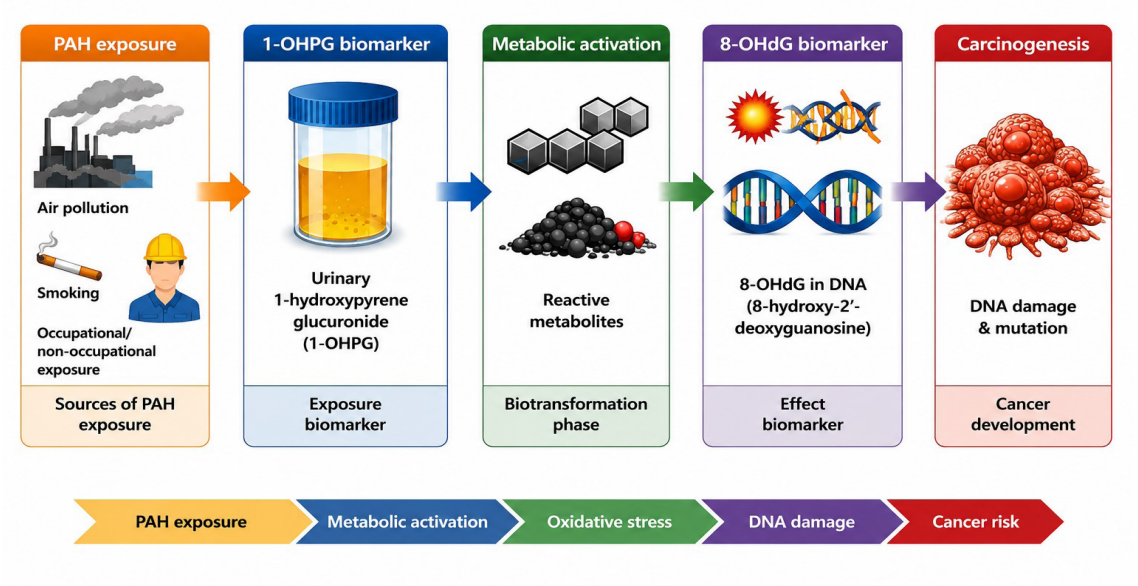


Figure 10. Integrated mechanistic pathway linking PAH exposure, biomarker formation, oxidative DNA damage, and carcinogenesis. Figure created by the author based on information from Refs.[38,178]

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Conflict of interest

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Availability of data

Not applicable.

Further disclosure

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