

# A Review on Pollutant-Induced Inflammation: Molecular Mechanisms and Implications for Disease Pathogenesis

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**Abstract:** Environmental pollutants, including persistent organic pollutants (POPs), heavy metals, and airborne particulate matter (PM), disrupt immune homeostasis by triggering oxidative stress, cytokine release, and activation of key inflammatory pathways such as AhR, HIF-1 $\alpha$ , Nrf2, NF- $\kappa$ B, MAPK, JAK/STAT, and EGFR. These molecular mechanisms amplify or sustain inflammation, contributing to diseases spanning the respiratory, cardiovascular, neurological, and oncogenic spectrum. This review synthesizes the current mechanistic insights into pollutant-induced inflammation, emphasizing the regulatory crosstalk among these pathways and the health implications. Understanding how pollutants modulate inflammation provides a foundation for developing targeted preventive and therapeutic strategies. Future research should focus on integrating both human and animal data, *in vitro* and *in vivo* studies, to clarify dose-response concentrations, identify biomarkers of exposure, and enhance translational relevance for public health.

**Keywords:** environmental pollutants; inflammation; inflammatory response; disease pathogenesis.

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## 1. Introduction

Inflammation is a fundamental biological process that serves as a protective mechanism against infections, injuries, and harmful substances. It involves a tightly regulated network of immune cells and signaling pathways that collectively maintain tissue homeostasis [1–3]. While acute inflammation is beneficial and self-limiting, chronic inflammation contributes to the onset and progression of multiple pathologies, including autoimmune disorders, cardiovascular diseases, and cancers. Increasing studies highlight that chronic inflammation is

not only driven by endogenous factors but can also be initiated or sustained by exposure to environmental pollutants [1,4].

Environmental pollutants, including persistent organic pollutants (POPs), heavy metals, airborne particulate matter (PM), and gaseous emissions, are recognized as major external stressors that can modulate inflammatory responses. These pollutants alter the production and function of inflammatory mediators such as cytokines, prostaglandins, and reactive oxygen species (ROS) [5,6]. It can activate pattern recognition receptors (PRRs) like Toll-like receptors (TLRs), induce oxidative stress, and disrupt signaling pathways such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and Mitogen-Activated Protein Kinase (MAPK), leading to the initiation or amplification of inflammation [6].

Increasing industrialization and urbanization have intensified human exposure to these pollutants, which can penetrate biological barriers and trigger molecular pathways that disturb systemic homeostasis [7–9]. Such exposures promote oxidative imbalance and immune activation, driving chronic inflammation linked to various pathological conditions, including cardiovascular, respiratory, neurological, and developmental disorders, as well as malignancies [4,8,9].

Recent studies emphasize that pollutant-triggered inflammatory signaling shares molecular interactions with metabolic and immune regulatory pathways, suggesting that environmental exposures can reprogram immune responsiveness at both cellular and transcriptional levels. Understanding these mechanistic interactions is vital for developing preventive and therapeutic approaches against pollutant-induced inflammation.

Therefore, this review aims to discuss molecular mechanisms underlying inflammation induced by environmental pollutants comprehensively, summarize the major pollutant classes associated with inflammatory responses, and evaluate the health impacts across organ systems. This review aims to provide mechanistic insights that support future strategies to prevent or mitigate pollutant-associated inflammatory diseases.

## **2. Environmental Pollutants Associated with Inflammatory Responses**

### *2.1. Persistent organic pollutants (POPs).*

Persistent organic pollutants (POPs) such as dioxins, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) that come from industrial activities are highly lipophilic and resistant to degradation, leading to bioaccumulation and chronic human exposure [10,11]. Beyond the persistence, POPs act as potent immunomodulators that trigger inflammation primarily through the aryl hydrocarbon receptor (AhR). Upon ligand binding, AhR translocates to the nucleus and regulates genes including cytochrome P450 1A1 (CYP1A1), promoting oxidative stress and macrophage activation [12,13]. This activation shifts macrophage polarization toward a pro-inflammatory M1 phenotype and enhances NF- $\kappa$ B signaling, amplifying cytokine release. Chronic exposure to dioxin-like compounds has been linked to systemic inflammation, hepatic injury, and autoimmune disorders, mediated by dysregulated ROS production and impaired regulatory T-cell function [14]. Thus, POP-associated inflammation reflects persistent receptor-dependent signaling rather than mere chemical accumulation.

## 2.2. Heavy metals.

Heavy metals such as arsenic, cadmium, lead, and mercury that come from industrial activities or volcanic eruptions induce inflammation primarily through oxidative stress and redox-sensitive transcription factors. These metals catalyze ROS generation that activates NF- $\kappa$ B, MAPK, and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, leading to cytokine release such as interleukin-6 (IL-6), interleukin-1 beta (IL-1 $\beta$ ), and tumor necrosis factor-alpha (TNF- $\alpha$ ), and apoptosis resistance in macrophages and epithelial cells [15,16]. For example, cadmium suppresses Nrf2 antioxidant signaling, allowing excessive ROS buildup, while arsenic triggers NF- $\kappa$ B-dependent expression of adhesion molecules and matrix metalloproteinases, promoting vascular inflammation [17]. Thus, prolonged exposure leads to endothelial dysfunction, neurotoxicity, and hepatic fibrosis, which are the outcomes consistent with chronic, low-grade inflammatory stress.

## 2.3. Air pollutants and particulate matter (PM).

Airborne pollutants and particulate matter, such as PM<sub>2.5</sub> and PM<sub>10</sub>, from industrial activities or forest fires provoke inflammation mainly through oxidative and immune-receptor-mediated pathways. Fine particles penetrate deep into the lungs, where they activate alveolar macrophages and epithelial Toll-like receptors (TLR2/4), stimulating NF- $\kappa$ B and MAPK signaling pathways [8,9]. These lead to the increase of the secretion of IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , promoting neutrophil infiltration and systemic spillover of cytokines. Chronic PM exposure also stabilizes Hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ), enhancing glycolytic metabolism and sustaining inflammatory cell recruitment [18]. Thus, air pollutants induce both local respiratory inflammation and systemic endothelial activation, which contribute to the pathogenesis of cardiovascular and pulmonary disease.

Although POPs, heavy metals, and airborne PM differ chemically, the inflammatory responses within the human body may show similarities. POPs act through receptor-dependent transcriptional control, such as AhR-mediated, heavy metals trigger redox imbalance and protein thiol modification, whereas PM trigger innate receptors such as TLR2/4 and hypoxia-linked metabolic shifts. Despite all the differences, all pathways converge on NF- $\kappa$ B activation and sustained cytokine release, indicating that the pollutants' chemical nature determines the entry point, but not the final inflammatory trajectory. Therefore, this interaction supports a unified toxicodynamic framework for pollutant-induced inflammation.

## 3. Mechanisms of Inflammation Induced by Environmental

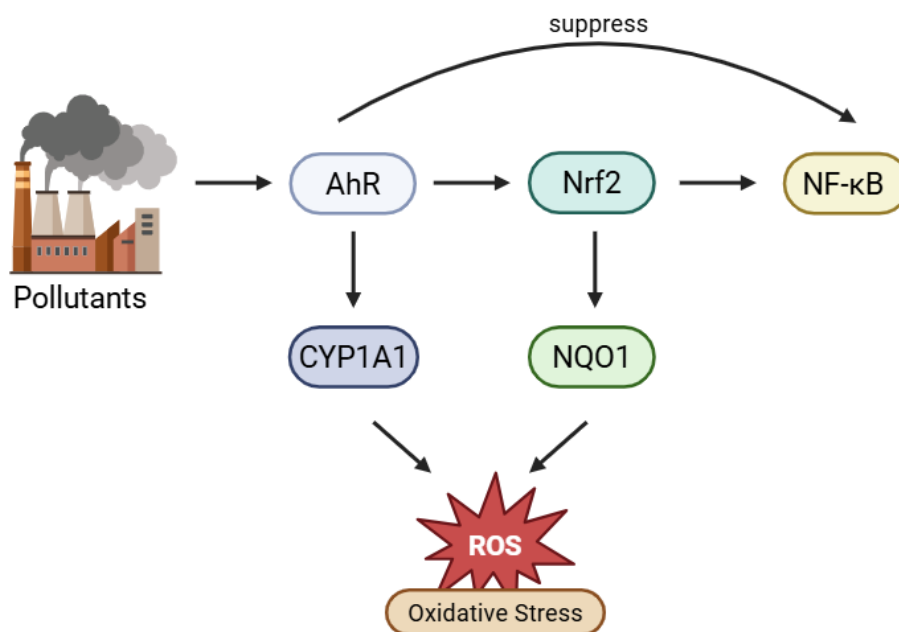
### 3.1. AhR-Nrf2-NF- $\kappa$ B crosstalk.

AhR serves as a xenobiotic sensor that recognizes ligands such as dioxins. Upon activation, AhR translocates to the nucleus and dimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT) to regulate detoxifying enzymes such as CYP1A1 and cytochrome P450 1B1 (CYP1B1) and immune genes. However, AhR also directly interacts with NF- $\kappa$ B subunits, such as the RELA proto-oncogene (RelA) and RELB proto-oncogene (RelB), thereby modulating pro-inflammatory gene transcription. In macrophages and epithelial cells, AhR activation can suppress excessive NF- $\kappa$ B activity by sequestering co-activators and stabilizing NF-kappa-B inhibitor alpha (I $\kappa$ B $\alpha$ ), therefore reducing IL-6 and

TNF- $\alpha$  production [12]. Thus, loss of AhR increases NF- $\kappa$ B phosphorylation and cytokine release [13].

Nrf2, a master regulator of antioxidant defense, complements AhR by promoting cytoprotective responses. Under oxidative stress, pollutants elevate ROS that modify Kelch-like ECH-associated protein 1 (Keap1), releasing Nrf2 to activate genes such as hemo oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1). These enzymes restore redox balance and indirectly suppress NF- $\kappa$ B activation. Nrf2 also directly interferes with transcription of IL-1 $\beta$  and IL-6 by blocking RNA polymerase II recruitment [19]. AhR and Nrf2 regulate each other through shared promoter elements: xenobiotic-response elements (XREs) within Nrf2 and antioxidant-response elements (AREs) within AhR, thereby reinforcing antioxidant and detoxification capacity [20].

NF- $\kappa$ B remains an important mediator of inflammatory gene expression. When pollutants trigger ROS formation or activate PRRs, I $\kappa$ B $\alpha$  is degraded, enabling NF- $\kappa$ B nuclear translocation and transcription of TNF- $\alpha$ , IL-6, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). Normally, balanced Nrf2 activity restrains this process; when antioxidant defenses fail, persistent NF- $\kappa$ B activation drives chronic inflammation. Thus, the AhR-Nrf2-NF- $\kappa$ B axis represents a molecular switch that determines the inflammatory trajectory following pollutant exposure, as shown in Figure 1 [21,22].

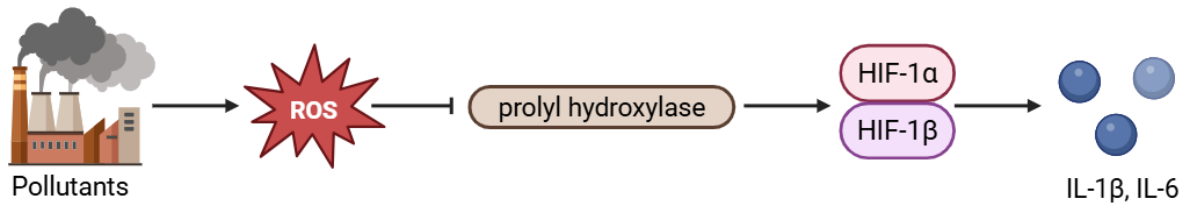


**Figure 1.** Summary of AhR-Nrf2-NF- $\kappa$ B crosstalk.

### 3.2. Integration with HIF-1 $\alpha$ and metabolic reprogramming.

Hypoxia and oxidative stress stabilize hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ), linking oxygen tension or partial pressure of oxygen (PO<sub>2</sub>) to inflammatory signaling. Pollutant-induced ROS inhibit prolyl hydroxylases, allowing HIF-1 $\alpha$  to accumulate and dimerize with hypoxia-inducible factor-1 beta (HIF-1 $\beta$ ) according to Figure 2. The resulting complex enhances glycolytic metabolism, promotes IL-1 $\beta$  and IL-6 expression, and supports T helper 17 cells (Th17) cell differentiation [18]. HIF-1 $\alpha$  also amplifies NF- $\kappa$ B activity through reciprocal promoter binding, whereas Nrf2 activation can limit this by restoring redox homeostasis. Therefore, through these interactions, metabolic adaptation and inflammatory

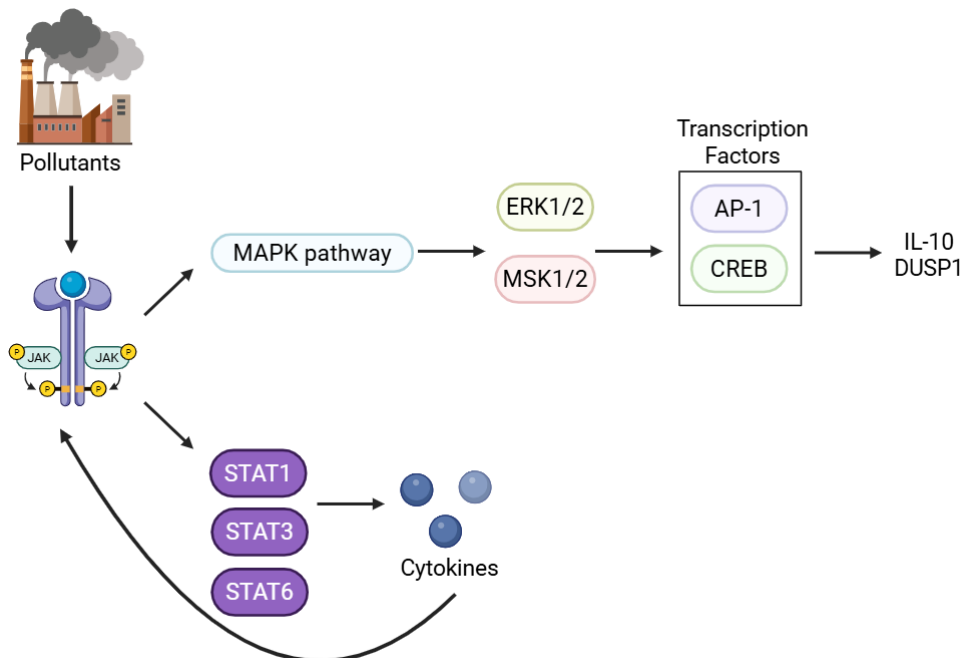
signaling converge, explaining how chronic exposure to PM or heavy metals can sustain chronic inflammation even under normoxic or normal conditions [23].



**Figure 2.** Summary of HIF-1 $\alpha$  and metabolic reprogramming.

*3.3. MAPK and JAK/STAT signaling as amplifiers.*

The mitogen-activated protein kinase (MAPK) family, such as extracellular signal-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK), and p38, acts downstream of many pollutant-activated receptors. MAPKs phosphorylate transcription factors such as activator protein-1 (AP-1) and cAMP response element-binding protein (CREB), reinforcing NF- $\kappa$ B-dependent cytokine production. p38 MAPK stabilizes mRNAs of TNF- $\alpha$  and IL-6, extending inflammatory responses, whereas ERK1/2 and mitogen- and stress-activated kinase (MSK1/2) activate anti-inflammatory genes like interleukin-10 (IL-10) and dual-specificity protein phosphatase 1 (DUSP1), providing negative feedback [24,25]. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway further translates cytokine signals into gene expression changes; signal transducer and activator of transcription (STAT1 and STAT3) promote pro-inflammatory polarization, while STAT6 drives M2-type anti-inflammatory responses. Therefore, persistent activation of JAK/STAT by pollutants or cytokine loops maintains systemic inflammation and has been implicated in neurotoxicity and vascular injury, as shown in Figure 3 [26].

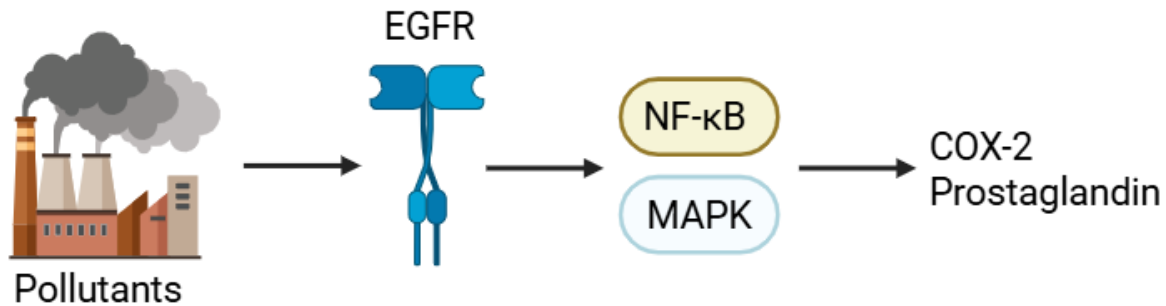


**Figure 3.** Summary of MAPK and JAK/STAT signaling.

*3.4. EGFR and secondary transactivation.*

Epidermal growth factor receptor (EGFR) activation by ligands such as transforming growth factor- $\alpha$  (TGF- $\alpha$ ) or amphiregulin, and transactivation by cytokines or angiotensin

II, links growth factor signaling to inflammation. EGFR downstream pathways converge on MAPK and NF- $\kappa$ B, up-regulating COX-2 and prostaglandin synthesis according to Figure 4. In pulmonary and renal tissues, pollutant-induced EGFR activation contributes to fibrosis and tissue remodeling [27]. Therefore, this pathway exemplifies how non-immune receptors integrate with inflammatory signaling to cause tissue injury.



**Figure 4.** Summary of EGFR and secondary transactivation.

The interactions among the AhR, Nrf2, and NF- $\kappa$ B pathways revealed a delicate balance between detoxification and inflammation. Current studies suggest that activation of AhR and Nrf2 is cytoprotective, whereas chronic or high-dose exposure may overwhelm the compensatory mechanisms, leading to persistent NF- $\kappa$ B signaling. However, conflicting studies among cell and animal models highlight that cell type, pollutant combinations, and exposure duration may influence the outcomes. Thus, future research should focus on quantifying the threshold interactions that shift inflammatory responses from adaptation to pathology for public health purposes.

#### 4. Health Impacts of Pollutant-Induced Inflammation

##### 4.1. Respiratory system.

Airborne pollutants such as PM and dioxins can directly interact with the airway epithelium, activating alveolar macrophages and epithelial cells through NF- $\kappa$ B and MAPK pathways. These pathways promote the release of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , causing airway remodeling, mucus hypersecretion, and fibrosis. Persistent exposure leads to chronic obstructive pulmonary disease (COPD), asthma exacerbation, and interstitial lung disease through oxidative stress, causing epithelial-mesenchymal transition (EMT) and inflammasome activation [28,29].

##### 4.2. Cardiovascular system.

PM and heavy metals can disrupt vascular homeostasis by inducing endothelial dysfunction and chronic vascular inflammation. Pollutants activate NF- $\kappa$ B and MAPK signaling, leading to increased expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and pro-inflammatory cytokines that recruit leukocytes into the vascular wall. These processes accelerate atherosclerosis, vascular remodeling, and myocardial injury [30,31]. Persistent exposure sustains chronic inflammation characterized by elevated C-reactive protein (CRP), a hallmark predictor of cardiovascular risk [32].

### 4.3. Nervous system.

Neurotoxic pollutants such as lead, mercury, and PCBs can cross the blood-brain barrier and activate microglia and astrocytes. This activation triggers NF-κB, JAK/STAT, and MAPK signaling, elevating ROS and cytokines that promote neuroinflammation, synaptic dysfunction, and neuronal death [33,34]. During development, chemicals such as bisphenol A and phthalates can alter AhR and Nrf2 pathways, disrupting neuronal differentiation and contributing to autism-spectrum-like outcomes [35].

### 4.4. Cancer.

Chronic pollutant exposure can maintain a pro-tumorigenic inflammatory milieu through sustained NF-κB and STAT3 activation, increased COX-2 expression, and ROS-mediated DNA damage. AhR activation by dioxins can enhance CYP1A1 and CYP1B1 expression, elevating the mutagenic burden. Inflammatory cytokines and prostaglandins (PGE<sub>2</sub>) promote angiogenesis, immune evasion, and tumor progression [36,37].

### 4.5. Translational relevance: from animal models to human health.

Animal models have been fundamental in elucidating pollutant-induced inflammatory mechanisms. Rodents exposed to diesel exhaust, PM, or dioxins show upregulation of NF-κB, AhR, and Nrf2-dependent genes similar to those observed in human epidemiological studies linking pollutant exposure with COPD, atherosclerosis, and neurodegeneration, according to Table 1 [8,34]. Despite species-specific differences in metabolism and lifespan, conserved pathways such as oxidative stress and cytokine activation support the translational value of these models. Thus, integrating *in vivo* animal findings with *in vitro* findings enhances the relevance of mechanistic data for public-health risk assessment and therapeutic targeting.

While cell and animal studies reliably replicate molecular signatures observed in humans, however, inconsistency in metabolic rates, lifespan, and different exposure doses are some of the disadvantages. Therefore, future studies should prioritize multi-species comparative toxicogenomics better to align experimental doses with environmentally realistic human exposures.

**Table 1.** Summary of pollutant classes, pathways, and related diseases.

Pollutant classes	Pathways	Related diseases	References
Persistent Organic Pollutants (POPs) (e.g., PCBs, dioxins, PBDEs)	AhR → CYP1A1/1B1; crosstalk with NF-κB and Nrf2	Liver toxicity, endocrine disruption, cancer	[12,36]
Heavy Metals (e.g., arsenic, cadmium, lead, mercury)	Nrf2 suppression, NF-κB activation, MAPK phosphorylation	Cardiovascular disease, neurotoxicity	[15,31]
Particulate Matter (e.g., PM <sub>2.5</sub> , PM <sub>10</sub> )	TLR4 → NF-κB → NLRP3 inflammasome activation	Respiratory inflammation, fibrosis	[9,28]

## 5. Conclusions

Environmental pollutants exert profound effects on inflammatory networks, primarily by disturbing redox balance, activating immune cells, and modulating signaling pathways such as AhR, Nrf2, and NF-κB. These pollutants underlie diverse chronic diseases, including pulmonary and cardiovascular disorders, neuroinflammation, and cancer. Beyond these

mechanisms, it is increasingly evident that pollutant-induced inflammation is shaped by complex crosstalk among transcriptional regulators and cell-type-specific responses.

Future research should move toward integrative and translational approaches, integrating omics analyses, *in vitro* and *in vivo* studies, and human epidemiological data to determine exposure thresholds and susceptible populations. Unresolved questions remain about how low-dose combinations of chronic pollutants interact with genetic and epigenetic factors to sustain inflammation. Developing intervention strategies that target inflammation-resolution pathways, such as Nrf2 activation or NF- $\kappa$ B modulation, may provide novel findings for mitigating pollutant-associated disease burdens.

### **Author Contributions**

Conceptualization, N.L.N.F., R.D., F.N.Z., E.V., and R.R.; investigation, N.L.N.F., R.D., F.N.Z., E.V., and R.R.; writing—original draft preparation, N.L.N.F.; writing—review and editing, N.L.N.F.; visualization, N.L.N.F., R.D., F.N.Z., E.V., and R.R.; supervision, R.D., F.N.Z., E.V., and R.R. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

### **Informed Consent Statement**

Not applicable.

### **Data Availability Statement**

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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## Conflicts of Interest

The authors declare no conflict of interest.

## Abbreviations

Abbreviation	Definition
AhR	Aryl hydrocarbon receptor
AP-1	Activator protein-1
ARE	Antioxidant-response elements
ARNT	Aryl hydrocarbon receptor nuclear translocator
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CREB	cAMP response element-binding protein
CRP	C-reactive protein
CYP1A1	Cytochrome P450 1A1
CYP1B1	Cytochrome P450 1B1
DUSP1	Dual-specificity protein phosphatase 1
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinase
HIF-1 $\alpha$	Hypoxia-inducible factor-1 alpha
HIF-1 $\beta$	Hypoxia-inducible factor-1 beta
HO-1	Hemo oxygenase-1
ICAM-1	Intercellular adhesion molecule-1
IL-1 $\beta$	Interleukin-1 beta
IL-10	Interleukin-10
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
I $\kappa$ B $\alpha$	NF-kappa-B inhibitor alpha
JAK/STAT	Janus kinase/signal transducer and activator of transcription
JNK	c-Jun N-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
MAPK	Mitogen-Activated Protein Kinase
MSK	Mitogen- and stress-activated kinase
NF- $\kappa$ B	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NQO1	NAD(P)H:quinone oxidoreductase 1
Nrf2	Nuclear factor erythroid 2-related factor 2
PBDE	Polybrominated diphenyl ethers
PCB	Polychlorinated biphenyls
PGE <sub>2</sub>	Prostaglandins
PM	Particulate matter
PO <sub>2</sub>	Partial pressure of oxygen
POP	Persistent organic pollutants
PRR	Pattern recognition receptors
RelA	RELA proto-oncogene
RelB	RELB proto-oncogene
ROS	Reactive oxygen species
STAT	Signal transducer and activator of transcription
TGF- $\alpha$	Transforming growth factor-alpha
Th17	T helper 17 cells
TLR	Toll-like receptors
TNF- $\alpha$	Tumor necrosis factor-alpha
VCAM-1	Vascular cell adhesion molecule-1
XRE	Xenobiotic-response elements

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