THE RELATIONSHIP BETWEEN PULMONARY SURFACTANT AND POLLUTANTS

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Abstract. Air pollutants impact on the pulmonary surfactant (PS) systems and its implications on disease treatment are investigated in this review. Various pollutants, including NO_2, SO_2, CO_2, O_3, tobacco smoke, silica, diesel exhaust, nanoparticles, and fibrous materials such as asbestos, have been identified as influencing the structure and function of surfactants. Acute and chronic diseases such as hypertension, heart disease, cancers, stroke, and respiratory diseases has been linked to long-term exposure to these pollutants. NO_2 affects lungs macrophage membranes and inhibits phagocytosis, whereas SO_2 alters alveolar properties, increasing vascular permeability and causing structural damage to cell membranes. Highly reactive compounds such as O_3 primarily affect the upper respiratory tract, in contrast, compounds that are less reactive like NO_2 can infiltrate the alveoli. Coming into contact with contaminants results in the build-up of surfactant phospholipids and proteins within the fluid collected from bronchial alveolar lavage, altering their structure and biological activity, particularly under oxidative stress. NPs, including metal oxides, polymers, and carbon particles, interact with PS, affecting their deposition and clearance in the lungs. Exposure to pollutants initiates inflammatory signaling, cytokine release, and oxidative stress in epithelial cells of lung, leading to DNA damage and apoptosis. Volatile organic compounds (VOCs) have been linked to adverse health effects such as lung cancer, tissue damage, and pulmonary function impairment. Both in vivo and in vitro research have shown that pollutants cause oxidative stress, fibrosis, and carcinogenesis. This review underscores the requirement of further research, and policy implementation to overcome adverse effects of environmental pollutants on public health. This study provides valuable insights for researchers and policymakers to develop more effective guidelines for pollution control and public health protection.
Keywords: *pollutant, PS, NO_2, SO_2, carbon nanotube, micro-plastic nanoparticle, residual oil fly ash*

Introduction

Pulmonary surfactant is a lipid-protein complex that covers the alveolar epithelium and allows the lung's gas-exchange surfaces to operate properly. Its primary role is to generate a surface-active layer, mostly consisting of phospholipids, which covers the air-liquid contact within the alveoli. This surfactant decreases surface tension (γ) during inhalation, reducing the mechanical effort required for breathing. During exhalation, it further lowers γ to very low levels, which helps maintain alveolar stability at small lung volumes and prevents fluid accumulation that could lead to pulmonary edema (Possmayer, 2004). Deficiency of pulmonary surfactant, which is typically detected in preterm babies, can lead to respiratory distress syndrome (RDS), a substantial cause of morbidity and death in newborns (Pfister and Soll, 2005). Reduced surfactant activity plays an important role in the course of acute lung injury (ALI) and acute respiratory

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distress syndrome (ARDS), both of which are significantly related to high rates of morbidity and death (Lewis and Veldhuizen, 2003). The major biophysical job of a pulmonary surfactant is to reduce surface tension at the air-liquid interface, which reduces breathing labor and prevents alveolar collapse during exhalation. For surfactant films to function effectively, they must exhibit three critical properties: the capacity to rapidly adhere to the boundary between air and water, to undergo efficient compression as the lung deflates, and to re-expand effectively during inhalation (Goerke, 1998). These functional properties of PS arise from the finely tuned interactions between their diverse lipid components and the associated hydrophobic surfactant proteins (SPs) (Guo et al., 2019).

Air pollution constitutes a critical environmental concern worldwide, with disproportionately severe effects in developing regions, where it represents a major determinant of adverse public health outcomes (Guo et al., 2019). Tropospheric ozone (O_3), generated as a secondary photochemical product of ambient air pollution, is a potent oxidizing agent with well-established deleterious effects on the bronchial epithelium. The coexistence of NO_2 and O_3 in the atmosphere is of particular concern, as their interactions contribute to the depletion of antioxidant defenses within respiratory tract lining fluid (RTLF), a phenomenon specifically pronounced within vulnerable populations, including individuals with asthma (Kelly et al., 1999). Particulate matter (PM), produced through both natural phenomena and human activities, is among the major contributors to atmospheric pollution (Madureira et al., 2016); Fine particulate matter ($PM_{2.5}$) with aerodynamic sizes less than 2.5 μm is a major problem. These ultrafine particles represent substantial health hazards because they can penetrate deep into the respiratory tract and produce systemic toxic effects (Jordanova et al., 2012), thereby contributing to the development of respiratory disorders, pulmonary cancers, and cardiovascular as well as cerebrovascular diseases (Hadei et al., 2017).

Toxicological investigations have revealed several cellular mechanisms underlying the harmful effects of $PM_{2.5}$, involving the initiation of cell death, an overproduction of reactive oxygen species, harm to DNA, changes that can lead to mutations, and by promoting the elevated production of inflammatory cytokines (Chen et al., 2019). Numerous environmental and work-related substances, include ozone, nitrogen dioxide, high levels of oxygen, emissions from diesel engines, smoke from tobacco, silica, and fibrous substances like asbestos, have been thoroughly studied for their potential to undermine the structural stability and operational efficacy of the pulmonary surfactant system (Müller et al., 1998). Exposure to environmental pollutants via inhalation has been strongly implicated in the onset and progression of diverse pathological conditions and illnesses affecting the respiratory system, include acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and lung cancer (Fan and Liu, 2021). Inhaled particles can penetrate deep into the respiratory passageways and concentrate in the alveoli, where they interact with the lung surfactant layer (Manojkumar and Srimuruganandam, 2021). Moreover, particulate matter can alter the chemical composition and lateral organization of the lung surfactant (LS) film, thereby compromising its functional efficiency. These interactions may activate pathways that facilitate particle translocation beyond the alveolar space, enabling their distribution to other tissues and organs (Mercer et al., 2008; Muthusamy et al., 2016) as shown in *Fig. 1*. Therefore, this review underscores requirements of further research and the enforcement of effective policies aimed at reducing the detrimental impact of environmental pollutants on public health. It also provides valuable insights for

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researchers and policymakers to develop more effective guidelines for pollution control and public health protection.

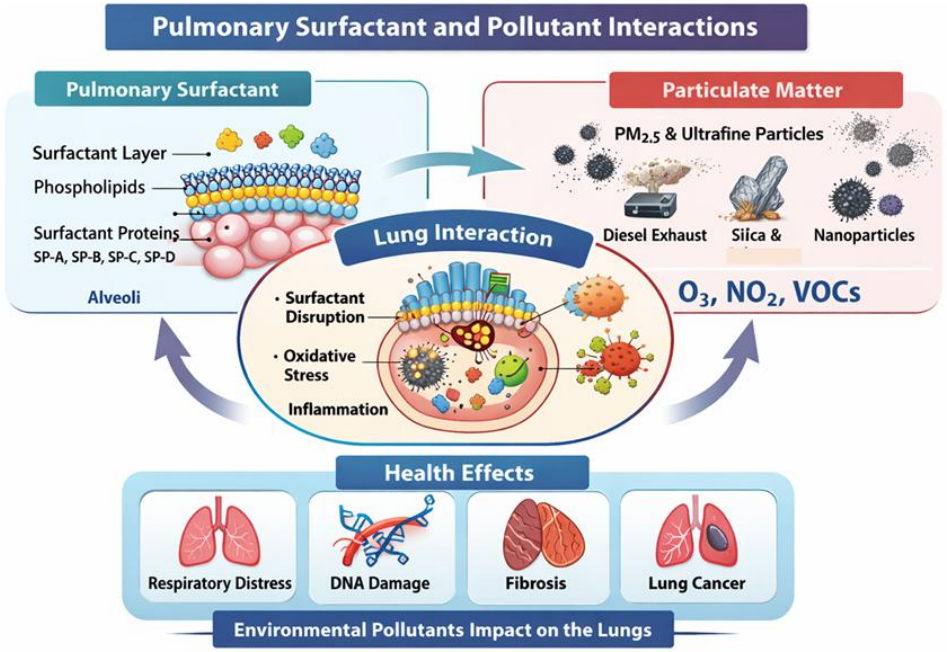

Figure 1. *Schematic illustration of pulmonary surfactant and pollutant interaction*

Pulmonary surfactant

In terms of composition, PS is largely made up of zwitterionic phospholipids, which account for around 80%, coupled with neutral lipids like cholesterol, which account for roughly 10%, and a little amount (approximately 8-10%) constituted of both hydrophobic and hydrophilic surfactant proteins (Goerke, 1998; Pérez-Gil and Keough, 1998). The hydrophilic surfactant proteins SP-A and SP-D play an important part in the alveoli's innate immune defense systems. They are responsible for recognizing infections, aiding their clearance, and controlling inflammatory reactions (Serrano and Pérez-Gil, 2006). In contrast, the hydrophobic surfactant proteins SP-B and SP-C, in coordination with surfactant lipids, are vital for maintaining the core biophysical properties and functional stability of pulmonary surfactant (Autilio and Pérez-Gil, 2019). Functional PS films are characterized by three critical biophysical properties: Rapid absorption at the interface between air and liquid, effective compression while exhaling, and efficient expansion during inhalation are key characteristics. These attributes are influenced by the precisely adjusted interactions among different lipid types and hydrophobic surfactant proteins (*Table 1*). Among the lipid ingredients, the saturated zwitterionic phospholipid di-palmitoyl phosphatidyl choline (DPPC) is the main component, accounting for approximately 40% of the total mass, and is principally responsible for the considerable drop in surface tension assisted by the surfactant system (Casals and Cañadas, 2012).

In mammals, the lungs represent the only internal organ directly exposed to the external environment, rendering them highly susceptible to the harmful effects of air pollution (Chen and Lippmann, 2009). When inhaled, pollutants reaching the alveolar region directly interact with the pulmonary surfactant, a thin film that lines the air-liquid interface of the alveoli (Valle et al., 2015). Once inhaled pollutants penetrate the alveolar

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region, they directly encounter the PS, this creates a thin layer that covers the air-liquid boundary of the alveoli and is crucial for decreasing surface tension, a function that is necessary for proper breathing (Yang et al., 2018). Consequently, the engagement of inhaled pollutants with a polystyrene (PS) film may modify its interfacial characteristics between air and liquid, which could result in the onset of a range of respiratory ailments. Prior research has shown that specific nanoparticles, including carbon-based substances and silica, have the ability to interfere with PS by altering its surface tension and phase behavior (Zhao et al., 2019b). Several heavy metal carcinogens, including arsenic (As), lead (Pb) and cadmium (Cd), are consistently detected in airborne particulate matter across different regions of the world (Boman et al., 2010). When inhaled particles are deposited on the lung surface, the associated heavy metals can be released into the alveolar region and subsequently enter the bloodstream, posing significant risks to human health (Zhang et al., 2019). However, understanding PS-pollutant interactions is crucial for elucidating respiratory toxicity mechanisms, particularly nanoparticle and heavy metal exposure, and for developing strategies to mitigate air pollution-induced lung diseases.

Table 1. *Surfactant proteins with its features and functions*

Protein	Features	Functions	Ref
SP-A (i) [a]	650 kDa, octadecameric glycoprotein, acidic	It enhances pathogen and immune effector clearance, inhibits secreted phospholipase A2 activity and helps maintain surfactant integrity during pulmonary injury.	(Voss et al., 1988, Chabot et al., 2003, Wang et al., 2020)
SP-B (o) [a]	18 kDa, 79–amino acid homodimer stabilized by disulfide bonds	It facilitates phospholipid adsorption to the interface and raises fatty acid collapse pressure, thereby preventing "squeeze-out."	(Wang et al., 2020, Hawgood et al., 1998)
SP-C (o) [a]	4.2 kDa, a nonpolar, α-helical protein composed of 35 amino acids	It promotes phospholipid stability and increases the viscosity of the interfacial layer.	(Wang et al., 2020, Johansson et al., 1994)
SP-D (i) [a]	43 kDa, a glycoprotein organized as dodecamer composed of four trimers	It regulates surfactant metabolism and enhances the uptake of pathogenic bacteria by epithelial cells.	(Wang et al., 2020, Lu et al., 1992)

Note= "i" represents hydrophilic and "o" represents hydrophobic

Composition of pulmonary surfactant

PS is a complex mixture of lipids and proteins synthesized and secreted by type II alveolar epithelial cells (Schulze et al., 2011; Finot et al., 2013). It is a complicated mixture of approximately 85–90% of phospholipids, along with a small amount of cholesterol and 10% proteins (DiPasquale, 2022). PS is made up of four distinct surfactant proteins: SP-A, SP-B, SP-C, and SP-D. All of these proteins are vital for preserving alveolar stability and play a key role in strengthening the body's innate defense mechanisms. When lung volumes are at their lowest, surfactant appears as a continuous thin layer, measuring around 0.5–1 μm in thickness, covering the plasma membrane of the cells lining the alveoli. Nearly 90% of the surfactant's total mass consists of lipids (Veldhuizen et al., 1998), with zwitterionic phosphatidylcholine (PC) lipids being the most prevalent type, making up about 80%. Approximately half of this is DPPC. However, in heterothermic mammals, the amount of DPPC is relatively small. The

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predominant unsaturated phosphatidylcholine species is palmitoyloleoylphosphatidylcholine (POPC). Negatively charged phospholipids, primarily phosphatidylglycerol (PG) and phosphatidylinositol (PI), which are largely unsaturated, account for approximately 8–15% of the total phospholipid content. Overall, lung surfactant generally maintains a relatively balanced ratio of saturated to unsaturated lipid types, although variations exist among different species. Cholesterol constitutes roughly 5–10% of the total mass, while smaller amounts of other components such as phosphatidylethanolamine (PE), free fatty acids, and glycolipids are also found in the mixture (Suri et al., 2012). L-α-DPPC represents the predominant component of pulmonary surfactant, accounting for approximately 41% of the total volume. It has a remarkably low critical micelle concentration (0.46 nmol/L), which suggests that, within the alveolar lining, DPPC is present in the form of micelles that contribute to structural and functional stability of the surfactant (Morley et al., 1978) (*Table 2*).

Table 2. *Composition of pulmonary surfactants and their functional role*

Component Type	Specific Component	Approx. Proportion (% by mass)	Functional Role	Ref
Phospholipid	Dipalmitoyl phosphatidylcholine (DPPC)	~40%	Major surface-active lipid; responsible for minimal surface tension	(Holm et al., 1996)
Phospholipid	Unsaturated phosphatidylcholine (PC)	~15%	Enhances fluidity and dynamic response of the surfactant film	(Bernhard et al., 2001)
Phospholipid	Phosphatidylglycerol (PG)	~10%	Supports lamellar body formation; aids SP-B/SP-C activity	(Hallman et al., 1985, Hite et al., 2005)
Phospholipid	Phosphatidylinositol (PI)	~2%	Participates in signal transduction and immune modulation	(Spengler et al., 2018)
Phospholipid	Phosphatidylethanolamine (PE)	~3%	Contributes to membrane curvature and lipid packing	(Batenburg and Haagsman, 1998)
Neutral Lipid	Cholesterol	~10%	Regulates the fluidity and phase behavior of surfactant film	(Keating et al., 2007)
Neutral Lipid	Triglycerides	<1%	Minor component; potential energy reservoir or surfactant turnover factor	(Hallman et al., 1985, Maher et al., 2023)
Protein (Hydrophobic)	Surfactant Protein B (SP-B)	~1%	Facilitates spreading, adsorption, and bilayer-to-monolayer transition	(Pérez-Gil, 2008)
Protein (Hydrophilic)	Surfactant Protein A (SP-A)	~4%	Innate immune defense; regulates surfactant homeostasis	(Nayak et al., 2012)
Lipid Derivative	Lysophosphatidylcholine (LPC)	<1%	Involved in surfactant remodeling and degradation pathways	(Agassandian and Mallampalli, 2013)
Lipid Derivative	Sphingomyelin	<1%	Potential structural role in surfactant membranes	(Agassandian and Mallampalli, 2013)

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Even slight molecular modifications can alter the hydrophobic or hydrophilic properties of surfactant end groups, while variations in the surrounding molecular environment can further influence their bulk characteristics. Pulmonary surfactant (PS) is a surface-active biological material that forms a thin fluid layer on the alveolar epithelium, resulting in films at the air-liquid interface. This film efficiently decreases surface tension, allowing regular breathing. PS is mostly made of lipids, which account for approximately 90% of its overall weight. The most prevalent of them is DPPC, a saturated phospholipid that accounts for around 40% of the total weight. Other lipid components include anionic phospholipids such as phosphatidylglycerol (PG), phosphatidylinositol (PI), and phosphatidylserine (PS), which account for around 15% of the total weight, as well as neutral lipids such as cholesterol, which account for about 8%. These elements work together to ensure the surfactant system's structural integrity and functional efficacy (Herman et al., 2022), as shown in *Fig. 2*. For elucidating the detailed composition of PS is essential for understanding its structural stability, biophysical performance, and susceptibility to environmental pollutants that may disrupt alveolar function.

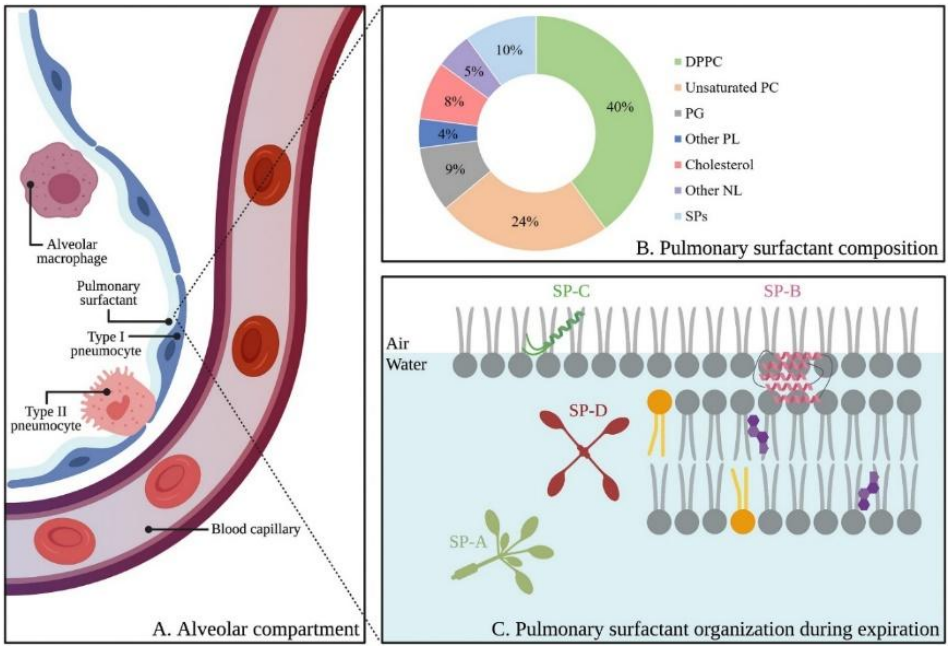

Figure 2. *An illustration of the alveolar region depicts type I and type II pneumocytes, alveolar macrophages, and the pulmonary surfactant layer (A). The makeup of the surfactant, in terms of its proteolipid content, is illustrated as a percentage by weight (B). During expiration, the squeeze-out model illustrates surfactant organization and lipid–protein interactions, with saturated (gray), unsaturated (orange), and cholesterol (purple) lipids (C). PS organization during expiration (Herman et al., 2022)*

Multiple studies have demonstrated that alterations or deficiencies in PS proteins are closely associated with the development of interstitial lung diseases in both pediatric and adult populations (Garcia, 2011). Surfactant proteins are vital for maintaining the lung's protective and functional integrity. The hydrophobic proteins, SP-B and SP-C, are primarily responsible for organizing the surfactant structure and regulating its surface-active behavior. Conversely, the hydrophilic proteins SP-A and SP-D, collectively known

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as collectins, play a central role in the innate immune defense. They recognize and bind to specific carbohydrate motifs on the surfaces of bacteria, fungi, and viruses, facilitating pathogen clearance. Moreover, these collectins help modulate immune activity by balancing pro- and anti-inflammatory responses, ensuring optimal alveolar function and preventing excessive inflammation (Glasser and Mallampalli, 2012). SP-A, accounting for about 5% of the total surfactant mass, interacts with surfactant lipids to strengthen the structural stability and optimize the surface activity of the surfactant film (Casals, 2001). Despite its tiny presence (about 0.5% of the total surfactant weight), surfactant protein D (SP-D) is not related with lipids; rather, it plays an important function in immunological regulation and pathogen clearance. In contrast, the hydrophobic surfactant proteins B (SP-B) and C (SP-C), while present in modest amounts (about 2% by weight), are critical for surfactant functioning and performance at the air-liquid interface. SP-C deficiency causes severe respiratory dysfunction, but the lack of SP-B is fatal. SP-B, a member of the saposin protein family, contains 79 amino acids and has a net positive charge of +7. It has a characteristic saposin-like fold with four to five α-helices joined by flexible loops and stabilized by three intramolecular disulfide connections created by six conserved cysteine residues (Johansson et al., 1992). SP-B occurs as a covalently connected homodimer held together by an intermolecular disulfide bond containing the seventh cysteine residue. Unlike other members of the saposin family, SP-B is always linked with lipids, making chemical production particularly difficult.

Although the entire three-dimensional structure of SP-B has yet to be fully defined, extensive structural information regarding its N-terminal region is known (Kurutz and Lee, 2002). Structural information on SP-B has largely been derived from studies of peptide fragments, particularly a construct combining its N- and C-terminal regions (residues 8–25 and 63–78), commonly known as “mini-B.” (Sarker et al., 2007) ,While the structural features of SP-B fragments have been well characterized, SP-C is identified as an extremely hydrophobic protein composed of 35 amino acids with a net positive charge of $^{+}3$. Structurally, SP-C adopts an α-helical conformation spanning residues 9 to 34 (Johansson et al., 1994). Besides, surfactant proteins are indispensable for preserving pulmonary stability, immunity, and respiratory mechanics. Understanding their structural roles and pathological alterations provides critical insight into mechanisms underlying interstitial lung diseases and surfactant dysfunction.

Pulmonary surfactant function

The primary purpose of PS is to maintain low surface tension throughout the respiratory cycle by rapidly spreading across the air-liquid interface, achieving near-zero tension during exhale and preventing excessive tension increases during intake. Surfactant lipids and proteins are produced by alveolar type II epithelial cells and released as lamellar bodies (LBs), which reorganize into tubular myelin (TM), an organized lipid lattice. Surfactant protein A (SP-A) plays an important role in aiding the structural transition (Korfhagen, 2001).

The predominant phospholipid in PS is DPPC, which is commonly referred to as lecithin. Its amphiphilic nature, with a hydrophilic head group and hydrophobic tails, makes it inherently surface-active. However, DPPC alone is inefficient at adsorbing to the air-liquid interface and remains in a gel phase at physiological temperatures. To overcome this limitation, the inclusion of unsaturated phospholipids and cholesterol introduces greater fluidity into the surfactant mixture, thereby facilitating more effective adsorption and dynamic behavior at the interface (Missana et al., 2008). The alveolar

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lining layer is a thin fluid that covers the whole alveolar surface of mammals' lungs. This layer is made up of an aqueous subphase (hypophase) protected by a phospholipid-rich coating (Weibel and Gil, 1968). The PS film primarily lowers alveolar surface tension, reducing the energy required for lung inflation and enhancing pulmonary compliance. In conducting airways, surfactants additionally maintain airway patency by stabilizing the lining fluid and lowering mucus surface tension, preventing bronchiolar adhesion and ensuring unobstructed airflow during respiration (Enhorning et al., 1995) as shown in *Fig. 3*. PS plays a pivotal biophysical role in maintaining alveolar stability by regulating surface tension. Understanding lipid-protein interactions, particularly DPPC dynamics and structural transitions, is essential for elucidating respiratory mechanics and surfactant-related pulmonary dysfunction.

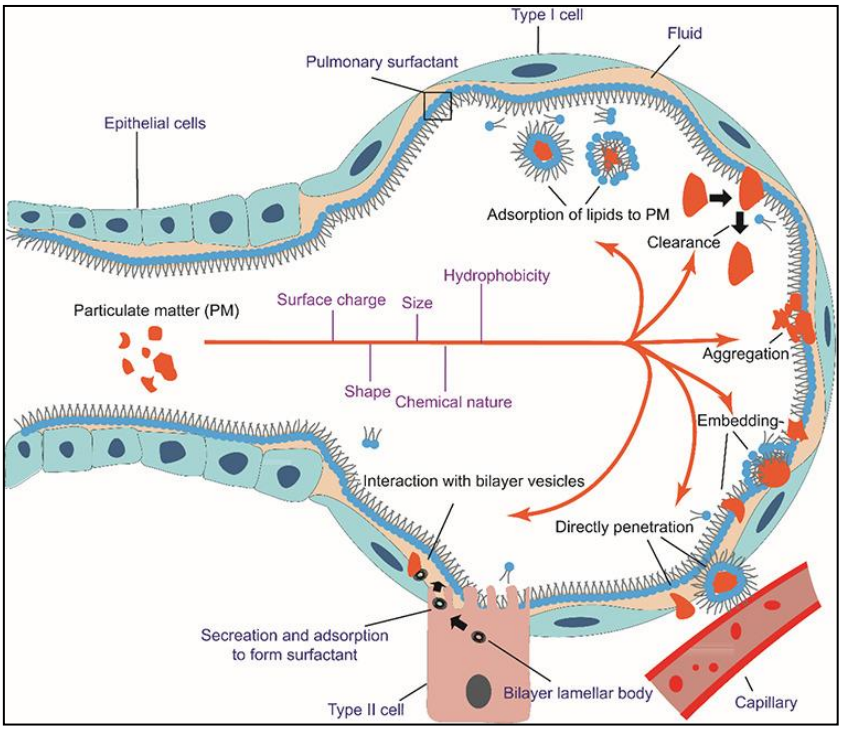

Figure 3. *Overview of pulmonary surfactant with particulate matter adopted from (Wang et al., 2020)*

Therapeutic role of PS in various pulmonary disorders

The PS system is essential for maintaining efficient respiratory function by reducing surface tension at the air-liquid interface, thereby preventing alveolar collapse (atelectasis) and minimizing the work of breathing. PS plays a crucial role in preventing alveolar collapse, thereby ensuring alveolar stability throughout the respiratory cycle. This decrease in surface tension not only minimizes the risk of atelectasis but also decreases the mechanical effort required for lung inflation, contributing to efficient gas exchange and overall respiratory function (Notter, 2000). Insufficient lung surfactant causes undeveloped lungs, resulting in newborn respiratory distress syndrome (NRDS), a primary cause of mortality in preterm babies until surfactant treatment was introduced in the early 1990s. Early physiological investigations discovered the critical link between surface tension and pulmonary elastic characteristics, defining the structures, functions,

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and genesis of the alveolar lining. These groundbreaking findings established the groundwork for comprehending the biophysical function of PS in preserving alveolar stability and supporting respiratory activity (Pattle, 1955). The connection between surfactant deficiency and NRDS in humans was later confirmed (Avery and Mead, 1959). Shortly after, a similar respiratory disease was noticed in foals, and their surfactant system was later researched by some of the same researchers, who first characterized it in human medicine (Lester, 2003). Since the initial identification of surfactants, significant progress has been made in understanding their composition and functionality, with particular surfactant proteins being recognized for their crucial roles in both biophysical activity and immune regulation (Kuroki and Voelker, 1994). Surfactant dysfunction has been linked to the development of different alveolar and airway diseases (Bernhard et al., 2001). Moreover, studies have shown that the composition and activity of surfactants differ depending on the species, stage of lung maturation, and specific physiological requirements (Hobo et al., 2001). However, there is scant evidence on surfactant modifications in spontaneously occurring disorders in veterinary medicine (Danlois et al., 2003; Christmann et al., 2008). Although previous research has shown that surfactants contribute to several lung homeostatic functions such as facilitating gas exchange and mediating host defense, their primary job is to reduce alveolar surface tension. Furthermore, because oxygen and carbon dioxide must diffuse through the surfactant coating at the air-liquid interface to reach the pulmonary parenchyma, any changes in surfactant amount, content, or structural organization can greatly impact the efficiency of gas exchange (Olmeda et al., 2010). By lowering alveolar surface tension, the surfactant monolayer at the air–liquid interface creates a barrier between the aqueous hypophase and the airspace. In order to preserve homeostasis, surfactant is recycled or broken down when it is produced by alveolar type II cells as lamellar bodies and arranged into tubular myelin. Despite having opposing impacts on the size of the surfactant pool, impaired clearance in pulmonary alveolar proteinosis (PAP) or inadequate production in preterm newborns (NRDS) impair gas exchange and increase breathing effort (Milad and Morissette, 2021), as shown in *Fig. 4*. PS therapy represents a cornerstone in managing respiratory disorders associated with surfactant deficiency or dysfunction. Understanding its physiological mechanisms and clinical applications is crucial for improving treatments for NRDS, PAP, and other pulmonary diseases.

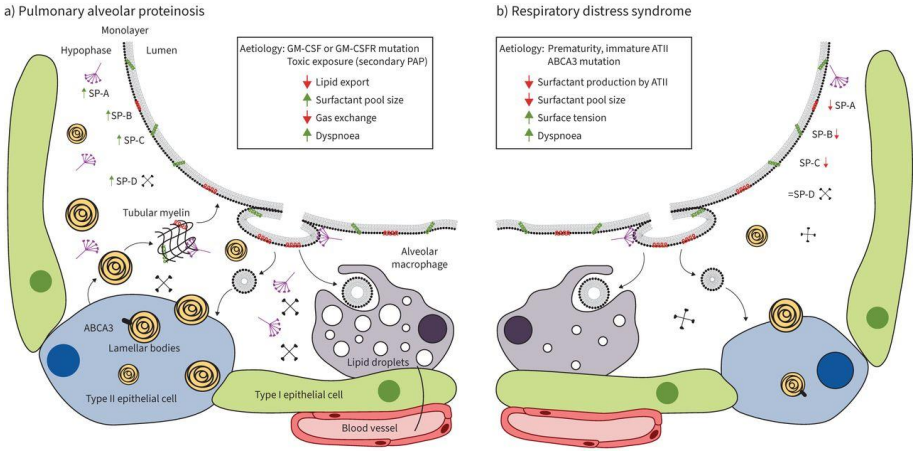

Figure 4. *Diagrammatic illustration of the alveolus and surfactant homeostasis in primary surfactant-associated disorders (Milad and Morissette, 2021)*

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Interactions between air pollution and pulmonary surfactant

Air pollution constitutes a momentous worldwide public health issue, playing a considerable role in the incidence and death rates linked to respiratory and cardiovascular illnesses (Li et al., 2019). It is important to highlight that extensive epidemiological and experimental evidence has demonstrated a strong association between long-term exposure to PM and the onset of multiple acute and chronic diseases. These include respiratory issues, cardiovascular conditions, high blood pressure, ischemic stroke, and specific forms of cancer (Charrier et al., 2014). The residual oil fly ash (ROFA), produced from low-grade oil combustion, contains metal salts (Fe, V, Ni), silicates, sulfates, and carbon- and nitrogen-based compounds (Mu et al., 2019). When lung epithelial cells and ROFAs interact, phosphorylation-dependent inflammatory pathways are started, which activate transcription. Pro-inflammatory cytokines such IL-8, IL-6, tumor necrosis factor (TNF), and macrophage inflammatory protein-2 (MIP-2) are produced and secreted in response to this process (Silbajoris et al., 2000). Moreover, metals in ROFAs promote the generation of cellular ROS, including H_2O_2, O_2, OH, and NO, via mitochondrial signaling pathways and iron redox activity (Dreher et al., 1997). ROFA-induced expression of epithelial inflammatory mediators and ROS generation contribute to lung surfactant inactivation. Chronic air pollutant exposure in rats has also been linked to reduced surfactant protein expression. Oxidative inactivation of surfactants is linked to lipid peroxidation and protein carbonylation (Andersson et al., 1999). Reactive oxygen species (ROS) are produced when hydrogen peroxide is exposed to A549 alveolar epithelial cells. These ROS damage DNA, trigger inflammatory signaling pathways, and start apoptotic cell death (Holm et al., 1991). Although it is clear that hydrogen peroxide and airborne pollutants have a detrimental effect on lung surfactant, it is unclear how precisely oxidative stress in epithelial cells affects surfactant characteristics (*Table 3*).

Table 3. *Interactions of air pollution and pulmonary surfactant*

Pollutant(s) Studied	Model/System Used	Key Findings	Ref
Diesel exhaust particles (DEP)	Human airway epithelial cells	DEP altered surfactant protein expression and impaired epithelial integrity.	(Jaspers et al., 2005)
PM2.5, ozone (O_3)	Mice (in vivo)	Combined PM2.5 and O_3 exposure reduced SP-A and SP-D expression, impairing innate immunity.	(Kierstein et al., 2006)
NO_2	Alveolar epithelial cell cultures	NO_2 exposure disrupted surfactant protein expression and caused oxidative stress.	(Li et al., 2024)
Carbon nanoparticles	Murine lung model	Carbon particles inhibited SP-A/SP-D function, reducing pathogen clearance.	(McKenzie et al., 2015)
Cigarette smoke extract	Human ATII cells	Smoke exposure reduced SP-B and SP-C levels, impairing surfactant function.	(Subramaniam et al., 1996)

The PS film in the alveolar lining lowers surface tension, thereby reducing breathing effort and preventing alveolar collapse, which is vital for normal lung function (Wüstneck et al., 2001). Consequently, interactions between PS and foreign substances, such as salts, can disrupt its stability and function (Christoforou et al., 2012), and inorganic gases (Podgórski et al., 2001) and particulate matter have received significant scientific attention (Kondej and Sosnowski, 2016). Disruption of surfactant in lung extracts leads

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to elevated surface tension. Numerous pollutants markedly alter the pulmonary surface lining; for example, inhalation of 15% CO_2 in guinea pigs induces acidaemia, atelectasis, and edema and increases surfactant surface tension (γ) (Scarpelli, 1977). Interactions between air pollutants and PS represent a critical mechanism underlying pollution-induced respiratory toxicity. Understanding how particulate matter, metals, and oxidative stress disrupt surfactant structure and function is essential for clarifying disease pathways and guiding preventive strategies.

Particulate matter and pulmonary surfactant interactions

PM adversely affects human health through both immediate and prolonged exposure. Brief exposure can initiate inflammatory responses in the respiratory system as well as within the blood (Salvi et al., 1999), On the other hand, prolonged exposure is strongly linked to higher death rates from lung cancer and cardiovascular disorders (Laden et al., 2006). The deposition of PM within the respiratory tract is primarily determined by particle size (Brain and Valberg, 1979) as shown in *Fig. 3*. However, smaller particles demonstrate higher overall and peripheral lung deposition, allowing them to penetrate more deeply into the distal airways (Usmani et al., 2005). In general, particles exceeding 10 μm in diameter are confined to the nasal and oral cavities, while PM_{10} particles (with an aerodynamic diameter of ≤10 μm) can penetrate into the trachea and bronchi, where they tend to deposit at airway bifurcation sites (Cormier et al., 2006). Among these particles, those larger than 8 μm are predominantly deposited in the upper airways (Mitchell et al., 1987). $PM_{2.5}$ and $PM_{0.1}$ particles are capable of reaching the nonciliated alveolar regions, resulting in deep lung deposition. Although particles smaller than 0.5 μm are typically exhaled after inhalation, $PM_{2.5}$ poses a particularly serious health threat, as particles of this size can persist within the respiratory tract, readily interact with cellular components, and translocate into the bloodstream and lymphatic system (Oberdörster et al., 2005).

A certain PM can be deposited within the PS and translocate across it. When penetration occurs, alveolar macrophages commence phagocytosis, resulting in the release of inflammatory mediators, including leukocytes and neutrophils that promote localized inflammation. The compromise of the surfactant film's integrity may additionally lead to mechanical injury to both surfactant and epithelial cells, which plays a role in the acute lung inflammation seen in both animals and humans after exposure to PM (Paunescu et al., 2019). Inflammation, which is the body's immune reaction to damaging factors, triggers cellular and molecular functions aimed at removing these threats and facilitating the healing of tissues (Chen et al., 2018) and is typically characterized by an increase in free cells, with a substantial proportion of neutrophils detected in the lavage fluid. If not properly controlled, this response may evolve into a chronic condition. For example, crystalline quartz induces persistent surface inflammation, increases pulmonary permeability, and stimulates type II cells to release plasma membrane components, leading to progressive tissue injury, whereas damage caused by amorphous ultrafine silica is generally reversible (Murphy et al., 1998).

The size of PM is a critical determinant of its behavior, distribution, and toxicological impact within the human body (Farina et al., 2011; Zhou et al., 2016). Small particles ($PM_{2.5}$, inhalable particles) with aerodynamic dimensions less than 2.5 μm can enter the lower respiratory tract deeply and build up in the alveoli (Falta et al., 2008). A significant number of research studies have shown that exposure to $PM_{2.5}$ is linked to various cardiopulmonary conditions, such as pneumonia, lung damage, and heart attacks

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(Donaldson et al., 2005). However, the exact processes by which $PM_{2.5}$ causes or worsens respiratory illnesses are not yet fully understood (Schleh et al., 2009). Once inhaled PM reaches the alveolar region, it first interacts with the PS lining the alveoli (Fan et al., 2011; Hu et al., 2013). Type II alveolar epithelial cells produce PS, a complex combination of proteins and phospholipids that has special surface-active qualities (Sweeney et al., 2016). At the alveolar air–liquid contact, it forms a thin layer and is crucial for lowering surface tension, which is necessary for effective respiration (Zuo et al., 2008). Consequently, the pulmonary surfactant (PS) film's air–liquid interfacial characteristics may be changed by the interaction of inhaled pollutants, which may result in a number of respiratory conditions. Research indicates that the bioavailability of heavy metals in particulate matter has a greater impact on health hazards than their overall content, with the water-soluble portion often being regarded as the bioavailable component (Karthikeyan et al., 2006). Thus, the solubility of heavy metals in lung fluids is intimately related to the pulmonary toxicity caused by particulate matter. However, the effects of exposure to ambient particulate matter dust have only been examined in a small number of research (Sosnowski et al., 2011); In contrast to research on manufactured nanoparticles, these investigations are still in their early stages. The diverse nature of $PM_{2.5}$, which varies by place and season in terms of composition, size, and physicochemical characteristics, is one of the primary obstacles. Langmuir monolayers are frequently used as physiologically realistic models of surfactant behavior in research that examine surfactant molecules' interactions with particles as either monolayers or bilayers (Nandi and Vollhardt, 2003). For the understanding of interaction between PM and PS is essential for elucidating the early events of respiratory toxicity. Fine and ultrafine particles can penetrate deeply into alveolar regions, where they directly disturb surfactant structure and function. Such disruption may impair surface tension regulation and initiate inflammatory cascades. However, the complexity and variability of ambient PM composition remain major challenges, highlighting the need for advanced experimental models to better clarify these interactions.

Particles and pulmonary surfactant

PM and gaseous pollutants make up the complicated combination that is air pollution. Various ultrafine particles included in dust, smoke, soot, and liquid aerosols make up PM, which can have a negative impact on human health after extended exposure. Major sources of these particles include emissions from industrial activities, vehicular exhaust, construction processes, combustion events, and natural contributors such as volcanic eruptions, sea spray, and power generation plants (Kelly and Fussell, 2012). Although particles can be classified in several ways, size is the most critical parameter, as particle toxicity increases with decreasing diameter (Ealia and Saravanakumar, 2017). Based on particle size, particulate matter is categorized into four main types: PM_{10} (coarse particles, 2.5–10 μm), $PM_{2.5}$ (fine particles, ≤2.5 μm), $PM_{0.1}$ (ultrafine particles, ≤0.1 μm), and nanoparticles (NPs, <100 nm) (Popa et al., 2020). The final category, nanoparticles (NPs, <100 nm), is present in atmospheric air and includes engineered nanoparticles generated through advanced nanotechnologies (Jeevanandam et al., 2018). Two mechanisms, direct and indirect, have been proposed to explain how air pollution contributes to CVD. Pro-inflammatory cytokines generated in the lungs indirectly enter the circulation and affect cardiac function. Directly, studies have shown that $PM_{2.5}$ and $PM_{0.1}$ can translocate into the bloodstream, exerting harmful effects on the heart and vascular system (Terzano et al., 2010). PM exposure has been linked to an increased risk of myocardial infarction,

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stroke, arrhythmia, and heart failure, according to recent studies (Brook, 2007). Numerous ailments, including ischemic heart disease, have been linked to long-term exposure to $PM_{2.5}$ (Brown et al., 2015), cerebrovascular disease (Matsuo et al., 2016), lung cancer (Raaschou-Nielsen et al., 2013), chronic obstructive pulmonary disease (Guo et al., 2018), and lower respiratory infections (Horne et al., 2018), and accounted for approximately 7.6% of total global deaths and 4.2% of global disability-adjusted life years (DALYs) in 2015 (Cohen et al., 2017). To date, research has offered only limited understanding of the mechanisms driving $PM_{2.5}$-induced toxicity. Hence, more detailed and systematic studies are required to clarify the specific contributions of individual pollutants within $PM_{2.5}$ and the molecular pathways through which they exert their harmful effects.

Silicon dioxide plays an important role in biomedical applications, serving as a carrier for drug delivery and gene transfer, as well as in imaging, owing to its ease of fluorescent labeling (Roy et al., 2005). Previous studies investigating the interaction between hydrophobic silicon dioxide particles and simplified lung surfactant (LS) models, particularly DPPC monolayers, demonstrated that particle incorporation disrupts molecular packing and lateral cohesion at the interface, thereby impairing the mechanical performance of LS films. These alterations may compromise the normal physiological function of lung surfactant (Guzmán et al., 2015). Although silicon dioxide particles are not typically considered major urban pollutants, their inhalation in nanopowder form is linked to silicosis, highlighting the need to assess their impact on the performance of the LS layer (Guzmán et al., 2015). This phenomena might be explained by the lipid phase's lower flexibility and the LS molecules' decreased lateral movement at the interface (Cao et al., 2021), This may result in decreased lateral cohesion and disturbed LS film packing. This lateral organization pattern in LS films following particle inclusion is consistent with findings published by Sosnowski et al. (2011), who used molecular dynamics calculations.

Carbon black (CB) describes a category of engineered materials composed of very fine particles that are sold under different brand names and show a variety of physical and chemical characteristics, yet they largely consist of elemental carbon (EC). CB has been in commercial production for over one hundred years, and in 2008, its global output reached around 9.8 million metric tons making it one of the 50 most extensively manufactured industrial chemicals worldwide (Long et al., 2013). Two key surface parameters of nanoparticle surface charge and hydrophobic/hydrophilic character are closely related to the molecular mechanisms governing protein-nanoparticle interactions (Shemetov et al., 2012). A defining characteristic of CB is its hydrophobic nature, whereby hydrophobic interactions, either attractive or repulsive, may influence the stability of protein-particle conjugates (Fertsch-Gapp et al., 2011). The interaction between inhaled particles and pulmonary surfactant represents a crucial yet insufficiently understood pathway of respiratory toxicity. Emerging evidence indicates that particle size, surface chemistry, and hydrophobicity strongly influence their ability to disrupt surfactant structure and function. Materials such as silica nanoparticles and carbon black can alter lipid packing and interfacial stability, potentially impairing surfactant performance. Therefore, deeper mechanistic investigations are essential to elucidate how different particles compromise pulmonary surfactant integrity and respiratory health.

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Nanoparticles and PS (microplastics, C60, carbon nanotubes)

NPs are those particles that have a diameter of <100 nm (Muhlfeld et al., 2008). Within this broad definition, several NP subcategories such as particulate matter ($PM_{0.1}$), ultrafine particles (UFPs), and engineered nanoparticles are encompassed. These particles can originate from natural processes, including wildfires and volcanic eruptions, as well as from anthropogenic activities such as welding (Zimmer, 2002), smoking or car traffic (Marshall and Behrentz, 2005). NPs generally do not exist as individual nano-sized particles but tend to form larger aggregates. This aggregation affects their deposition patterns within the lungs and alters their clearance pathways. Notably, these aggregates retain the inherent toxicity of the original nanoparticles (Borm et al., 2006).

In recent years, numerous studies have investigated the toxicological effects of various types of NPs on the lungs, as well as their subsequent fate within the respiratory system (Muhlfeld et al., 2008). Limited research has directly examined the impairment of LS resulting from the inhalation and infiltration of nanoparticles through surfactant layers. Nonetheless, in the majority of instances, this impairment has been documented to happen in a manner that is dependent on both dosage and duration, especially in regard to frequently utilized metallic nanoparticles. These particles represent a significant portion of airborne particulate matter and are also extensively utilized in medical diagnostic applications (Schleh and Hohlfeld, 2009). The tendency of certain NPs to persist within the surfactant film may be harnessed for drug delivery applications, enabling the sustained release of therapeutic agents prior to NP clearance. For such purposes, however, it is essential that these NPs exert minimal disruption to lung surfactant function. It is important to highlight that when carbon nanoparticles combine with Pb^{2+} and are exposed to human lung cells, there is a suppression in the expression of long noncoding RNAs that play a role in the regulation of inflammation (Pan et al., 2019). Pb^{2+} alone does not trigger inflammation, similar to Cr(VI); however, studies have revealed that their coexistence within $PM_{2.5}$ induces cytotoxic effects in lung cells (Jia et al., 2019). NPs (<100 nm) can aggregate, influencing deposition and clearance in lungs. Their interaction with pulmonary surfactant may impair film function, modulate inflammatory responses, and affect respiratory health depending on dose and composition.

Microplastics (MPs), which are characterized as plastic fragments measuring less than 5 millimeters in size, are predominantly formed through the degradation of larger plastic materials via processes such as ultraviolet (UV) irradiation, weathering, water erosion, biodegradation, and other environmental mechanisms (Prata, 2018). However, limited knowledge exists regarding the potential adverse effects of inhaled MPs, and further investigations are needed to clarify their impact. Current studies also suggest that the active components of LS may adsorb onto carbon particles, leading to elevated surface tension and alterations in membrane structure (Ahorsu et al., 2020). The harmful effects of inhaled microplastics (MPs) on the interfacial properties and composition of lung surfactant (LS) are still poorly understood. Graphene, fullerenes, and carbon nanotubes are examples of carbon nanoparticles that are produced extensively and used in a variety of applications (Maynard et al., 2006) Due to their extensive manufacturing and broad usage, greater amounts of carbon nanomaterials (CNs) are unavoidably discharged into the environment, potentially permeating and affecting ecological systems (Mercer and Helenius, 2008). Concern and attention have grown in response to the possible threats to the environment and public health. The unique properties of carbon nanosheets stem from their nanoscale size and comparatively large specific surface area, which enable them to pass through the skin, blood–brain barrier, alveolar–capillary barrier, and blood–placental

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barrier, among other biological barriers in the human body (Shvedova et al., 2005). Furthermore, Yang et al. (2018) reported that PS can promote the distribution of various nanomaterials that are based on metals, and Wang et al. (2010) reported that single-walled carbon nanotubes can be distributed by natural lung surfactant; however, it remains unclear whether all carbon nanotubes undergo dispersion within the phospholipid film. Furthermore, the specific roles of phospholipids and surfactant proteins in stabilizing carbon nanotubes have yet to be fully elucidated. Inhaled microplastics and carbon nanomaterials can interact with lung surfactant, potentially altering film structure and membrane tension. Their nanoscale size and surface properties raise concerns for respiratory and systemic health.

Carbon nanotubes (CNTs) represent a significant category of nanomaterials noted for their distinct mechanical, electrical, and thermal characteristics. As their utilization expands across various applications, apprehensions have grown regarding their possible detrimental effects on human health and the environment. Individual CNTs exhibit an exceptionally high aspect ratio and often cluster into structures at the micrometer scale in a dry form or when suspended in both polar and nonpolar solvents. Research involving animal exposure has revealed that pulmonary fibrosis is a primary pathological result of CNT exposure, and this outcome is considerably affected by the CNTs physicochemical properties (Luanpitpong et al., 2014). The dispersion state of single-walled carbon nanotubes (SWCNTs) has been found to greatly influence their deposition behavior within the lungs and the resulting biological responses (Ema et al., 2016). CNTs, with high aspect ratios and unique physicochemical properties, can aggregate and alter lung deposition patterns. Animal studies indicate that exposure may induce pulmonary fibrosis, highlighting the critical influence of dispersion, size, and surface characteristics on toxicity. Both in vivo and in vitro studies have demonstrated that carbon nanotubes (CNTs) elicit inflammatory responses (Muller et al., 2005). Recent studies have revealed that multiwalled carbon nanotubes (MWCNTs) measuring approximately 6 μm in length, as well as shorter ground CNTs around 0.7 μm, tend to persist within the lungs and exhibit slow clearance rates (Muller et al., 2006). A recent review of the literature on CNT-induced pulmonary toxicity highlights the ongoing debate, with contradictory findings regarding their toxic potential. Nonetheless, despite methodological limitations across studies, the prevailing conclusion is that CNTs exhibit toxicity to some extent.

Nanocarriers and pulmonary surfactant

Nanocarriers designed for use in the lungs must possess properties that make them compatible with biological systems, able to break down naturally, suitable for inhalation, and stable enough to endure the forces associated with aerosolization. Additionally, they should demonstrate a significant ability to load drugs effectively (Loira-Pastoriza et al., 2014). A range of pharmaceutical nanocarriers, such as nanospheres, liposomes, cell ghosts, micelles, nanocapsules, and lipoproteins, have been extensively researched for the experimental delivery of therapeutic and diagnostic agents. Modifying the surfaces of these carriers is often used to customize their physicochemical characteristics and allow for multiple functions. While many investigations have focused on the toxicological effects of polymeric nanoparticles given through the pulmonary route in both in vitro and in vivo systems (Gill et al., 2007), limited knowledge concerning their impact on the biophysical properties of pulmonary surfactant (PS). Considering the vital role of the surfactant layer in lung function, any factor that disrupts its activity may result in serious adverse outcomes (Frerking et al., 2001). Indeed, substantial evidence has demonstrated

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that PS function can be significantly disrupted by inhaled environmental toxins (Stenger et al., 2009), therapeutic drugs (Palmer et al., 2000), microparticles, and inorganic nanoparticles. Consequently, nanoparticles have the potential to alter both the structure and function of PS.

Interactions between gaseous pollutants and pulmonary surfactants

Ozone and pulmonary surfactant

During respiration, pulmonary surfactant is directly exposed to various gaseous pollutants present in ambient air (Finlayson-Pitts and Pitts Jr, 1997). Ozone is a highly reactive substance formed through photochemical reactions that involve nitrogen oxides (NO_x) and volatile organic compounds (VOCs) when they come into contact with ultraviolet light. The World Health Organization (WHO) recommends a guideline concentration of 50 parts per billion (ppb) for ozone, averaged over an 8-hour timeframe, whereas typical ambient concentrations at Earth's surface generally fall within the range of several tens of ppb (Iriti and Faoro, 2008). Although such low-level exposure was once considered harmless, extensive epidemiological studies have established a statistically significant association between ambient ozone concentrations and increased mortality from respiratory diseases (Kim et al., 2020). The lung surfactant layer at the air–aqueous interface represents the first barrier encountered by inhaled ozone. Experimental studies have recorded changes in the surface pressure (π) of lipid monolayers and, in some cases, lipid/peptide monolayers when exposed to low levels of ozone gas (Link, 2019). In addition to air pollution itself, individual susceptibility factors play an important role. Pulmonary function is known to decline with increased abdominal adiposity or body mass index (BMI), which may increase vulnerability to ozone-related effects (Snow et al., 2021).

Animal models have demonstrated that ozone-induced pulmonary inflammation is more pronounced in obese individuals than in their lean counterparts, suggesting a greater risk of adverse outcomes in obese individuals (O'Toole et al., 2008). Indeed, both genetic and diet-induced obese mice exhibit exacerbated pulmonary inflammation and injury following short-term ozone exposure (Campolim et al., 2020). Linked with increased concentrations of proinflammatory cytokines and chemokines including IL-6, CXCL1, MIP-2, and MCP-1. Similar observations in human groups reinforce this association, as individuals with obesity exhibit heightened inflammatory responses to ozone exposure, potentially exacerbating bronchoconstriction, airway hyperreactivity, and mucus production, consequently reducing the width of the conducting airways (Mancuso et al., 2010; Gordon et al., 2017). Moreover, elevated levels of proinflammatory cytokines and adipokines in the serum have been observed in individuals with obesity, which may play a role in the increased inflammation of the airways (Sideleva et al., 2012). A research study examined the influence of exposure to oxidizing gases, including ozone (O_3) and nitrogen dioxide (NO_2), on the interfacial chemistry of pulmonary surfactant (PS) and its role in promoting oxidative damage in the lungs. The results show that these gases alter the PS surface tension, phase behavior, and foaming ability. These compounds induce lipid peroxidation and protein damage within PS, impairing its function. O_3 radiation caused more severe effects than NO_2. Additionally, both reactive oxygen species (ROS) and gaseous oxidants were found to contribute to oxidative damage, highlighting the potential risk of air pollutants to respiratory health via PS disruption (Li et al., 2024), as shown in *Fig. 5*.

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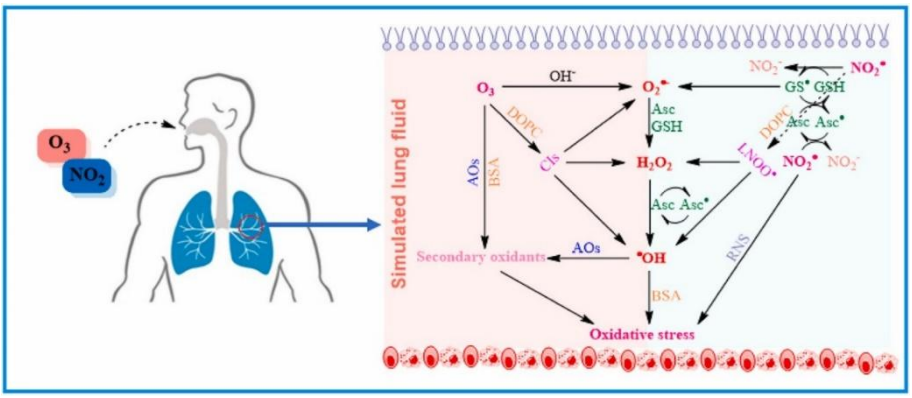

Figure 5. *Exposure to ozone (O_3) and nitrogen dioxide (NO_2) profoundly influences the interfacial chemistry of pulmonary surfactants, thereby contributing to the mechanisms underlying lung oxidative damage (Li et al., 2024)*

Nitrogen dioxide and pulmonary surfactant

NO_2 constitutes a significant atmospheric pollutant that can be reduced partially through the presence of vegetation, since plants can take in NO_2 through their stomata while simultaneously absorbing CO_2 during photosynthesis, as well as O_2 during the process of respiration. Inside the leaf tissues, NO_2 can interact with water to generate nitric and nitrous acids, which may later participate in additional reactions with various components of the plant (Jim and Chen, 2008). In the atmosphere, NO_2 participates in chemical reactions that lead to the formation of nitric acid (Teklemariam and Sparks, 2006) and contributes to acid rain, which has detrimental effects on ecosystems. From a health perspective, NO_2 is one of the most critical atmospheric pollutants and has been shown to impair lung immune defense mechanisms. Experimental studies in guinea pigs have demonstrated that NO_2 exposure alters the permeability of lung macrophage membranes and inhibits phagocytosis processes closely associated with cellular morphology, structure, and metabolism (van Bree et al., 2000). Structural damage to macrophage membranes may therefore represent a key factor underlying reduced phagocytic function (Gao et al., 2017).

Sulfur dioxide and pulmonary surfactant

The lungs serve as the main organ affected by SO_2 exposure in human beings. Elevated levels of SO_2 have been demonstrated to modify the physical and chemical characteristics of alveoli in rat models, leading to heightened permeability of the pulmonary vasculature and damage to the membrane structure of alveolar cells. These abnormal alterations are marked by increased permeability of the alveoli, swelling of the surrounding tissue, and dysfunction of organelles (Yu et al., 2018). Notably, recent studies have indicated that SO_2 toxicity initially manifests through damage to the structure and function of cellular membranes (Navari-Izzo et al., 1992). Inhaled SO_2 alters the distribution and functionality of erythrocyte membrane components, thereby increasing membrane permeability. Once inside cells, SO_2 induces lipid peroxidation of unsaturated fatty acids within cellular and organelle membranes. Its reaction with these fatty acids generates free radicals, which further disrupt membrane lipid fluidity and enhance lipid peroxidation. These processes compromise membrane integrity, leading to pore formation and leakage of intracellular components, including lactate dehydrogenase (Başkurt et al., 1990).

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Interactions between organic pollutants and pulmonary surfactants

PAHs and pulmonary surfactant

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous atmospheric pollutants characterized by persistence, semivolatility, bioaccumulation, and high toxicity. These properties render PAHs highly mobile and capable of transformation across different environmental media (Delgado-Saborit et al., 2011), thereby posing a significant threat to ecosystems and human health. Among them, benzo[a]pyrene (BaP), a prototypical carcinogenic PAH, has been associated with multiple adverse health outcomes, including reproductive toxicity, cardiovascular impairment, immunosuppression, hepatotoxicity, and carcinogenicity (Muthusamy et al., 2016). PM is recognized as an important carrier of toxic compounds, particularly PAHs (Zhao et al., 2012), and PS may enhance the solubilization process of PAHs. Nevertheless, research specifically focused on the solubilization of PAHs in the context of PS remains sparse. For instance, one study indicated that phenanthrene's apparent solubility rose when exposed to Curosurf® (a commercially available PS formulation), while our research indicated that PS derived from pig lungs markedly boosted the solubilization of anthracene (Zhao et al., 2019b). Notwithstanding these results, the majority of recent studies have focused on atomistic simulations of BaP-lipid interactions (e.g., using DPPC), and little is understood about how BaP affects the structural organization and gas-liquid interfacial characteristics of natural PS. Furthermore, research has mostly concentrated on low-molecular-weight PAHs, even though tests have shown that Curosurf® can solubilize phenanthrene linearly (Nguyen et al., 2020). The solubilization behavior of highly toxic, high-molecular-weight PAHs such as BaP (≥ four aromatic rings) remains largely unexplored. Recent work has begun to investigate PS–NP–PAH interactions under inhalation-relevant conditions. For example, one study examined the interaction between porcine lung extract (EPS) and NPs with PAHs. Nanosilica, which represents inorganic dust, was employed as a model NP, and three environmentally relevant low-molecular-weight PAHs-pyrene, phenanthrene, and acenaphthene-were tested for their respiratory exposure potential. This study assessed how nanosilica influences the interfacial behavior and foaming capacity of EPS, the solubilization of PAHs by EPS and its active components, and the adsorption of PAHs onto nanosilica in the presence of PS, thereby contributing to a deeper understanding of PS-NP-PAH interactions in the context of inhalation exposure (Zhao et al., 2019a), as shown in *Fig. 6*.

Interactions between metal pollutants and pulmonary surfactants

In the case of silver nanoparticles (AgNPs), although the precise mechanisms of toxicity have not been fully elucidated, recent evidence suggests that the release of Ag^+ ions is a primary pathway underlying their bioreactivity (El Badawy et al., 2011). Ionic silver (Ag^+), a well-known oxidation catalyst, can damage proteins through desulfurization, promote the generation of ROS (Levard et al., 2011), and disrupt nitric oxide (NO) redox equilibria in the lung (Park et al., 2009). The oxidative capability could heighten the lung epithelium's permeability to AgNPs, which may ultimately result in DNA injury, disruption of lipid membranes, chromosomal irregularities, and halting of the cell cycle (Li et al., 2010). Thus, Ag^+ ion release is considered a critical determinant of the downstream toxicological effects of AgNPs on human health (Elzey and Grassian, 2010).

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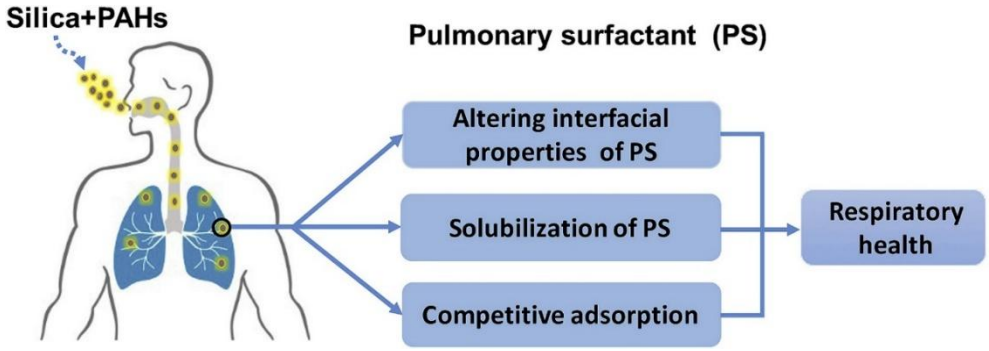

Figure 6. *Interactions of pulmonary surfactants with silica nanoparticles and polycyclic aromatic hydrocarbons (PAHs) play critical roles in modulating interfacial behavior, solubilization processes, and potential toxicological outcomes (Zhao et al., 2019a)*

Particles of anthropogenic origin have been shown to directly interact with PS components (Kendall et al., 2007). NPs can impair surfactant function, and potent PS dysfunction has been observed at low concentrations (~2 μg/mL) of gold nanoparticles. While the impact of TiO_2 NPs on surfactant function in healthy lungs may be minimal, in individuals with preexisting respiratory conditions, additive effects on PS function and ultrastructure cannot be excluded. Furthermore, NPs are capable of inducing oxidative stress and lipid peroxidation (Arora et al., 2008), processes that increase surface tension (Shelley, 1994). Engine-emitted NSPs are frequently contaminated with alkanes and sulfates; notably, eicosane, an n-alkane component of diesel exhaust, has been shown to interfere with the biophysical activity of PS (Manousakas et al., 2014). Conversely, the addition of DPPC to simulated lung fluid (SLF) has been found to increase the dissolution fraction of aerosol particles. However, despite these insights, relatively few studies have investigated the effects of full-component natural PSs on the solubility and bioavailability of heavy metal constituents in particulate matter. Metal pollutants, including Ag^+ and nanosized particles, can disrupt pulmonary surfactant function, induce oxidative stress, and alter lipid membranes, highlighting their critical role in respiratory toxicity.

Conclusion

This detailed review highlights the essential function of PS in sustaining the health of alveoli and promoting effective breathing. The makeup and role of PS, which mainly consists of phospholipids and surfactant proteins, differ among different species and stages of development. The harmful impacts of air pollution, such as ozone, nitrogen dioxide, sulfur dioxide, and particulate matter, on lung health are well established. Prolonged exposure to particulate matter is linked to a variety of both chronic and acute health issues, underlining the need to reduce pollution levels. Furthermore, a lack of PS results in underdeveloped lungs, which can lead to neonatal respiratory distress syndrome, a significant contributor to mortality rates in premature infants. This review delves into the intricate interactions between nanoparticles and surfactants, highlighting their aggregation, deposition, and clearance mechanisms within the lung. Notably, PS films exhibit rapid adsorption at air-water interfaces, which is crucial for efficient respiratory mechanics. Furthermore, this review elucidates the potential therapeutic implications of PS in mitigating the adverse effects of pollutant nanoparticles,

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emphasizing the need for further research in this domain. Ultimately, this review provides valuable insights into the complex interplay among PS, air pollutants, and nanoparticle interactions, paving the way for innovative approaches in disease treatment and pollution management.

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