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Review

Multiphase Radical Chemical Processes Induced by Air Pollutants and the Associated Health Effects

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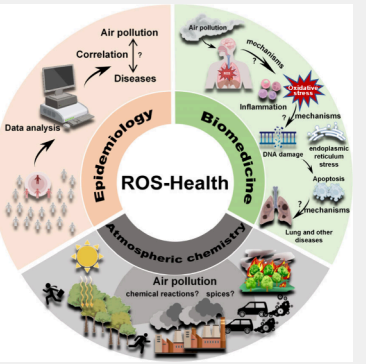
ABSTRACT: Air pollution is increasingly recognized as a significant health risk, yet our understanding of its underlying chemical and physiological mechanisms remains incomplete. Fine particulate matter ($PM_{2.5}$) and ozone (O_3) interact with biomolecules in intracellular and microenvironments, such as the epithelial lining fluid (ELF), leading to the generation of reactive oxygen species (ROS). These ROS trigger cellular inflammatory responses and oxidative stress, contributing to a spectrum of diseases affecting the respiratory, cardiovascular, and central nervous systems. Extensive epidemiological and toxicological research highlights the pivotal role of ROS in air pollution-related diseases. It is crucial to comprehend the intricate chemical processes and accompanying physiological effects of ROS from air pollutants. This review aims to systematically summarize ROS generation mechanisms in the ELF and measurement techniques of oxidative potential (OP), taking the kinetic reactions of ROS cycling in the ELF as an example, and discusses the general health implications of ROS in respiratory, cardiovascular, and central nervous systems. Understanding these processes through interdisciplinary research is essential to develop effective and precise strategies as well as air quality standards to mitigate the public health impacts of air pollution globally.



KEYWORDS: *Air Pollution, ROS, Multiphase Chemical, ELF, Health Effects*

1. INTRODUCTION

Air pollution, a critical factor that profoundly impacts human health, has become a globally significant research focus. Among all pollutants, $PM_{2.5}$ and O_3 are recognized as particularly harmful.[1,2] Epidemiological studies have indicated a significant increase in mortality due to $PM_{2.5}$ and O_3 exposure.[3] However, the interactions and toxicity of these species remain unclear.[4,5]

Air pollutants enter the lungs through the respiratory tract, encountering the epithelial lining fluid (ELF) that covers the respiratory tract surfaces. The ELF is composed of a complex mixture, including phospholipids, proteins, antioxidants, and other substances. The lower layer of the ELF consists of a mucus gel phase and an aqueous sol phase. Specifically, the mucus gel phase can capture microorganisms and large particles, while the aqueous sol phase surrounds the lining epithelial cells, including a large number of biological antioxidants between them.[6] Therefore, when airborne pollutants deposit at the air−liquid interface, they react with various components in the ELF. The resulting products then diffuse downward into the epithelial cells, undergoing complex multiphase chemical processes.[6,7] Particularly, pollutants such as $PM_{2.5}$, due to their small particle size, and O_3, with its low water solubility, tend to deposit in the ELF.[3,8] Within the ELF, $PM_{2.5}$ components, such as reactive secondary organic matter or transition metal ions (TMIs) initiate the generation of ROS through complex redox reactions. Common types of ROS include superoxide radicals (O_2^-), hydroxyl radicals (OH), singlet oxygen ($^1O_2$), hydroperoxyl radicals (HO_2), and hydrogen peroxide (H_2O_2).[9] Additionally, organic radicals such as R, RO, and RO_2 can also induce oxidative stress and have longer lifetimes compared to other ROS.[10] O_3 can also contribute to ROS production by reacting with antioxidants or surfactants present on cell surfaces, potentially damaging cell membranes.[9] Excessive ROS levels within the ELF disrupt surfactant molecules on cell membranes, allowing ROS to penetrate into the aqueous phase (cytoplasm). These processes trigger cellular inflammation, oxidative stress, and subsequent lung injury. Furthermore, these effects can extend beyond the respiratory system, impacting cardiovascular, central nervous,

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or even reproductive systems through various physiological processes.[11,12]

Although numerous *in vitro* and *in vivo* studies have explored the effects of ROS on health, there remains a lack of clarity regarding the chemical and biological processes of air pollutants in intracellular and microenvironments. This limitation has often prevented studies from fully simulating the multiphase chemical interactions occurring in both the gas phase (air pollution) and the liquid phase (cellular environment).[6,13,14] To gain a deeper understanding of the multiphase chemical reaction processes of environmental pollutants, this review systematically summarizes the generation mechanism of ROS in the ELF and the various methods used to measure the induction of ROS. It also delves into the complex kinetic modeling of ROS cycling within the ELF. Furthermore, this review provides an overview of how ROS contribute to disease pathology and proposes future interdisciplinary studies which would integrate atmospheric chemistry with toxicology, epidemiology, and biomedicine to enhance our understanding of how environmental pollutants interact with biological systems, particularly focusing on the role of ROS in mediating health effects.

2. MULTIPHASE CHEMICAL PROCESSES OF $PM_{2.5}$ AND O_3 IN PULMONARY EPITHELIAL LINING FLUID

The importance of the substantial risk of ROS to health has driven extensive research into their generation, cycling mechanisms, and methods of precise and quantitative detection.[15,16] In the field of environmental health, acellular measurements are commonly utilized to quantitatively assess ROS production rates induced by air pollutants. This approach facilitates studies on the relationship between air pollutants and their associated health effects.[17,18]

2.1. Generation Mechanism of ROS within ELF

When $PM_{2.5}$ and O_3 are inhaled and deposited in the ELF, these air pollutants undergo complex redox reactions, leading to the production of ROS.[19−21] $PM_{2.5}$ contains various redox-active substances, such as TMI, quinones, secondary organic aerosols (SOAs), humic-like substances (HULIS), and other components,[22−24] which interact with antioxidants in the ELF and generate ROS.[25,26] Specifically, TMI and quinones in $PM_{2.5}$ can generate O_2^- by reacting with molecular oxygen (O_2).[27] Involvement of iron and copper ions can lead to Fenton-type reactions, producing OH.[28,29] Furthermore, antioxidants can react with TMI or quinones to form reduced metal ions or semiquinones. TMI and quinones can further react with O_2 to form H_2O_2 and regenerate superoxide radicals.[30] Additionally, HULIS, a term encompassing complex organic matter in atmospheric aerosols with diverse functional groups to include groups chelated to transition metals, is potentially involved in redox cycling.[31] O_3, on the other hand, is highly oxidizing and causes oxidative stress. It reacts with antioxidants such as ascorbic acid (AA), uric acid (UA), and glutathione (GSH) to form secondary oxidation products, and its decomposition on surfactant lipids can also produce H_2O_2.[32,33] O_3 can also oxidize lipids on cell membranes, leading to lipid peroxidation.[30] It is important to note that these chemical reactions within the ELF are complex and involve multiple oxidative pathways, contributing to oxidative stress and potential damage to lung tissues.

2.2. Assays for Measuring Oxidative Potential

Oxidative potential (OP) is used to define ROS produced by the reaction between inhaled particulate matter (PM) and antioxidants, and acellular measurements have been performed by *in vitro* simulated ELF (sELF).[34−42] The sELF contains antioxidants (AA, UA, and GSH), inorganic salts and radical-capturing probes, metal-binding proteins, and lipids.[43−45] In simulated lung fluid (SLF), the oxidative potential of air pollutants can be detected with numerous methods.[17,45] Here, we summarize the current major OP measurement assays in Table 1. These methods are elaborated in more detail below.

Table 1. Methods for Measuring Oxidative Potential of $PM_{2.5}$

	assay	target molecule	measurement end point
depletion of antioxidant	lung lining fluid assay	urate (UA)	%UA depleted after 4 h
		glutathione (GSH)	%GSH depleted after 4 h
		ascorbate (AA)	%AA depleted after 4 h
	dichlorofluorescin assay	dichlorofluorescin (DTT)	rate of DTT depletion over 1 h
trapping hydroxy radical	electron spin resonance (ESR) spectroscopy	hydrogen peroxide (H_2O_2)	OH generation in the presence of H_2O_2
chemical reaction	hydroxyl radical (OH) assay	disodium terephthalate (TPT)	Reaction with TPT after 4 h
	H_2O_2 assay	horseradish peroxidase	reaction with horseradish peroxidase after 4 h

2.2.1. Lung Lining Fluid Assay. The ELF serves as the primary protection barrier against air pollutants entering the body through the respiratory tract.[37] Within this fluid, GSH reacts with reactive species (such as quinones, Cu^{2+}, Fe^{3+}) in $PM_{2.5}$, generating thiyl radicals (GS·) that further form glutathione radical disulfide anions ($GSSG^-$), leading to the production of O_2^- radicals and GSSH. This method is cost-effective and health-oriented, commonly employed to determine the oxidative potential (OP) of aluminum (Al), iron (Fe), and lead (Pb).[46] AA, characterized by its enediol and lactone ring structure, acts as a reducing agent reacting with oxidative substances in $PM_{2.5}$ to form ROS and dehydroascorbic acid.[47] AA is ideal for low-cost, automated measurements. It is often used to evaluate particle sizes ranging from 3.2 to 5.6 μm, which are sensitive to ROS production catalyzed by TMI.[48,49] UA reacts with oxidative substances in $PM_{2.5}$ to produce H_2O_2 and 5-hydroxyisourate acid.[50] These measurements estimate the OP of air pollutants by calculating the rate of antioxidant consumption.[49]

Shahpoury et al. utilized this method to conduct experiments, demonstrating that the consumption rate of AA increased linearly with PM concentrations ranging from 25 to 100 μg mL^{-1}. The PM concentration influenced the linear range of AA; for instance, at a concentration of 50 μg mL^{-1}, the linear range of AA decreased to 180 min, and at the highest concentration of 100 μg mL^{-1}, it further decreased to 120 min. Below concentrations of 100 μg mL^{-1}, the consumption rate of GSH exhibited a nonlinear dose−response relationship.[17] This suggests that the consumption rate of antioxidants correlates with both PM concentration and reaction time, and various measurement environments can influence OP. UA acted as a potent ROS scavenger, but its reactivity toward PM was

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minimal, typically used alone or in combination with AA and GSH. However, a previous study indicated that UA can enhance the antioxidant capacity of SLF and protect against the loss of AA, thereby affecting its consumption rate.[51−53] In contrast, Charrier et al. found that UA has little to no effect on the consumption of GSH, ascorbate, or the generation of OH in the presence of PM or metal.[45,54] This indicates that antioxidant mechanisms and reactive properties vary under different conditions for antioxidants.

2.2.2. Dichlorofluorescin Assay. Dichlorofluorescin (DTT) is a potent reducing agent that is capable of replacing intracellular antioxidants. Within $PM_{2.5}$, oxidative compounds catalyze DTT to transfer electrons to oxygen, resulting in the generation of O_2^- radicals. These radicals further react to produce H_2O_2 and O_2, thereby oxidizing DTT in the process. This method is straightforward and effective for assessing polycyclic aromatic hydrocarbons (PAHs), HULIS, quinones, copper (Cu), and manganese (Mn) within a sensitive particle size range of 0.32 to 1.8 μm. However, it is limited by photoinstability and other factors.[55]

A study noted that DTT assays demonstrate a nonlinear dose−response relationship within PM concentrations ranging from 25 to 100 $\mu g\ mL^{-1}$. Specifically, at a reaction time of 120 min, the consumption rate of DTT increases with higher PM concentrations.[17] Meanwhile, Charrier et al. discovered that the consumption rate of OP^{DTT} is influenced by the concentration of metallic ions in ambient PM.[56] Subsequent research has indicated that while OP^{DTT} is notably sensitive to metals, it may also exhibit relatively high sensitivity to organic components.[56−58] Furthermore, studies have reported inconsistent associations between OP^{DTT} and biological markers, such as inflammatory responses and oxidative stress indicators. For instance, Akhtar et al. utilized DTT assays to gauge the ROS generation potential of atmospheric PM in Toronto, assessing cell viability and interleukin-8 (IL-8) levels in human alveolar epithelial cells (A549). Their findings revealed no apparent correlation between OP^{DTT} and biological effects.[59] However, Velali et al. identified a significant correlation between OP^{DTT} and both cell viability and lactate dehydrogenase (LDH) activity in their study on OP and cytotoxicity of atmospheric PM in Thessaloniki, Greece.[60] This further suggests that OP^{DTT} represents only the chemical reactions between atmospheric particulate matter and DTT, while the actual cellular responses to PM are more complex.

2.2.3. Electron Spin Resonance (ESR) Spectroscopy. ESR is a method that directly measures the rate of OH production, using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a spin trap in electron spin resonance to measure the generation of OH.[61] In this process, O_2^- radicals are generated when O_2 accepts electrons under the influence of environmental persistent free radicals (EPFRs), subsequently forming H_2O_2. In the presence of Fe^{2+}, H_2O_2 can further generate OH through the Fenton reaction.[62] This method is highly sensitive and accurate for assessing the OP of transition metals, such as Cu, Fe, and vanadium (V), demonstrating sensitivity to both coarse and fine particulate matter. However, it requires complex and expensive measuring apparatus,[49] which limits its practical application.

Research indicates that BMPO−OH undergoes gradual dissociation upon interaction with Fe, significantly affecting the capture of free radicals. Consequently, experimental results suggest that OP^{ESR} demonstrates lower sensitivity compared with alternative assays. Furthermore, because the ESR assay does not include antioxidants in its reaction mixture, OP^{ESR} cannot effectively reflect the impact of antioxidants on free radical formation.[17]

2.2.4. H_2O_2 Assay. Dichlorofluorescein (DCFH) is initially nonfluorescent and reacts with H_2O_2 in the presence of horseradish peroxidase (HRP) to form HRP-II, which then interacts with DCFH to produce the red fluorescent compound 2′,7′-dichlorofluorescein (DCF).[63] This method is noted for its simplicity, cost-effectiveness, and suitability in the detection of organic pollutants (OC, PAHs) and various inorganic ions. It offers sensitivity across a particle size range of 0.32 to 1.8 μm. However, it is noted for its limitation in achieving high measurement accuracy.[55]

Shahpoury et al.'s experiments found that at PM concentrations below 50 $\mu g\ mL^{-1}$, H_2O_2 levels increased with reaction time, showing a nearly linear response up to 180 min. Beyond this point, however, the formation of H_2O_2 starts to decline. At higher PM concentrations, $OP^{H_2O_2}$ exhibits nonlinear dynamics, stabilizing after 60 min but showing another increase after 120 min, though the reasons for this are unclear.[17] Additionally, Boisa et al. discovered that physiological concentrations of thiol antioxidants (e.g., GSH) in SLF significantly diminish the assay's dynamic range.[43] Moreover, the assay necessitates the use of PBS to stabilize H_2O_2 and ensure optimal pH conditions for the peroxidases. However, during sample processing, PBS might adversely impact the stability of enzymes.[64] This suggests that the stability of the measurement system significantly influences the accuracy of the measurements.

2.2.5. OH Assay. Terephthalic acid (TA) is utilized as a specific method to measure OH in simulated lung fluid. OH reacts with TA to produce a stable and intensely fluorescent compound called 2-hydroxyterephthalic acid (TAOH). The rate of OH generation can be quantified based on the fluorescence intensity of TAOH formed.[65]

For OH measurement, at low PM (25 $\mu g\ mL^{-1}$) concentrations, OP^{OH} exhibits first-order kinetics, but at 50 $\mu g\ mL^{-1}$, it shows linear kinetics within 120 min. At a PM concentration of 100 $\mu g\ mL^{-1}$, OP^{OH} displays nonlinear kinetics. However, the dose−response relationship of OP^{OH} may be significantly influenced by the reaction time. At PM concentrations ranging from 25−100 $\mu g\ mL^{-1}$ with incubation times shorter than 120 min, the relationship shows linearity. When the incubation time is extended to 120 min at a PM concentration of 100 $\mu g\ mL^{-1}$, OP^{OH} shows a decreasing trend.[17] This could be related to a significant loss of antioxidants due to prolonged incubation times at high PM concentrations.

In addition to the TA method, there are the salicylic acid (SA) and benzoate (BA) methods, both of which determine OH indirectly. The SA method involves reacting with OH in aqueous solution to produce 2,5-dihydroxybenzoic acid and 2,3-dihydroxybenzoic acid. These substances exhibit strong absorbance in the UV region, so pretreatment is required before detection using a UV spectrophotometer. The BA method uses benzoic acid as a probe, effectively quantifying the OH generated by other chemical substances. Benzoic acid reacts with OH to form *p*-hydroxybenzoate (*p*-HBA), which is then measured.[65]

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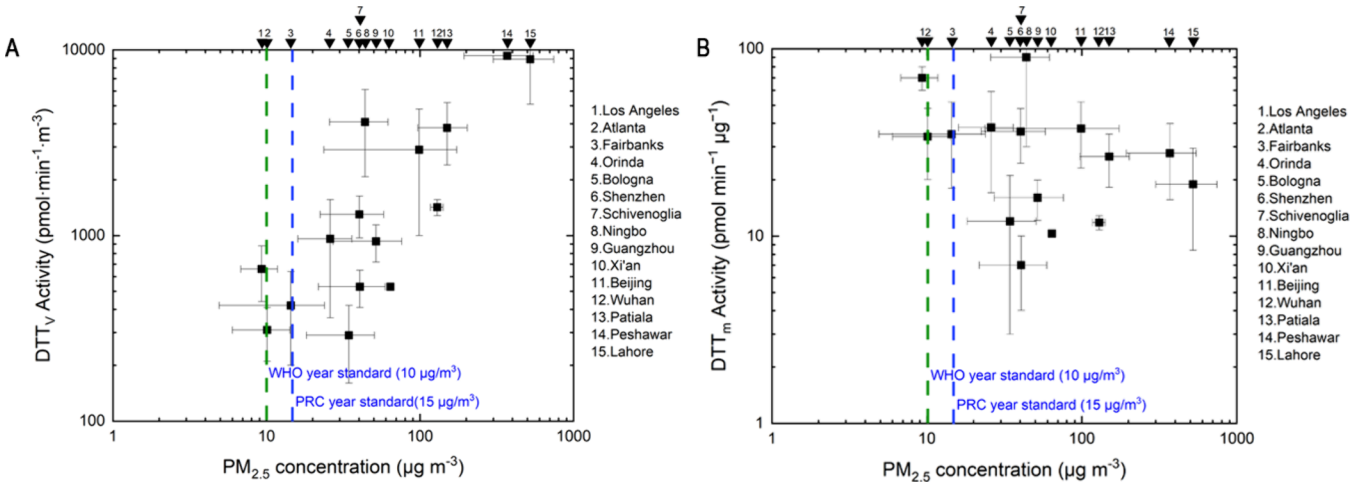

Figure 1. Correlation between the concentration of $PM_{2.5}$ and DTT_v (A) and DTT_m (B) in different cities globally.[68−77] The green dashed line represents the $PM_{2.5}$ standard of the World Health Organization (WHO), while the blue dashed line represents the $PM_{2.5}$ standard of the Ministry of Ecology and Environment of China.

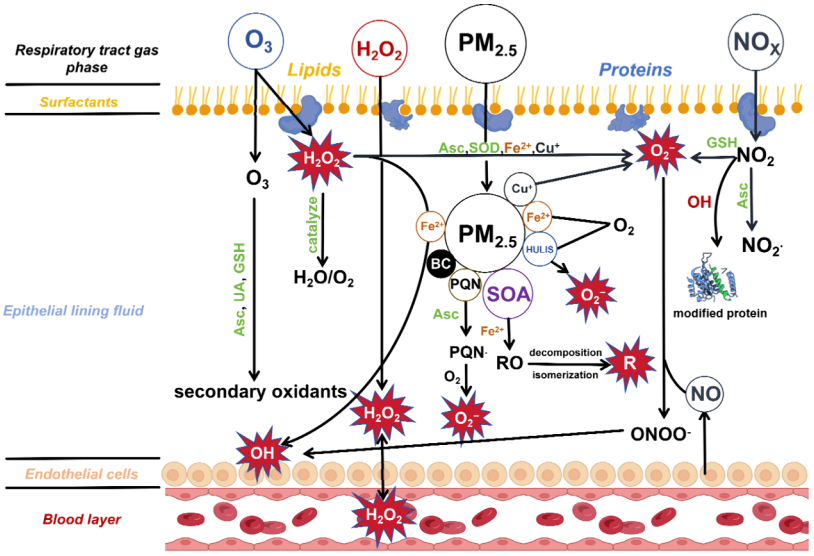

Figure 2. Multiphase chemical kinetic model of ROS cycling in epithelial lining fluid. This model includes five main components: inspired gas phase, surfactant layer, epithelial lining fluid, endothelium, and blood layer. $PM_{2.5}$ contains various redox components (such as Cu, Fe, SOA, HULIS, PQN, and black carbon) that catalyze ROS formation via processes like the Fenton reaction. Antioxidants and enzymes (highlighted in green) are sensitive to oxidants like O_3 and NO_2. O_3 reacts with antioxidants to form secondary products and oxidizes surface lipids to produce H_2O_2. NO_2 reacts with antioxidants to produce O_2^- and modifies proteins with OH. Additionally, endogenous and exogenous H_2O_2 participate in multiphase cycling.

2.3. Analysis of the Correlation between OP^{DTT} and $PM_{2.5}$ Concentration

Among these assays, the DTT assay is widely used as an acellular method to quantify OP and has shown strong correlations with various biological indicators of adverse health effects due to particulate matter exposure.[66] The rate of DTT depletion is directly proportional to the concentration of the redox-active substances in $PM_{2.5}$. DTT activity is reported in two units: pmol min^{-1} m^{-3} (volume-normalized DTT activity, DTT_v) and pmol min^{-1} μg^{-1} (mass-normalized DTT activity, DTT_m). DTT_v, which considers emission rates, dilution, and other factors, is more closely associated with human health end points. On the other hand, DTT_m reflects inherent characteristics of particulate matter and its sources.[37,67]

To explore the correlation between $PM_{2.5}$ concentration and OP, we evaluated DTT consumption rates across 15 global cities, as depicted in Figure 1.[68−77] Under World Health Organization (WHO) standards, only two cities, Los Angeles and Atlanta, have $PM_{2.5}$ concentrations within the recommended range. According to Chinese standards, Fairbanks' $PM_{2.5}$ concentration also falls within the acceptable range. However, $PM_{2.5}$ concentrations in Shenzhen, Ningbo, Guangzhou, Xi'an, Beijing, and Wuhan are significantly higher than the standard values. Moreover, as $PM_{2.5}$ concentrations increase, so does DTT_v. Peshawar's DTT_v value is as high as 9300 ± 3900 pmol min^{-1} m^{-3}. This underscores the critical need for implementing measures to regulate particulate matter levels. Despite exceeding WHO and PRC annual standards, many cities neglect the toxic impacts of particulate matter on human health in their mitigation strategies. Moreover, a consistent and predictable pattern of DTT_m variation remains elusive.

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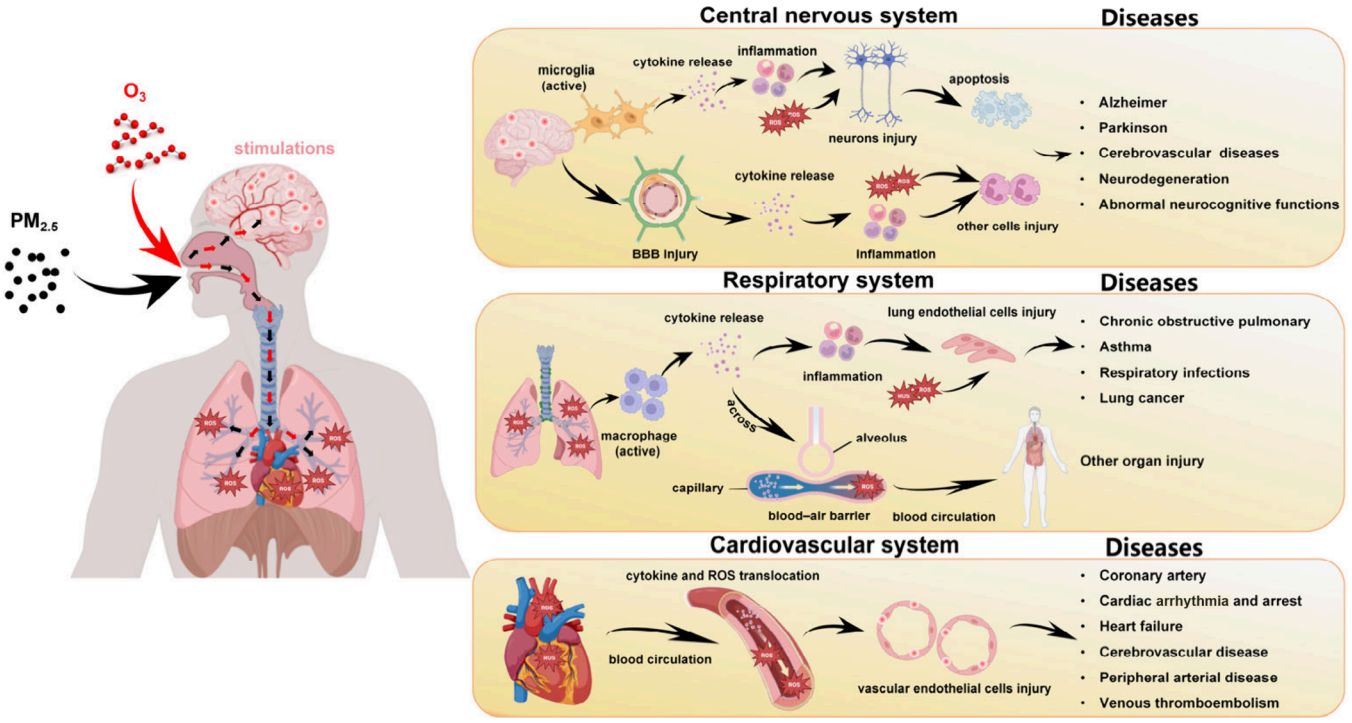

Figure 3. Impairments of $PM_{2.5}$ and O_3 exposure on various human body systems. In the central nervous system, $PM_{2.5}$ and O_3 enter via the olfactory nerve, activating microglial cells (yellow) that release inflammatory cytokines (purple dots) and ROS (red polygons). This process damages neurons and promotes apoptosis (blue-purple cells). They can breach the blood–brain barrier (green hexagons), releasing more inflammatory cytokines and ROS and damaging other brain cells. In the respiratory system, $PM_{2.5}$ and O_3 enter the lungs, inducing ROS production in the epithelial lining fluid and activating macrophages (purple cells) that release inflammatory cytokines. This damages lung epithelial cells (pink cells). Inflammatory cytokines and ROS can cross the alveolar–capillary barrier, causing systemic inflammation. In the cardiovascular system, ROS and inflammatory cytokines in the bloodstream damage vascular endothelial cells (hollow circular pink cells).

3. MULTIPHASE CHEMICAL KINETIC MODEL OF ROS CYCLING IN ELF

3.1. Overview of Kinetic Multilayer Model

Despite there being numerous acellular assays available for measuring ROS, there has been comprehensive simulation of ROS production rates and concentrations induced by air pollutants in the ELF.[19] To address this gap and deepen the understanding of multiphase chemical processes at the air–epithelial cell interface within the ELF, Berkemeier et al. introduced the kinetic multilayer model (KM-SUB-ELF) in 2016. This model comprises five components, including the respiratory tract gas phase, surfactants, ELF, endothelial cells, and the blood layer.[30,78] It effectively simulates both surface and bulk chemistry within the ELF, facilitating the quantification of ROS formation and assessment of the redox capacity of air pollutants.[22,30] By simulating diverse biochemical reactions, the KM-SUB-ELF model is instrumental in investigating how air pollution triggers ROS production in the respiratory system, thereby contributing to our understanding of respiratory diseases.

Since the inception of model construction in 2016, researchers have continually expanded upon the foundational basis of the model to refine the chemical mechanisms within the model. Here, we present a summary of the current model, as illustrated in Figure 2.[29,30,78] Dovrou et al. noted that H_2O_2 concentration in the ELF primarily stems from endogenous release and ambient gas-phase inhalation, with $PM_{2.5}$ inhalation playing a negligible role in H_2O_2 production.[18] SOAs, crucial $PM_{2.5}$ components, enhance ROS formation in the ELF.[29] This enhancement is linked to Fe^{2+}, which catalyzes ROOR degradation and organic radical formation.[79,80] Mishra et al. also highlighted the synergistic regulation of nitrotyrosine formation by OH and NO_2, impacting protein modification.[81] Additionally, Lelieveld et al. reported elevated endogenous nitric oxide levels, leading to increased OH production via peroxynitrite formation.[82] From this, it is evident that while many studies simulate the ROS cycling process in the epithelial lining fluid using dynamic models, the mechanism of ROS generation remains incomplete due to the complexity of air pollutant components, with only a few models considering cellular feedback mechanisms.[78] Therefore, cellular feedback mechanisms and complex chemical reaction processes may be crucial for kinetic modeling studies.

3.2. Practical Applications of the Model

KM-SUB-ELF has found significant applications in subsequent research. For example, Lakey et al. revealed that in heavily polluted environments, elevated levels of metals, particularly copper and iron, quinones, and SOAs contribute to ROS levels in the ELF, surpassing those found in healthy individuals. Additionally, studies across various global regions indicate that aerosol-induced ROS levels in polluted cities are markedly higher compared to those in pristine rainforests.[30] Furthermore, Dovrou et al. identified that under clean urban conditions, H_2O_2 primarily originates from the gas phase, circulating blood, and cellular layers, with minimal contributions from O_3- and $PM_{2.5}$-induced H_2O_2. In urban pollution scenarios, environmental gas-phase H_2O_2 emerges as the predominant factor increasing H_2O_2 levels in the ELF. Calculations across six typical atmospheric settings revealed

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the lowest production of H_2O_2 and OH in remote, rural, and indoor environments. Elevated environmental gas-phase H_2O_2 concentrations in polluted urban air may slightly elevate H_2O_2 concentrations in the ELF, whereas high levels of $PM_{2.5}$ could significantly enhance OH production. In highly clean indoor spaces, elevated environmental gas-phase H_2O_2 can regulate H_2O_2 concentrations in the ELF and promote OH production.[18] Additionally, Lelieveld et al. discovered that widespread increases in endogenous nitric oxide concentrations in diseased individuals can augment OH production through peroxynitrite formation. This newly identified mechanism elucidates the vulnerability of diseased individuals to air pollution.[82] Moreover, Mishra et al. found that OH and NO_2 synergistically elevate the nitrotyrosine (Ntyr) content in proteins, thereby modifying them. Severe air pollution conditions lead to a significant increase in Ntyr content.[81] Fang et al. quantified the production rates and concentrations of ROS in different regions of the ELF, highlighting higher ROS concentrations in the extrathoracic region compared to those in the bronchial and alveolar regions. Additionally, biomass burning significantly increases ROS production due to HULIS during winter.[15] These applications have provided valuable insights into the complex multiphase chemical processes and health effects occurring within the ELF.

4. HAZARDS OF ROS ON HUMAN HEALTH AND PATHOGENIC MECHANISMS

The generation of ROS through $PM_{2.5}$ and O_3 not only triggers lung inflammation and oxidative stress but also systemically disseminates via the circulatory system in a similar way. ROS can affect various cell types including neurons, lung epithelial cells, and vascular endothelial cells, crossing the blood−brain barrier (BBB) and contributing to a wide spectrum of health conditions including respiratory, cardiovascular, and central nervous system disorders.[83−86] To elucidate the intricate relationship between ROS and disease, we illustrate these complex physiological processes in Figure 3.

4.1. Respiratory System

Atmospheric pollution significantly impacts the human respiratory system by inducing inflammation and oxidative stress within the respiratory tract,[87] which results in various lung diseases, including chronic obstructive pulmonary disease (COPD),[88] asthma,[89] respiratory infections,[90] and lung cancer.[91] Studies have demonstrated that an elevation of 10 $\mu g/m^3$ in $PM_{2.5}$ levels substantially increases the risk of asthma development in children. Similarly, a comparable increase of 10 $\mu g/m^3$ in O_3 concentration results in a 0.55% mortality in respiratory disease mortality rates.[92,93]

The assault of ROS triggered by $PM_{2.5}$ and O_3 on airway epithelial cells triggers the activation of inflammatory cells, notably alveolar macrophages.[94−96] Excessive ROS also impair the antioxidant defensive systems,[97] reducing the activity of bronchial epithelial cells and alveolar cells in the lung, thereby damaging cell membranes.[98,99] This cascade ultimately stimulates and damages various cell types, leading to inflammation and oxidative stress. Specifically, $PM_{2.5}$ induces ROS generation in response to lung epithelial lining fluid, triggering upregulation of inflammatory factors such as interleukin-6 (IL-6), interleukin-8 (IL-8), and nuclear factor kappa B (NF-κB).[100] Animal model studies suggest that $PM_{2.5}$ causes abnormal expression of nuclear factor erythroid 2-related factor 2 (Nrf2), which in turn inhibits the down-regulation of antioxidant gene expression, thereby promoting oxidative stress.[101] Furthermore, $PM_{2.5}$ activates the transforming growth factor beta (TGF-β1)/ small mother against decapentaplegic (Smad) pathway, which enhances NF-κB activation, causing an inflammatory response and ultimately leading to lung function impairment in mice.[102] Additionally, O_3 oxidizes membrane lipids and proteins of epithelial cells and macrophages, generating hydroperoxides.[99] This process promote autophagy and the expression of inflammatory factors such as IL-1, IL-1β, and interleukin-18 (IL-18), contributing to lung injury.[103] These mechanisms collectively highlight how atmospheric pollutants such as $PM_{2.5}$ and O_3 disrupt respiratory health through inflammation and oxidative stress.

4.2. Cardiovascular System

Air pollutants, specifically $PM_{2.5}$ and O_3, not only exert a profound impact on lung health but also contribute to the development of cardiovascular diseases, especially in vulnerable populations.[104,105] Epidemiological studies have established connections between air pollutants and cardiovascular diseases, including coronary artery disease,[106−108] cardiac arrhythmia and arrest,[109−111] heart failure,[112,113] cerebrovascular disease,[114−116] peripheral arterial disease,[117,118] and venous thromboembolism.[119]

$PM_{2.5}$ and O_3 deposit in the lungs, inducing the generation of ROS and inflammatory factor.[120] Immediately, some pollutants and inflammatory factor enter the cardiovascular system and undermine the tight junctions of epithelial cells (ECs), thereby disrupting the blood−brain barrier and ultimately leading to increased vascular permeability, DNA damage, mitochondrial dysfunction, and other physiological processes occurring.[121,122] Furthermore, inflammation and ROS lead to the dysfunction of vascular endothelial cells, and $PM_{2.5}$-induced superoxide inhibits vasodilatation caused by reacting with NO.[123−126] Toxicological studies in mice propose that $PM_{2.5}$ induces ROS and activates extracellular signal-regulated kinase (ERK)/protein kinase B (AKT) and NF-κB pathways, fostering inflammation and cardiovascular dysfunction.[122,127] Although O_3 cannot enter the blood circulation through penetrating the respiratory epithelial cells,[8] ROS, inflammatory factors, and oxidation products produced by O_3 can through the air−blood barrier, thus causing damage to vascular cells. Research has shown that short-term O_3 exposure correlates positively with systemic inflammatory biomolecules, like C-reactive protein (CRP),[128,129] immune cells,[130,131] inflammatory cytokines (IL-6,[132] IL-8,[133] TNF-β),[134] and monocyte chemoattractant protein-1.[130] These alterations in physiological processes are associated with cardiovascular damage.

4.3. Central Nervous System

Additionally, air pollution severely impacts the respiratory and central nervous systems, and it is also linked to neurological dysfunction.[135] High concentrations of $PM_{2.5}$ or O_3 have been associated with increased incidence of Alzheimer's disease, Parkinson's disease, and cerebrovascular diseases and may also lead to abnormal neurocognitive functions.[136−139] Two studies have shown that for every 10 $\mu g/m^3$ rise in $PM_{2.5}$, the risk of stroke increases by 0.69%. Furthermore, with every 10 $\mu g/m^3$ increase in O_3, the risk of recurrent stroke subtypes increases by approximately 12%, and the risk of large artery stroke increases by around 8%.[140,141]

$PM_{2.5}$ and O_3 have been found to activate microglia and astrocytes, thereby promoting inflammation and oxidative

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stress in both human and rodent research models. Long-term exposure to ambient air pollution seems to increase the levels of certain proinflammatory markers such as cyclooxygenase 2 (COX2), IL-1β, inducible nitric oxide synthase (iNOS), and monocyte differentiation antigen CD14 in the human brain.[142] This elevation potentially leads to neuroinflammation, neurodegeneration, and breakdown of the blood−brain barrier.[143] The primary mechanisms of $PM_{2.5}$-induced brain damage are inflammatory responses and oxidative stress.[144−146] *In vivo* studies have found that exposure to $PM_{2.5}$ leads to the activation of microglia, inflammatory responses (IL-1β and TNF-α), and neuronal atrophy.[147] Additionally, reactive oxygen species (ROS) generated by $PM_{2.5}$ damage biological macromolecules, disrupt lipid metabolism, and induce brain inflammation by releasing interferon-γ (IFN-γ) and TNF-α.[148] Although O_3 cannot directly pass through cells into the blood circulation, it reacts with antioxidants in epithelial fluid to produce a large amount of ROS, which enters the whole body through circulation and causes inflammation and oxidative stress.[86,149] Animal studies have also shown that ROS increase promotes the expression of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α and disrupts communication between neurons and neuroglial cells in rats, leading to nerve injury.[150]

5. CONCLUSIONS AND PERSPECTIVES

The health effects caused by $PM_{2.5}$- and O_3-induced ROS can be assessed by using various acellular assays. Multiphase chemical process simulations enhance our understanding of how ROS circulate in the lungs. For $PM_{2.5}$, however, different precursor substances and chemical reaction processes can lead to compositional changes, such as the complex formation pathway of SOAs.[151] In terms of the components of the particulate matter, different components may be accompanied by different health effects. For example, the concentration of black carbon is related to the occurrence of cardiovascular, respiratory, and nervous system diseases, but the pathogenic mechanism is still unclear.[152] Thus, understanding the intricate response mechanisms and competitive pathways among single and multiple species in the ELF is essential. Currently, most acellular methods for measuring OP use SLF, potentially ignoring differences from the real physiological environment. Moreover, the complexity of cellular systems complicates the accurate reproduction of biochemical changes induced by various reactions within the cells. Current kinetic models also neglect substance exchanges between aqueous and gas phases,[80,153] including the impact of endogenously produced substances (such as endogenous ROS) through reactions.[82] For O_3, the mechanism by which it generates ROS in the ELF is still not fully understood. Therefore, future work should integrate more physiological experimental data and combine cellular and acellular approaches to deepen our understanding of the intricate interplay between air pollutants and human health.

Air pollutants induce oxidative stress by generating ROS, which subsequently initiate various pathological processes. However, the precise physiological mechanisms underlying these effects remain unclear.[11] For example, the process by which air pollutants enter cells is not yet fully understood. Intact cell membranes play a crucial role in controlling the active and passive transport of substances across them,[154] while membrane proteins facilitate the orderly exchange and transport of specific substances inside and outside the cell.[155] Yet, the specific pathways through which air pollutants enter cells, interact with receptors, and affect transport mechanisms are not well-defined. Further investigations need to clarify the toxic effects of various pollutants and their interactions and to determine whether their physiological impacts go beyond inflammation and oxidative stress in cells. Notably, ROS, being a nonselective oxidant, impair a variety of organic biomolecules,[156] so we speculate that atmospheric ROS may impair the microorganisms adsorbed on $PM_{2.5}$, affecting the lipids and proteins of cellular membranes and other organelles, leading to the inactivation of those creatures. However, this intriguing hypothesis requires further verification.

In summary, current research predominantly focuses on multiphase chemical processes in the lungs, while our understanding of similar processes in the brain, cardiovascular, and other systems remain limited. Future studies should integrate disciplines such as atmospheric chemistry, toxicology, epidemiology, and biomedical sciences to explore how air pollutants undergo multiphase chemical processes across various bodily systems. This approach aims to clarify the potential chemical mechanisms and molecular pathways involved in disease development. Through comprehensive interdisciplinary research and consideration of various factors, effective strategies, as well as air quality standards for environmental management, can be proposed to mitigate the occurrence and progression of related health issues.

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Author Contributions

K.L. and H.S. conceived the study. Q.W. summarized the influences of multiphase ROS on human health and wrote the manuscript. H.D., S.G., M.Y., and Y.W. provided guidance on the manuscript and made modifications to the framework.

Notes

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