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Bioaccessibility and Toxicity of Particle-Bound Metals and Polycyclic Aromatic Hydrocarbons: Sources, Respiratory Fate, Mechanisms, and Risk Assessment

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Abstract

Particulate matter (PM) mass is widely used to estimate health risk, yet particles with similar mass concentrations can produce very different biological effects. Toxicity depends on source, size, atmospheric aging, chemical speciation, and the mixture of compounds carried on particle surfaces. This critical narrative review examines particle-bound metals and polycyclic aromatic hydrocarbons (PAHs), following their pathway from respiratory deposition and bioaccessibility to oxidative stress and toxicity. Metal release varies with element, source, particle size, extraction conditions, and solid-to-liquid ratio, while acidic lysosomal environments often increase dissolution compared with near-neutral extracellular fluids. PAH release is shaped by hydrophobicity, binding to soot, surfactants, proteins, and changes in the respiratory environment during inflammation. Once released, or when particles are taken up by cells, these constituents may contribute to oxidative stress, antioxidant depletion, inflammation, genotoxicity, and vascular injury. Poorly soluble particles can still remain biologically active even when only a small fraction of their chemical content is released. Interactions between metals and organic compounds may be synergistic or antagonistic, further complicating interpretation of complex PM mixtures. Differences in simulated lung fluids, dosimetry, speciation, and biological validation also limit comparisons across studies. We therefore propose a tiered framework integrating PM mass, source, size, speciation, compartment-specific bioaccessibility, oxidative potential, and delivered-dose toxicology. Bioaccessibility should complement, rather than replace, whole-particle testing. Greater consistency and attention to real-world mixtures may improve source prioritization and health-risk interpretation.

1 Introduction

Ambient particulate matter (PM) is not a single pollutant, but a complex and continuously changing mixture of solid and liquid particles suspended in the air. Regulatory classifications are largely based on aerodynamic diameter. PM_{10} can penetrate into the thoracic airways, whereas the smaller $PM_{2.5}$ fraction can travel deeper into the lungs and reach the small airways and alveolar region. Ultrafine particles (< 0.1 µm), although contributing relatively little to total particle mass, are present in much greater numbers and provide a disproportionately large surface area for interactions with biological tissues. Growing evidence of health effects at relatively low exposure levels led the World Health Organization (WHO) to reduce its annual $PM_{2.5}$ air-quality guideline to 5 µg m^{-3} in 2021 (WHO 2021). The global burden remains substantial, with the State of Global Air 2024 report estimating that air pollution contributed to 8.1 million deaths worldwide in 2021 (Health Effects Institute 2024). Evidence from long-term cohort studies has consistently associated fine-particle exposure with increased cardiopulmonary mortality and lung cancer (Dockery et al. 1993; Pope et al. 2002). Similar patterns have emerged from natural experiments in Utah Valley, Dublin, and Hong Kong, where reductions in major pollution sources or implementation of emission controls were followed by measurable declines in respiratory illness or mortality (Pope 1989; Clancy et al. 2002; Hedley et al. 2002). Reflecting this body of evidence, the International Agency for Research on Cancer has classified outdoor air pollution and particulate matter as carcinogenic to humans (IARC 2016).

Mass remains the foundation of exposure assessment, yet it gives only limited information about which sources or particle properties are driving toxicity. The same microgram of PM can represent aged secondary aerosol, brake dust, residual-oil ash, wildfire smoke or mineral dust, each carrying a different combination of transition metals, metalloids, carbon, salts and organic toxicants. These components are co-emitted, transformed in the atmosphere and continue to interact after deposition in the respiratory tract. As a result, an epidemiological association with one constituent may reflect that constituent itself, the broader source mixture or residual confounding by correlated pollutants. A recent cohort meta-analysis nevertheless found reproducible mortality associations for several $PM_{2.5}$ constituents, including black carbon, sulfate, nitrate, ammonium, zinc, nickel and silicon, while also reporting substantial heterogeneity and exposure uncertainty (Chen S et al. 2024).

Metals and polycyclic aromatic hydrocarbons (PAHs) illustrate why PM composition matters. Metals can catalyze redox reactions, displace essential ions, bind proteins and damage membranes or mitochondria, but their effects depend strongly on oxidation state, coordination, solubility and the mineral or particle phase in which they occur. PAHs arise mainly from incomplete combustion. Following metabolic activation, some can form electrophilic intermediates and quinones, activate the aryl hydrocarbon receptor (AhR), generate reactive oxygen species (ROS) and produce DNA adducts. Higher-molecular-weight PAHs are predominantly particle-bound, whereas lighter PAHs partition more strongly into the gas phase. Nitro- and oxy-PAHs may be emitted directly or formed during atmospheric processing, and some derivatives are more mutagenic or redox-active than their parent compounds (Bandowe and Meusel 2017; Yang et al. 2021).

The biologically relevant dose is therefore not necessarily the mass collected on a filter. After deposition, particle constituents may desorb, dissolve, transform, remain reactive at the particle surface or be taken up by cells before reaching a biological target. Inhalation bioaccessibility assays estimate the fraction released into a defined surrogate respiratory fluid and can help connect chemical monitoring with toxicological interpretation. They do not, however, measure bioavailability directly. A major difficulty is the lack of protocol harmonization: differences in fluid composition, loading and extraction conditions can be large enough to rival differences between sampling locations (Kastury et al. 2017, 2018; Ren et al. 2020; Soares et al. 2025).

Most earlier reviews have focused on metal(loid) bioaccessibility, simulated-lung-fluid methodology or a single contaminant class. Here, metal and PAH release are considered together with whole-particle oxidative potential and toxicology along one exposure-to-risk pathway. The review compares extracellular, epithelial-lining and lysosomal compartments, considers both soluble and persistent fractions, examines metal-organic interactions, and develops a tiered framework that links ambient mass and source information with delivered dose and biological validation. A minimum reporting checklist is also proposed to improve comparability between laboratories.

Five questions guide the review: Which current sources and atmospheric processes shape exposure? How do deposition and lung microenvironments determine the accessible dose? Which methodological

choices most strongly influence simulated-lung-fluid results? How do soluble and insoluble fractions contribute to pulmonary and systemic toxicity? And how can component-resolved evidence improve source control and risk assessment without overstating causal certainty?

2 Review approach

A critical narrative approach was used because the relevant evidence spans atmospheric chemistry, analytical methodology, toxicology, controlled exposure studies, epidemiology and risk assessment, with outcomes that are too heterogeneous for meaningful quantitative pooling. Searches of titles, abstracts and keywords in PubMed and publisher platforms were supplemented by backward and forward citation chaining and updated through 1 October 2026. Search concepts included particulate matter, $PM_{2.5}$, PM_{10}, road dust, wildfire smoke, metals, metalloids, PAHs, nitro-PAHs, oxy-PAHs, inhalation, bioaccessibility, simulated lung fluid, artificial lysosomal fluid, epithelial lining fluid, oxidative potential, inflammation, genotoxicity, cardiovascular effects and source apportionment. For the final update, recent literature was reviewed section by section, and bibliographic details were checked against publisher, DOI or PubMed records before inclusion.

Priority was given, where possible, to peer-reviewed human, animal, cellular, acellular and analytical studies published from 2020 to 2026. Older studies were retained when they established methods or mechanisms that remain relevant, which is why the mechanistic sections combine foundational experiments with newer composition-resolved work. Evidence was interpreted with attention to sample matrix, particle size, source, extraction conditions, speciation, dose metric and biological model rather than treating all study types as equivalent. Human studies provide real-world relevance but remain vulnerable to confounding by correlated exposures. Controlled and animal studies strengthen temporal and mechanistic inference, although experimental doses may not always reflect environmental exposure. Cellular and acellular systems help isolate pathways but do not capture whole-body kinetics. The review is therefore a state-of-the-science narrative synthesis rather than a systematic review or meta-analysis, and no formal risk-of-bias score was assigned.

3 Sources, size distribution, and atmospheric processing

PM source profiles vary substantially across places and seasons. Urban particles may contain traffic and industrial emissions, non-exhaust wear, resuspended soil and road dust, biomass- or coal-combustion products, sea salt, and secondary inorganic and organic aerosol. A global review showed that traffic, industry, domestic fuel use, other anthropogenic activities, and natural dust or salt can all contribute materially to urban $PM_{2.5}$, although their relative importance differs widely among cities (Karagulian et al. 2015). During severe haze episodes, secondary aerosol can become dominant even when the event begins with primary combustion emissions, as reported in several major Chinese cities (Huang et al. 2014). Source-apportionment results are therefore most informative when time-resolved chemistry is interpreted together with meteorology and uncertainty rather than treated as a fixed source inventory.

Non-exhaust sources account for an increasing share of traffic-related metals. Brake wear commonly contains Fe, Cu, Sb, Ba, Sn and other formulation-dependent elements, while tire and road wear contribute Zn, Fe, organic additives, rubber-derived particles and mineral material. Resuspension can also reintroduce legacy Pb and older industrial contaminants. Cleaner exhaust and fleet electrification reduce tailpipe emissions but do not eliminate particles from brakes, tires, road surfaces or resuspended dust; vehicle mass, driving behavior and road conditions can also modify these emissions (Fussell et al. 2022). In Karachi and Shikarpur, recent work detected bioaccessible As, Cr and Pb in the $PM_{2.5}$ fraction of road dust (Moryani et al. 2026). The wider recent literature is consistent with the growing relevance of non-exhaust emissions, but reported emission factors, particle composition and toxicological findings vary considerably with sampling method, vehicle technology, road conditions and particle-size fraction (Piscitello et al. 2021; Forest and Pourchez 2023; Beddows et al. 2023; Wang Y et al. 2024; Thodhal Yoganandham et al. 2024; Xu Q et al. 2024; Wagner et al. 2024; Saladin et al. 2024; Christou et al. 2025; Puisney-Dakhli et al. 2023; Mohanraj et al. 2024; Chae et al. 2024; Li X et al. 2025; Li X et al. 2026).

Fuel combustion and industry often leave recognizable metal signatures. Residual-oil burning is usually linked to V and Ni; coal can contribute As, Se, Pb and Hg; iron and steel production emits Fe, Mn, Cr and Ni; non-ferrous smelting adds Pb, Zn, Cd, Cu and As; and cement, construction and quarrying generate mineral particles rich in Ca, Al, Si and Fe. None of these markers belongs to one source alone, and toxicity shifts with oxidation state or mineral host. Cr(III) and Cr(VI) carry very different hazards, and Fe locked in a silicate behaves nothing like soluble Fe salts or freshly abraded metallic Fe.

Combustion generates PAHs across a broad volatility range. Gasoline and diesel exhaust, coal and household solid-fuel use, industrial coking, waste burning, cooking and wildfires all produce PAH mixtures. Lower-molecular-weight compounds are found mainly in the vapor phase, whereas four- to six-ring PAHs associate more strongly with soot and organic PM; the balance depends on temperature, organic-aerosol composition and black-carbon surface properties. Filter-only sampling can therefore miss part of the semivolatile fraction and can be affected by positive or negative sampling artifacts. Wildfire smoke creates episodic, sometimes long-range exposure to fine particles, oxygenated organics and PAHs, an issue of increasing concern as fire seasons lengthen in many regions (Rizzo and Rizzo 2025). Recent reviews and exposure studies describe respiratory and cardiovascular outcomes associated with wildfire smoke and discuss oxidative, inflammatory and infectious-disease pathways, while also emphasizing substantial uncertainty in exposure measurement and dose characterization (Lei et al. 2024; Jiao et al. 2024; Gould et al. 2024; Nazli et al. 2025; Islam et al. 2025; Mylonaki et al. 2024; Mahendran et al. 2025; Etherington et al. 2025; Gordon et al. 2023).

Atmospheric aging does not move toxicity in only one direction. Oxidation can lower concentrations of parent PAHs while generating quinones, nitro-PAHs, peroxides and secondary organic material. Sulfate and nitrate acidity can alter metal dissolution, and organic ligands may either chelate metals or help keep them in solution. In one recent size-resolved study, aging increased the bioaccessibility of Mn and Cr; soluble sulfate salts and possible Cr(VI) formation were proposed as contributing mechanisms (Hua et al. 2025). Fresh source profiles therefore cannot be assumed to represent the reactivity of particles

after atmospheric transport. Table 1 summarizes the main source mixtures and the cautions needed when interpreting them.

Table 1
Major sources of particle-bound metals and PAHs and their interpretation

Source or process	Indicative constituents	Size and transformation	Interpretive significance
Tailpipe combustion	Black carbon; Fe, Cu, Zn; lubricant-derived Ca, P, Zn; parent and substituted PAHs	Mainly fine and ultrafine; rapid dilution and oxidation; PAH gas–particle repartitioning	Declining with stringent exhaust controls but still important in older fleets and high-emitting vehicles
Brake, tire, road wear, and resuspension	Fe, Cu, Sb, Ba, Sn, Zn, Ti; rubber/organic additives; legacy Pb; road-deposited PAHs	Brake wear spans fine to coarse; tires and road dust mainly coarse but include fine particles; repeated aging/resuspension	Growing relative importance as tailpipe emissions fall; profiles depend on vehicle technology, road surface, and driving
Coal and residual-oil combustion	As, Se, Pb, Hg; V and Ni for residual oil; soot and PAHs	Fine fly ash; acid sulfate coatings can change dissolution; plume aging forms secondary aerosol	High potential for long-range transport and metal–organic interactions
Biomass, household fuel, and wildfire	K, black/organic carbon, PAHs, oxy-PAHs, quinones; variable metals from fuel and ash	Predominantly fine smoke with semivolatile organics; strong photochemical aging	Fuel type and combustion efficiency dominate composition; wildfire episodes create acute regional exposure
Metallurgy and industry	Fe, Mn, Cr, Ni, Pb, Zn, Cd, Cu, As; source-specific PAHs	Fine fumes plus coarse mechanically generated dust; oxidation state can change after emission	Speciation and process knowledge are essential; occupational and fence-line exposures may be high
Soil, mining, tailings, and construction	Al, Si, Fe, Ca, Mn; geogenic or contaminated As, Pb, Cd, Cr, Ni; sorbed PAHs	Usually coarse, but fine enriched fractions travel far; mineralogy controls dissolution	Total abundance may not predict accessibility; weathering and acidity can increase release
Secondary aerosol and atmospheric aging	Sulfate, nitrate, ammonium, oxidized organics; redistributed metals; nitro-/oxy-PAHs	Primarily fine; coatings, acidity, and ligands alter dissolution and OP	Not a simple primary source; chemistry can increase or decrease biological reactivity during transport

Note

Markers are indicative, not unique. Source attributions should use multiple species, meteorology, and uncertainty analysis. Adapted conceptually from Karagulian et al. (2015), Daellenbach et al. (2020), Fussell et al. (2022), *and* Yang et al. (2021).

4 Respiratory deposition, clearance, and biologically relevant dose

Respiratory deposition depends on aerodynamic diameter, density, shape, hygroscopic growth, breathing pattern, airway geometry and disease. Coarse particles are removed efficiently by impaction and sedimentation in the nose and larger conducting airways, whereas fine particles can reach terminal bronchioles and alveoli and ultrafine particles deposit largely by diffusion. The same ambient concentration can therefore produce different regional doses in children, people exercising outdoors and patients with obstructed or inflamed airways. Hygroscopic particles may also grow in the humid respiratory tract and shift their deposition pattern. Work on ultrafine particles and lung-deposited surface area further indicates that particle number, hygroscopicity and regional deposition can provide dosimetric information that PM mass alone does not capture (Rumi et al. 2025; Bergmann et al. 2026; Chen et al. 2025a; Chen et al. 2025b; Lepistö et al. 2023; Abdillah and Wang 2023; Hong et al. 2025; Vallabani et al. 2023). Once deposited, particles can follow several competing clearance and retention pathways. Mucociliary transport moves material from the conducting airways toward the pharynx, where it may be swallowed; this secondary ingestion pathway should be distinguished from direct pulmonary uptake. In the alveolar region, macrophage phagocytosis, dissolution, lymphatic transport and long-term retention can unfold over hours to months. Poorly soluble particles may persist, continue to generate surface-mediated ROS, stress lysosomes or promote frustrated phagocytosis. Dissolved ions and small organic molecules may instead cross the epithelium, bind proteins, enter the circulation or be transformed locally. Clearance kinetics can therefore be as important as a single extraction endpoint (Lippmann et al. 1980; Möller et al. 2004). Recent studies of deposited metals and macrophage responses similarly highlight the continued relevance of retained particles and particle-associated metals after clearance has begun (Ellwanger et al. 2025; Khoshakhlagh et al. 2024; Priyadarshini et al. 2024; Zhang X et al. 2022). Bioaccessibility and bioavailability refer to different stages of this process. Inhalation bioaccessibility is the fraction of a constituent released from the particle matrix into a defined surrogate respiratory fluid under specified conditions. It estimates what may become available for local interaction or subsequent absorption in the modeled compartment. Bioavailability goes further and refers to the fraction that actually crosses a biological barrier and reaches the circulation or a target tissue. Dissolved metals may reprecipitate, bind proteins, be internalized by macrophages or be cleared, while a particle-bound compound may enter a cell without appearing in a filtered extract. In vitro bioaccessibility is therefore best treated as an exposure-refinement metric rather than a direct measure of absorption.

No single simulated fluid can represent every microenvironment in the lung. Near-neutral Gamble-type solutions are commonly used to approximate extracellular or interstitial conditions. Synthetic epithelial-lining fluids add antioxidants, salts, proteins and surfactants to better reflect the air-lung interface, whereas artificial lysosomal fluid (ALF), usually near pH 4.5, is designed to mimic the acidic, ligand-rich

phagolysosome after macrophage uptake. ALF often releases more of many metals than neutral fluids, but this should not be interpreted as evidence that the entire deposited dose experiences lysosomal conditions. Parallel extractions answer different compartment-specific questions; sequential designs may better approximate transfer from lining fluid into macrophages but are more difficult to standardize (Ren et al. 2020; Soares et al. 2025). Table 2 relates the major respiratory compartments to commonly used surrogate systems.

Table 2
Respiratory compartments and commonly used surrogate fluids

Compartment or process	Physiological characteristics	Common surrogate	What the result can—and cannot—represent
Airway surface and alveolar lining layer	Near-neutral pH; salts, antioxidants, proteins, pulmonary surfactant; very small fluid volume	Synthetic epithelial lining fluid (SELF) or respiratory-tract lining-fluid formulations	Early extracellular release and antioxidant depletion; composition varies among formulations and does not reproduce clearance
Interstitial extracellular environment	Near-neutral pH with bicarbonate/carbonate, phosphate, salts, and proteins	Gamble's solution or artificial interstitial fluid	Dissolution after contact with extracellular fluid; may underextract hydrophobic PAHs and omit surfactant/proteins
Macrophage phagolysosome	Acidic (about pH 4.5), ligand-rich, intracellular; reached after phagocytosis	Artificial lysosomal fluid (ALF)	Potential release from internalized particles; often higher metal dissolution but not applicable to all deposited PM
Inflamed or diseased lining fluid	Altered pH, proteins, lipids, enzymes, oxidants, and barrier permeability	Modified healthy fluid with disease-relevant constituents	Tests host-dependent release; formulations require clinical justification and validation
Mucociliary clearance and swallowing	Transport from conducting airways to gastrointestinal tract	Sequential lung-to-gastrointestinal extraction	Can estimate secondary ingestion; should be reported separately from direct pulmonary uptake
Systemic uptake	Epithelial crossing, protein binding, metabolism, circulation, and tissue distribution	No acellular lung fluid alone is sufficient	Requires cellular barriers, pharmacokinetic models, animals, controlled exposure, or biomarkers; this is bioavailability, not only bioaccessibility

Note

*Fluid names are not interchangeable; complete recipes, pH, loading, extraction time, and phase-separation method must be reported (*Ren et al. 2020; Soares et al. 2025).

5 Measuring inhalation bioaccessibility

Methodological choices can account for a substantial part of the variation reported between bioaccessibility studies. Fluid composition and pH influence proton-promoted dissolution, complexation, redox state and precipitation. Citrate and other ligands in ALF can keep released metals in solution, whereas phosphate and carbonate in neutral fluids may precipitate Pb and other ions. Antioxidants can alter metal redox chemistry, while proteins and surfactant lipids can increase the apparent accessibility of hydrophobic organics. Even the operational definition of a 'dissolved' fraction depends on whether extracts are centrifuged, membrane-filtered, ultrafiltered or analyzed without phase separation. Recent studies using simulated lung fluids alongside dosimetry or source-specific interpretation reinforce the need to report the modeled compartment and experimental conditions explicitly (Novo-Quiza et al. 2023; Tang et al. 2023; Sun et al. 2022; Ren Y et al. 2024). The solid-to-liquid ratio is another large source of variation. With too little fluid, saturation or readsorption can suppress dissolution and break sink conditions; with too much, the system becomes unrealistically dilute next to the very thin epithelial lining layer. Published PM methods span several orders of magnitude in particle loading, which makes direct comparison hard. In a factorial study of $PM_{2.5}$, fluid composition had the strongest influence, and a ratio of about 1:5000 with end-over-end agitation and a 24-h endpoint gave reproducible results for the metals tested, although the best ratio still depends on the analyte, the matrix and the purpose of the study (Kastury et al. 2018). Results should be reported both as a percentage of total content and as mass released per mass of PM or per volume of air, so that a high percentage at a low ambient concentration is not mistaken for a high dose. Kinetics matter too. Highly soluble salts may release most of their content within minutes, whereas mineral phases, soot-associated metals and strongly sorbed PAHs can take days to dissolve or stay largely on the surface. One 24-h measurement may hide these distinct processes and need not match residence time in the compartment of interest. It needs at least one early and one later time point, and kinetic models that separate fast desorption from slower matrix dissolution. Experiments should hold 37°C, measure pH instead of assuming it, control headspace and light exposure for PAHs, and use agitation that mixes the sample without abrading it unrealistically.

Sampling and analytical recovery deserve the same care as the extraction itself. High-volume filter extractions can produce particle loadings far above physiological surface doses, and filter fibers or binders may hold back metals and organics. Field and filter blanks, spiked recoveries, replicate extractions, certified reference materials and a full mass balance are therefore essential. Total digestion should be run on an analytically comparable aliquot. Where oxidation state affects hazard, metals need speciation measurements or suitable geochemical modeling. For PAHs, isotopically labeled standards, protection from light, controls for vapor loss and measurement of transformation products are all needed; restricting analysis to the 16 priority parent PAHs can miss important nitro- and oxy-derivatives.

Recent studies illustrate how strongly bioaccessibility depends on method and context. In Mexico City, metal(loid) release differed among ALF, simulated epithelial and interstitial fluids, Gamble's solution and water, and also varied by season, location and sample handling; delaying measurement without acidification changed the result (Andrade-Oliva et al. 2025). Size-resolved work likewise shows that the fraction with the highest total concentration is not necessarily the fraction with the highest accessible risk (Jia et al. 2022; Hua et al. 2025). For $PM_{2.5}$-bound PAHs, mean in vitro accessibility increased from a healthy-fluid model to models representing mild and severe inflammation, indicating that host conditions can modify the released dose (Zhou et al. 2022). Table 3 summarizes representative studies and the methodological lesson from each. Other recent investigations have paired accessible fractions with source apportionment, speciation or health-risk assessment; taken together, they show why total and accessible concentrations should not be assumed to rank sources or risks in the same way (Boutamba Mbina et al. 2025; Xie et al. 2020; Li W et al. 2023; Rahat et al. 2025; Yadav et al. 2024; Feng X et al. 2026; Kumari et al. 2025; Gupta et al. 2024; Ma et al. 2021; Zupančič et al. 2024).

Standardization should improve comparability without forcing every research question into a single fluid system. A practical minimum panel would pair a near-neutral extracellular fluid with an acidic macrophage-lysosomal fluid and, when hydrophobic organics are central to the question, add a lipid- and protein-containing epithelial fluid. A common core protocol could standardize temperature, blank correction, mass balance, reporting units and quality control while still allowing justified disease- or compartment-specific variants. The most important remaining needs are interlaboratory comparison studies and stronger in vitro-in vivo validation (Ren et al. 2020; Soares et al. 2025).

Table 3
Representative recent studies of inhalation bioaccessibility and related reactivity

Study	Material and test design	Principal observation	Methodological lesson
Kastury et al. (2018)	$PM_{2.5}$; factorial variation of simulated fluid, solid-to-liquid ratio, time, and agitation	Fluid composition was the dominant determinant; 24 h approached a plateau for tested conditions	Optimize and report each parameter; do not compare percentages from unmatched protocols
Liu et al. (2019)	PM from contrasting atmospheric sources; bioaccessibility incorporated into metal risk estimates	Accessible rather than total metal changed source and risk rankings	Use source-specific accessible concentration, not a universal literature fraction
Ren et al. (2020)	Critical synthesis of metal(loid) and organic-contaminant extraction in simulated lung fluids	Large heterogeneity in fluid formulation and operational definitions	Standardization and explicit terminology are prerequisites for comparability
Zhao et al. (2021)	$PM_{2.5}$ trace metals; respiratory and digestive in vitro accessibility, availability proxies, and OP	Accessible fractions and OP varied by element and biological system	Pulmonary and post-clearance ingestion pathways should not be conflated
Cigánková et al. (2021)	Seasonal PM_1 and $PM_{2.5}$; three fluids plus DTT oxidative potential	Element release and OP differed by size, season, and fluid	Bioaccessibility and OP provide complementary rather than interchangeable information
Zeng et al. (2021)	Ambient $PM_{2.5}$-bound PAHs in Caofeidian; inhalation accessibility and source-resolved risk	PAH accessibility ranged from 17.8% to 67.9%; source contributions differed	Total PAHs can misstate the accessible dose and source priority
Jia et al. (2022)	Size-resolved PM; seasonal potentially toxic elements	Accessible dose and inhalation risk peaked in specific fine and intermediate size ranges	Measure size-specific release; $PM_{2.5}$ or PM_{10} averages can mask risk-relevant modes
Zhou et al. (2022)	$PM_{2.5}$-bound PAHs in healthy and inflammatory lung-fluid models	Mean accessibility increased from 24.5% in the healthy model to 28.6% and 32.3% with increasing inflammation	Host state and surfactant composition can alter hydrophobic-contaminant release
Andrade-Oliva et al. (2025)	Mexico City $PM_{2.5}$ in ALF, SELF, artificial interstitial fluid, Gamble's solution, and water	Solubility varied by fluid, season, location, and handling time; ALF generally extracted more	Preserve and acidify extracts appropriately; include multiple physiologically justified fluids
Hua et al. (2025)	Size-resolved atmospheric particles	Fine-particle Cu, Mn, Cr, and V showed high accessibility; aging	Atmospheric processing and chemical form

Study	Material and test design	Principal observation	Methodological lesson
	with source and aging analysis	enhanced Mn and Cr release	should accompany source attribution
Soares et al. (2025)	Methodological review covering inorganic and organic contaminants	Terminology and protocols remain inconsistent and in vitro–in vivo links are weak	Adopt common reporting standards while retaining compartment-specific designs
Moryani et al. (2026)	$PM_{2.5}$-fractionated road dust from Karachi and Shikarpur; ALF plus speciation modeling	Cr, As, and Pb showed moderate accessibility with species-dependent behavior	Combine measured release with speciation and local source context

Note

Values are study-specific and should not be transferred to other matrices without validation. DTT, dithiothreitol; OP, oxidative potential.

6 Toxicity of particle-bound metals

Metal toxicity depends on dose, chemical form and biological setting, so total concentration alone is an incomplete measure of hazard. Redox-active Fe and Cu can promote Fenton-type chemistry and lipid peroxidation, while V and Cr can cycle between oxidation states. Ni, Cd, As and Pb disrupt enzymes, DNA repair, calcium signaling and antioxidant defenses through different mechanisms. Even essential elements such as Fe, Cu, Mn and Zn can become harmful once exposure exceeds normal homeostatic control. Metals that are not directly redox-active may still increase oxidative stress by depleting glutathione, inhibiting antioxidant enzymes, damaging mitochondria or activating inflammatory cells.

Some of the clearest mechanistic evidence for acute PM injury comes from soluble transition metals. In classic studies of residual-oil fly ash and ambient-particle extracts, chelation or removal of soluble metals reduced epithelial injury and inflammation, while comparable metal mixtures reproduced part of the response (Costa and Dreher 1997; Dreher et al. 1997; Prieditis and Adamson 2002). Human studies have also shown that aqueous PM extracts can injure airway epithelium and that concentrated ambient particles can provoke pulmonary inflammation, supporting the biological activity of environmentally relevant mixtures at the respiratory surface (Frampton et al. 1999; Ghio et al. 2000; Ghio and Devlin 2001).

Solubility is not the whole story. Poorly soluble particles can generate ROS at their surfaces, carry catalytic inclusions into cells, disturb lysosomes and activate pattern-recognition pathways in macrophages and epithelial cells. Fractionation experiments have demonstrated DNA damage from both soluble metals and the residual particle fraction (Knaapen et al. 2002). Retained particles may continue to sustain inflammation after rapidly soluble ions have disappeared, whereas highly soluble constituents may disperse before reaching a critical intracellular target. Mechanistic studies should therefore compare whole particles, extracted fractions and post-extraction residues at matched deposited doses.

At the respiratory surface, metal-rich PM can deplete ascorbate and glutathione, disrupt epithelial barrier proteins, increase cytokine release, recruit neutrophils and activate NLRP3-related inflammasome signaling. Mitochondrial dysfunction and lipid peroxidation link oxidative stress with apoptosis, pyroptosis and, more tentatively, ferroptosis; the contribution of each pathway at ambient exposure levels remains uncertain (Li et al. 2022b; Vilas-Boas et al. 2024). Particle chemistry may also influence antigen presentation and airway hyperresponsiveness, and metal composition has altered the severity of allergic inflammation in animal models (Gavett et al. 2003). More recent mechanistic studies have examined mitochondrial dysfunction and ferroptosis, while air-liquid-interface systems offer a more exposure-relevant way to study epithelial responses to PM (Ahn et al. 2024; An et al. 2024; Park et al. 2023).

Composition-resolved toxicology also shows why chemistry should be interpreted alongside the dose delivered to cells or tissue. In human lung epithelial cells, urban $PM_{2.5}$ metals, organic carbon and environmentally persistent free radicals were associated with oxidative, inflammatory and membrane-injury responses (Li et al. 2022a). A 2025 study combined metal extraction in simulated biological fluids with cellular and animal endpoints, directly testing bioaccessibility against biological response rather than treating it as a stand-alone hazard surrogate (Rimauro et al. 2025). This type of evidence is valuable, but it does not remove the need to compare whole particles, extracts and residues at matched doses. Air-liquid-interface research has also expanded to repeated exposures, combustion smoke, mixed-pollutant designs, three-dimensional cultures and source-specific particles, allowing a closer examination of how exposure system and delivered dose influence epithelial responses (Navarrete-Aliaga et al. 2025; Chivé et al. 2025; Ashrin et al. 2025; Henriquez et al. 2025; El Hajjar et al. 2026; Küstner et al. 2024; Chen W et al. 2024; Ji et al. 2025).

Systemic effects may arise through inflammatory mediators released from the lung, autonomic imbalance, endothelial dysfunction, altered coagulation or translocation of a small fraction of particle constituents. In animals exposed to panels of PM-associated metals, individual elements produced different pulmonary and cardiac response profiles, arguing against treating 'metals' as a single toxic category (Wallenborn et al. 2009). Experimental work has also reported impaired microvascular relaxation and altered cardiovascular function after exposure to metal-rich $PM_{2.5}$ (Niu et al. 2013). Epidemiological studies have associated long-term exposure to Ni, Zn and other component markers with cardiovascular or mortality outcomes, but correlation with broader combustion mixtures and differences in exposure models prevent a simple ranking of metal potency (Liu et al. 2021; Chen S et al. 2024).

Speciation should therefore be treated as a primary variable rather than an afterthought. Cr(VI) crosses membranes more readily and is more genotoxic than Cr(III); inorganic As species differ in metabolism and toxicity; and Pb or Ni bound within stable minerals may be released more slowly than the same elements in soluble salts, although low solubility can also prolong residence time. Recent road-dust work from Pakistan paired ALF extraction with equilibrium modeling and showed the value of relating accessible concentration to predicted chemical species rather than reporting total metal alone (Moryani

et al. 2026). Spectroscopy, sequential extraction and kinetic dissolution measurements could strengthen this type of source-specific interpretation. Recent human and experimental studies likewise examine metal burden, chemical form and exposure context as determinants of deposited dose and oxidative response (Hsu et al. 2024; Khoshakhlagh et al. 2024; Zhang X et al. 2022; Lang et al. 2025).

7 Toxicity of particle-bound PAHs and their derivatives

Inhaled PAHs are distributed across both gas and particle phases. Two- and three-ring compounds are mainly present in vapor, whereas five- and six-ring PAHs, including benzo[a]pyrene, are much more strongly associated with particles. Partitioning shifts with temperature, dilution, atmospheric oxidation, quantity and composition of organic and elemental carbon. A review focused on particle-bound PAHs therefore captures an important but incomplete part of total PAH exposure. The particle phase is particularly relevant for persistent, high-molecular-weight and carcinogenic compounds carried deep into the lung on fine soot (Ravindra et al. 2008; Yang et al. 2021). Recent work has broadened exposure assessment beyond the traditional parent compounds to include personal exposure, household sources, and nitro- and oxy-PAH mixtures (Barbosa et al. 2023; Zhang Y et al. 2024; Lara et al. 2023; Fu et al. 2025). Many parent PAHs become strongly reactive only after metabolic activation. AhR signaling induces CYP1A1 and related enzymes that can generate epoxides, diol epoxides, phenols and quinones. These metabolites may form bulky DNA adducts, generate ROS through redox cycling, alter DNA methylation and contribute to mutation when repair or apoptosis fails. Nitro-PAHs can be activated by reduction and are often directly mutagenic, while oxy-PAHs and quinones add electrophilic and oxidative activity. These mechanisms underpin the carcinogenic classification of several individual PAHs and are consistent with the broader carcinogenicity of outdoor air pollution (IARC 2010, 2016; Bandowe and Meusel 2017). More recent toxicological and epidemiological syntheses continue to identify genotoxic and carcinogenic concerns for PAHs and particle-associated combustion mixtures, while also emphasizing heterogeneity in dose, mixture composition and susceptibility (Barbosa et al. 2023; Arif et al. 2024).

Particle binding changes both PAH delivery and what a bioaccessibility assay measures. Strong sorption to black carbon may limit immediate desorption into simple saline, yet macrophage lipids, proteins and surfactants can increase solubilization, and uptake of the carrier particle may bring sorbed PAHs close to metabolically active cell membranes. In Caofeidian, China, $PM_{2.5}$-bound PAHs showed marked compound-specific differences in bioaccessibility as well as seasonal and source-related differences in apportioned risk (Zeng et al. 2021). Another study found higher mean accessibility in inflammatory than in healthy lung-fluid models, suggesting that disease-related changes in surfactant and protein composition can modify the effective dose (Zhou et al. 2022). The numerical estimates from both studies are summarized in Table 3.

Parent PAHs alone do not account for the genotoxicity of ambient organic extracts. Diesel and urban PM extracts can activate oxidative and electrophilic stress pathways in bronchial epithelial cells, and oxidative DNA damage provides one plausible link between repeated inflammation and carcinogenesis

(Li et al. 2002; Risom et al. 2005). Extraction method is critical: solvent extracts may recover compounds that are not readily released in the lung, whereas aqueous extracts may underrepresent hydrophobic constituents. Effect-directed approaches that combine physiologically relevant extraction with high-resolution mass spectrometry and endpoints such as AhR activity, mutagenicity or DNA adduct formation are therefore more informative than assigning all activity to benzo[a]pyrene equivalents.

Source-resolved cell studies add some of the environmental complexity that is lost in single-chemical experiments. Road-tunnel particles produced AhR activity and pro-inflammatory responses that varied with particle size and composition in bronchial epithelial models (Holme et al. 2023). At the air-liquid interface, $PM_{2.5}$ from different sources and with different metal and PAH profiles produced distinct cytotoxic responses in A549 cells, with traffic-derived material among the more active samples (Yan et al. 2024). These findings support pairing chemical characterization with biological testing instead of attributing toxicity to total PAH concentration alone. Work with benzo[a]pyrene and physiologically relevant particle extracts also shows that epithelial model choice and exposure method can influence the observed response (Boulé et al. 2025).

Cancer-risk calculations commonly convert PAHs to benzo[a]pyrene toxic equivalents and combine total or accessible concentrations with default inhalation factors. This is useful for screening, but the result inherits uncertainty from toxicity-equivalency factors, gas-particle partitioning, bioaccessibility, exposure duration and metabolic susceptibility. Scenario-based ranges are therefore more defensible than highly precise probabilities, and neither approach should distract from controlling the combustion sources that emit the full mixture. Recent meta-analyses and cohort syntheses have examined air-pollution-related cancer risk across ambient, household and constituent-specific exposure settings, underscoring both the overall concern and the importance of keeping these exposure contexts distinct (Wang M et al. 2025; Arif et al. 2024; Ramamoorthy et al. 2024; Peng et al. 2025; McAllister et al. 2025).

8 Mixture effects and oxidative potential

Metals and organic compounds coexist on the same particles and can modify one another's behavior. Cu and Fe can catalyze quinone redox cycling, while humic-like substances and dicarboxylic ligands may solubilize metals, alter their redox potential or bind them in less reactive complexes. Whether the net effect is synergistic, additive or antagonistic depends on concentration and ligand chemistry. Experiments with defined PM components have demonstrated both synergy and antagonism in cytotoxicity, showing why effects cannot simply be summed across individual components (Wang et al. 2020). Simulated-fluid studies likewise indicate that metal-organic interactions can modify oxidative potential (Wu et al. 2022; Lin and Yu 2026). A 2025 comparison of $PM_{2.5}$ from two Chinese megacities integrated trace metals, PAHs, biological constituents and source information and reached the same broader conclusion: particle mass alone does not reliably predict toxicity (Wang Y et al. 2025).

Oxidative potential (OP) describes the capacity of PM to consume antioxidants or generate oxidants under a defined assay condition. Common acellular methods use dithiothreitol, ascorbate, glutathione,

synthetic respiratory-tract lining fluid or electron paramagnetic resonance, but these assays probe different aspects of reactivity and are not interchangeable. Dithiothreitol tends to respond to quinones and some transition metals, whereas ascorbate depletion may be particularly sensitive to Cu and Fe. Reporting OP both per volume of air and per mass of particles helps distinguish exposure intensity from intrinsic particle activity. European source-apportionment data show that the sources contributing most to PM mass are not necessarily those contributing most to OP (Daellenbach et al. 2020). Field measurements have linked OP with Fe, Cu and aged organic aerosol, although the strength of these relationships varies by assay and location (Gao et al. 2020). In size-resolved urban PM, element bioaccessibility and dithiothreitol activity also followed different patterns across fluids and seasons (Cigánková et al. 2021). OP is therefore most useful as a complementary measure of particle reactivity, not a substitute for chemical characterization. Recent source-resolved studies similarly report assay-, size-, solubility- and source-dependent differences in OP (Kim et al. 2025; Famiyeh et al. 2023; Liu et al. 2023; Xu X et al. 2025; Koo et al. 2025; Zhang LY et al. 2025; Famiyeh et al. 2025; Fadel et al. 2023). Acellular OP assays cannot reproduce cellular uptake, metabolism, repair or immune signaling. Some OP metrics correlate with cellular oxidative responses or selected human outcomes, but this relationship is inconsistent across assays and settings (Øvrevik 2019; Gao et al. 2020). A low OP result does not exclude receptor-mediated PAH toxicity, metal substitution in enzymes or chronic genotoxicity, and a high result does not by itself establish an adverse effect at an ambient dose. Table 4 therefore places OP within a broader mechanistic evidence matrix rather than treating it as a universal toxicity index.

Table 4
Integrated evidence matrix for metals, PAHs, and particulate-matter mixtures

Mechanistic domain	Metals	PAHs and derivatives	Key limitation or modifier
Initial dose	Dissolution, speciation, surface catalysis, cellular particle uptake	Desorption, gas–particle partitioning, carrier uptake, metabolism	Ambient concentration, deposited dose, and extracted fraction are different metrics
Oxidative stress	Fe/Cu redox cycling; antioxidant depletion; mitochondrial injury	Quinone redox cycling; electrophilic stress; metabolic ROS	Acellular assays differ in sensitivity and omit metabolism and repair
Inflammation and barrier injury	Epithelial cytokines, macrophage activation, inflammasome signaling, neutrophilia	AhR-dependent and oxidative signaling; epithelial and immune modulation	Dose rate, endotoxin, salts, and co-pollutants can modify response
Genotoxicity and carcinogenesis	Oxidative lesions; interference with repair; Cr(VI), Ni, As, and Cd have species-specific pathways	DNA adducts, mutations, epigenetic change; strong evidence for selected PAHs and combustion mixtures	Solvent extracts and benzo[a]pyrene equivalents may misrepresent the in-lung mixture
Cardiovascular and systemic effects	Endothelial dysfunction, autonomic imbalance, coagulation, mediator release, limited translocation	Systemic metabolites and inflammation; vascular oxidative stress	Human constituent associations are vulnerable to source confounding
Mixture interaction	Complexation can increase or decrease solubility and redox activity	Quinones and humic-like organics can interact with Fe/Cu/Mn	Responses can be synergistic or antagonistic and concentration-dependent
Weight of evidence	Strong mechanistic evidence for some soluble transition metals; important roles for insoluble particles and speciation	Strong mechanistic evidence for metabolically activated PAHs; incomplete coverage of derivatives	No universal toxicity ranking applies across sources, sizes, and populations

Note

The matrix identifies converging mechanisms, not equivalence of evidence across endpoints. Interpret alongside whole-particle testing and human exposure data.

9 From experimental evidence to human health

Human evidence is strongest for PM mass and broad source mixtures and is less certain for isolated constituents. Component-specific models face collinearity, spatial exposure misclassification, multiple

comparisons and sparse monitoring. Metals may serve as markers for residual-oil combustion, industry, brake wear or resuspended dust, while PAHs often track combustion, black carbon and other organics. An association with Ni or benzo[a]pyrene therefore does not, by itself, establish that the measured constituent caused the effect. Confidence is stronger when multi-pollutant or source-resolved analyses are replicated across settings with different source mixtures and supported by appropriate sensitivity analyses. Recent component-specific epidemiology and exposure-method studies further illustrate that estimated health associations can vary with constituent mixture and with the model used to assign $PM_{2.5}$ exposure (Yan et al. 2025; Kazemiparkouhi et al. 2022; Yu et al. 2024).

A 2024 meta-analysis of long-term $PM_{2.5}$ constituents reported associations between several components and total or cause-specific mortality, including a comparatively large estimate for Ni, while also documenting substantial heterogeneity across regions and populations (Chen S et al. 2024). Long-term studies from China have likewise linked selected constituents with cardiovascular disease (Liu et al. 2021). These findings are consistent with composition modifying PM risk, but they do not justify a stable global ranking of constituent potency because source profiles, exposure models and baseline vulnerability differ between populations. The more defensible interpretation is that transition-metal-rich mixtures warrant both source control and continued mechanistic study. Large cohort, multicohort and systematic-review studies have also examined constituent-resolved associations with cardiovascular disease, infection-related admissions and other outcomes across diverse settings, including low- and middle-income countries (Feng Y et al. 2024; Gyaase et al. 2025; Wang S et al. 2023; Feng Y et al. 2026; Luo et al. 2026; Guo et al. 2023; Karimi and Samadi 2024).

Experimental studies can add causal detail, but they do so at some cost to realism. Intratracheal instillation delivers a bolus and bypasses normal upper-airway deposition; submerged cell cultures do not reproduce the air-liquid interface; filter extracts remove insoluble particles and volatile species; and nominal concentration in a culture dish is not the same as delivered cellular dose. Controlled inhalation studies are more realistic but are expensive and ethically constrained. Translation is strongest when deposited-dose modeling, air-liquid-interface systems, repeated low-dose exposure, atmospherically aged source mixtures and matched chemical measurements are combined across acellular, cellular, animal and human evidence tiers.

Susceptibility is part of the exposure-response pathway rather than statistical noise. Asthma, chronic obstructive pulmonary disease, infection, antioxidant depletion, age, pregnancy, cardiometabolic disease, genetics, nutrition and co-exposures can all influence deposition, barrier integrity, metabolism and clearance. The greater PAH accessibility observed in inflammatory lung-fluid models provides one example of host state altering the effective dose (Zhou et al. 2022). Studies based only on healthy adult physiology may therefore underrepresent dose or response in more vulnerable groups. Recent reviews addressing children, pregnancy and populations with higher personal exposure further support explicit consideration of life stage and setting when interpreting exposure-response relationships (Li K et al. 2025; Lim et al. 2022; Daba et al. 2024; Wang W et al. 2023).

10 Implications for risk assessment and regulation

Mass-based standards remain central to air-quality protection. No single composition metric captures the full harm of PM, monitoring networks are built largely around mass, and reducing mass generally lowers population exposure. The 2024 U.S. revision of the annual $PM_{2.5}$ standard to 9.0 μg m^{-3} and the lower WHO guideline both reflect the continuing public-health importance of mass control (U.S. EPA 2024; WHO 2021). On 26 June 2026, the U.S. Court of Appeals for the District of Columbia Circuit denied challenges to the rule and EPA's request for vacatur (U.S. Court of Appeals 2026). Composition-resolved evidence can refine priorities, but it is not a reason to delay broad reductions in PM exposure.

A tiered approach offers a practical way to use bioaccessibility without giving it more weight than it can support. Tier 1 would characterize PM mass, particle size, source markers, total metals and a broad organic profile. Tier 2 would add compartment-specific release in a neutral extracellular fluid and ALF, with a lipid- and protein-containing fluid when PAHs are central. Tier 3 would extend the analysis to metal speciation, PAH transformation products, multiple OP assays, and matched-dose comparisons of whole particles, extracts and residues. Tier 4 would test the highest-priority sources in controlled inhalation, biomarker or epidemiological studies. The tiers are intended to work iteratively: an unexpected toxicological signal can prompt non-target chemical analysis, while a strong chemical signal can guide source-specific monitoring.

For screening purposes, accessible concentration should be derived from the total airborne concentration and an experimentally measured accessible fraction appropriate to the particle size and physiological compartment being modeled. Uncertainty should include sampling error, digestion recovery, fluid choice, solid-to-liquid ratio, kinetic behavior and day-to-day variation. Applying a single literature-derived percentage from one city or source to another is rarely defensible. Where possible, metals should be evaluated with speciation-specific toxicity information; where this is unavailable, assumptions should be explicit and conservative. For PAHs, gas and particle phases and important derivatives should be reported separately whenever the available data allow.

Source control is generally more robust than attempting to manage one constituent at a time. Relevant measures include cleaner household energy, industrial capture and fuel substitution, tighter control of residual-oil and coal combustion, brake and tire standards, street and construction-dust management, stabilization of mine tailings and preparation for wildfire-smoke episodes. The balance of benefits will vary by location. A source that contributes only moderately to PM mass may still merit attention if it repeatedly shows high accessible-metal concentrations or OP and the finding is reproducible. Equity also needs to be considered from the outset. People living near major roads, workers in informal recycling or smelting, households dependent on solid fuels, and communities near mines or industrial corridors may experience mixtures and concentrations that central monitoring stations represent poorly. Low- and middle-income regions remain underrepresented in standardized bioaccessibility and speciation studies despite often high exposure. Portable size-resolved sampling, community-engaged monitoring and more accessible analytical methods could help narrow this evidence gap. Recent environmental-justice

research has examined how exposure burdens and the benefits of air-quality improvement are distributed, supporting the use of place-based exposure assessment, equity metrics and risk communication in intervention planning (Sandoval et al. 2025; Mustansar et al. 2025; Chambliss et al. 2024; Gohlke et al. 2023; Xu Y et al. 2024; Freeman et al. 2024).

11 Research priorities and minimum reporting standards

A first priority is methodological harmonization around a question-specific core rather than a single rigid protocol. Laboratories should use agreed reference materials, report fluid recipes in molar units, verify pH before and after extraction, document particle loading and mixing, distinguish dissolved material from colloids, and account for the full mass balance. For metals, neutral extracellular and acidic lysosomal conditions should be examined in parallel; when hydrophobic organics are central, a surfactant- and protein-containing condition should be added. Before any fixed regulatory cutoff is considered, interlaboratory studies need to establish how reproducible these measurements actually are.

Chemical resolution also needs to improve. Total element concentrations should be paired, where relevant, with oxidation state, mineralogy or binding phase. Organic analysis should extend beyond the 16 legacy PAHs to include nitro-PAHs, oxy-PAHs, quinones and non-target features. Time-resolved sampling and controlled-aging experiments can help distinguish fresh emissions from products of atmospheric transformation. Studies should keep ambient dose and intrinsic potency in view at the same time so that a highly reactive but low-concentration sample is not mistaken for a large population exposure.

A third priority is to connect extraction results directly with biology. Whole PM, extracts and extracted residues should be compared at equivalent deposited doses in air-liquid-interface co-cultures containing both epithelium and macrophages. Useful endpoints include barrier integrity, cytokine release, mitochondrial function, oxidative damage, genotoxicity and cell-death pathways, measured at enough time points to distinguish transient adaptation from sustained injury. Physiologically based models and animal or controlled-human data can then test whether the accessible fraction predicts tissue dose better than total concentration alone.

Mixture studies are also needed to move beyond one-chemical-at-a-time extrapolation. Factorial and response-surface designs can test interactions among Fe, Cu, quinones, black carbon, sulfate acidity and organic ligands. Multiple OP assays can be paired with mechanistic perturbations such as metal chelation, antioxidant depletion, AhR antagonism or metabolic inhibition to identify the pathways that contribute most strongly to a response. Machine-learning approaches may assist source attribution, but mechanistic interpretation requires external validation and transparent, interpretable features. Finally, human studies would benefit from pairing high-resolution exposure assessment with repeated biomarkers and clinically meaningful outcomes. Personal and microenvironmental monitoring can reduce exposure error, while natural experiments around source controls can strengthen causal inference. Cohorts should include sufficient numbers of children, older adults, pregnant people, workers

and patients with cardiopulmonary disease rather than relying mainly on healthy adults. Sharing protocols, raw chemical data, code and negative findings would also make the evidence easier to reproduce and synthesize. Table 5 summarizes a minimum reporting checklist that could be implemented now.

Table 5
Minimum reporting checklist for inhalation-bioaccessibility studies

Domain	Minimum information	Why it is necessary
Sampling	Location, dates, meteorology, source context, sampler, inlet, flow, duration, particle-size cut, filter type, storage, blanks	Defines the exposure and identifies sampling artifacts
Particle characterization	Air concentration, recovered mass, size distribution, morphology, carbon, major ions, total metals, target organics, and source markers	Prevents interpretation of an isolated percentage without ambient dose or matrix context
Fluid	Full recipe and supplier/purity, target compartment, pH before and after, temperature, oxygen/headspace, proteins/lipids/antioxidants	Fluid chemistry controls dissolution, transformation, and apparent accessibility
Extraction	Solid-to-liquid ratio, loading per surface area, time points, mixing, vessel, light control, sequential/parallel design, replicate number	Enables reproducibility and physiological interpretation
Phase separation	Centrifugation, filter material and pore size, ultrafiltration if used, acidification and storage delay	Operationally defines dissolved, colloidal, and particle-bound fractions
Chemical analysis	Digestion/extraction, instrument, detection limits, blanks, spikes, reference material, isotope standards, speciation, transformation products	Demonstrates analytical validity and captures hazard-relevant forms
Mass balance and units	Total, accessible, residual, and recovered mass; percentage; mass per PM mass; mass or activity per air volume	Distinguishes intrinsic accessibility from population exposure
Toxicology	Whole PM, extract, and residue at matched delivered	Tests whether the chemical metric predicts biological response

Domain	Minimum information	Why it is necessary
	dose; model, exposure route, controls, viability, mechanism-specific endpoints	
Statistics and data	Prespecified comparisons, uncertainty, censoring, batch effects, raw data, code, and deviations	Supports replication, synthesis, and assessment of bias

Note

A harmonized core should be supplemented—not replaced—by disease- or compartment-specific variants that are explicitly justified.

12 Conclusions

Particle-bound metals and PAHs contribute to PM toxicity through several overlapping but distinct pathways, including dissolution and ion-mediated reactions, reactive particle surfaces, macrophage uptake, metabolic activation, receptor signaling, oxidative stress, inflammation, genotoxicity and systemic vascular responses. Total concentration remains essential for exposure assessment, but it cannot represent this mechanistic diversity on its own. The accessible fraction varies with source, particle size, atmospheric aging, speciation, respiratory compartment and extraction protocol, while insoluble material can remain biologically active even when little of it enters solution.

Three points emerge most clearly from the evidence reviewed here. First, compartment-specific simulated fluids are more informative than water or a single generic extract when they are used to answer a clearly defined physiological question. Second, metal-organic interactions can make mixture toxicity non-additive, so oxidative potential and component concentrations need to be interpreted together rather than in isolation. Third, standardized reporting and biological validation are necessary before bioaccessibility measurements can be used confidently in regulatory decision-making. A tiered framework that combines particle mass, source, speciation, bioaccessibility, OP and delivered-dose toxicology provides a practical route from ambient measurement to source prioritization. It should complement, not replace, continued efforts to reduce population exposure to PM mass.

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Figures

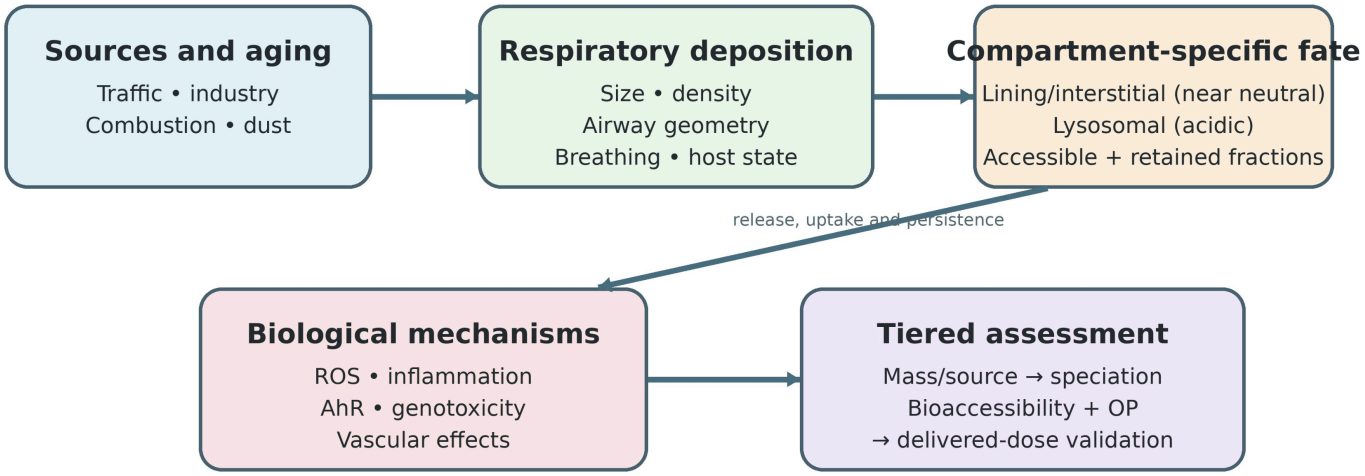


Figure 1

Conceptual pathway linking PM source and atmospheric processing to respiratory deposition, compartment-specific bioaccessibility, particle persistence, biological effects, and the tiered assessment framework. OP, oxidative potential. The conceptual content was developed by the author; OpenAI ChatGPT (GPT-5.6) assisted with code generation for figure rendering, and the author reviewed and verified the final figure. No empirical data are plotted.