

Review

Analytical Methods for Physicochemical Characterization and Toxicity Assessment of Atmospheric Particulate Matter: A Review

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Abstract: Particle-bound pollutants are a critical risk factor for human respiratory /cardiovascular conditions. A comprehensive analysis of the physicochemical characteristics of PM is often challenging since it requires combining different practical methods with a good understanding the of characterization outputs. The present review aims to (1) provide a comprehensive assessment of the underlying mechanisms of PM cytotoxicity and the related biological response; (2) evaluate the selected methods for PM characterization in terms of outputs, technical aspects, challenges, and sample preparation; (3) present effective means of studying PM physicochemical toxicity and composition; and (4) provide recommendations for enhancing the human health risk assessment. The cellular response to potentially toxic elements in PM is complex to understand as exposure includes systemic inflammation, increased ROS accumulation, and oxidative stress. A comprehensive toxicity assessment requires blending morphological features and chemical composition data. For the morphological/chemical characterization, we recommend first using SEM-EDS as a practical method for the single-particle analysis. Then, the bulk chemistry of PM can be further studied using either a dry analysis (e.g., XRF) or wet analysis techniques (e.g., ICP and IC). Finally, when used on a need basis, the reviewed complementary laboratory methods may further add valuable information to the characterization. The accuracy of the human health risk assessment may be improved using bioaccessible/soluble fractions of the contaminants instead of the total contaminant concentration. Having an integrated understanding of the covered analytical methods along with the health risk assessment guidelines would contribute to research on atmospheric chemistry, molecular biology, and public health while helping researchers better characterize human exposure to PM and the associated adverse health effects.

Keywords: atomic force microscopy (AFM); bioaccessibility; cytotoxicity; inductively coupled plasma (ICP); scanning electron microscopy (SEM); transmission electron microscopy (TEM); X-ray diffraction (XRD); X-ray fluorescence (XRF)



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1. Introduction

Airborne PM consists of solid or liquid particles in the air with varying sizes and chemical compositions. Depending on the mechanism of formation, PM could be categorized as either primary (emitted to the air) or secondary (formed in the air) and once emitted or formed, may go through further physicochemical transformations. PM concentration, size, morphology, and elemental composition are among the important indicators of air pollution. The presence of PM in the air could adversely impact human health, disrupt ecosystem stability, induce changes in weather patterns and climate, and impair atmospheric visibility [1]. A key parameter influencing human exposure to PM is its particle size,

as characterized by the aerodynamic diameter (d , diameter of a perfect sphere particle with a unit density exhibiting same aerodynamic properties), which is further defined as: TSP ($d < 100 \mu\text{m}$), PM_{10} ($d < 10 \mu\text{m}$), coarse PM ($2.5 < d < 10 \mu\text{m}$), $\text{PM}_{2.5}$ or fine PM ($d < 2.5 \mu\text{m}$), and $\text{PM}_{0.1}$ or ultrafine PM ($d < 0.1 \mu\text{m}$) [2].

Adverse human health effects from airborne PM exposure include chronic lung and cardiovascular diseases, heart attacks, asthma, limited lung functions, and breathing difficulties [3]. It is estimated that exposure to fine PM is responsible for approximately 2.1 million deaths [4]. In 2015, the IARC expert board on outdoor air pollution unanimously decided to include PM in the group of carcinogenic air pollutants [5]. Furthermore, many countries enforce limits on the allowable PM mass concentrations, some including both PM_{10} and $\text{PM}_{2.5}$, as a response to the public concerns and numerous studies confirming the adverse health effects of PM (e.g., [6–8]). Although the link between PM levels and adverse health impacts is well established, the mechanisms on how PM exposure leads to these impacts is less clear.

A significant determinant of PM toxicity is its physicochemical characteristics. Physical characteristics including particle size, shape, surface area, and solubility affect the toxicity induced by PM exposure. For example, fine PM fractions exhibit greater deposition rate in the respiratory tract along with an ability to penetrate deeper into the alveoli [9,10], resulting in the accumulation of ROS and the induction of oxidative stress. Regarding the chemical composition, for instance, PTEs in PM may reduce cell viability [11–13]. This happens via disrupting cellular functions and inducing an inflammatory response by increasing the number of inflammatory markers and inflammatory cells (e.g., lymphocytes and macrophages) [13–16]. Exposure to PM could also cause cellular apoptosis [12,17,18]. Numerous studies have investigated the changes in cell viability, the number of inflammatory markers, and cellular oxidative potential induced by PM exposure [19–23].

Various analytical techniques and assays have been developed to assess the toxicity of PM. A comprehensive analysis of the physicochemical characteristics of atmospheric particles could be challenging, since characterizing particle size, morphological features, molecular structure, and chemistry requires implementing a variety of practical methods along with a deep understanding of the characterization outputs. Several review studies have focused on PM characterization techniques using various real-time on-line and off-line laboratory analytical methods with the focus on PM sampling, sample preparation and handling, technique availability, and analytical instrument principles and performance [24–28]; (summarized in Table 1). However, these reviews have not fully investigated the molecular mechanisms of PM toxicity and are lacking details on methods that are yet to be thoroughly reviewed. The present review fills the literature gap by first giving a comprehensive analysis of the cytotoxic and inflammatory potential of PM that varies depending on particle size, morphology, and chemical composition. Moreover, this review focuses on the practical application of various off-line laboratory methods for PM characterization and provides guidelines for choosing appropriate analytical tools based on the specific aim of the experimental work.

Moreover, bioaccessibility and health risk assessment are discussed as valuable components of comprehensive PM characterization.

The present review aims to (1) reveal the underlying mechanisms of PM cytotoxicity; (2) assess methods of PM chemical speciation; (3) present effective means of studying PM physicochemical toxicity and composition; and (4) provide recommendations for the enhancement of the human health risk assessment framework.

Table 1. Summary of reviews on analytical methods for PM characterization.

Reference	Major Analytical Techniques Reviewed	Content
[28]	ICP-MS, XRF, PIXE, LA-ICP-MS, and INAA	✓ WHO, CEN, and U.S. EPA guidelines for monitoring PM elemental composition ✓ On-line techniques for PM characterization (XRF) ✓ PM sampling methods ✓ Comparison between common microwave digestion ICP-MS and direct analysis methods (sample preparation, elemental range, optimum filter matrix, sample introduction and calibration, validation of analytical method, availability and cost, and performance)
[27]	GS, LC, and CE	✓ PM sampling techniques ✓ On-line and off-line techniques for PM characterization ✓ Extraction and clean-up techniques for organic contaminants ✓ Determination of analytical techniques for characterization of organic contaminants based on study interest
[25]	ICP, AAS, CE, XRF, PIXE, PIGE, PESA, GS, LC, IC, TOC, XPS, XRD, SIMS, SEM, SPEM, PEEM, Raman, Mossbauer, and AES	✓ PM sampling and sample preparation ✓ Atomic spectrometry-based techniques ✓ X-ray-based techniques ✓ Surface analysis techniques ✓ Techniques for the analysis of organic and carbonaceous compounds ✓ On-line particle analysis techniques
[26]	ICP, XRF, XRD, SEM, and TEM	✓ Typical PM_{2.5} and PM_{0.1} concentrations for different microenvironments ✓ Methods for PM_{2.5} and PM_{0.1} collection ✓ Destructive and non-destructive techniques for PM characterization ✓ In vitro analyses for the assessment of PM toxicity ✓ Optimization in particle collection
[24]	ICP, SEM, TEM, XPS, SIMS, EXAFS, EELS, PIXE, LMMS, and SPMS	✓ Air sampling techniques (active and passive samplers, sampling substrates) ✓ Electron microscopy-based techniques ✓ Atomic spectroscopy-based techniques ✓ On-line analytical techniques for PM characterization
The present study	ICP-MS/OES, IC, SEM, TEM, AFM, XRD, XRF, XPS, DCFM-DA, DHE, MitoSOX, and Bioaccessibility	✓ Physicochemical determinants of PM toxicity ✓ Destructive and non-destructive techniques for PM characterization ✓ Techniques for determination of cellular/mitochondrial ROS ✓ In vitro bioaccessibility assessment ✓ Health risk assessment

2. Methodology

The present review is based on scientific articles on the physicochemical characteristics of ambient PM, PM-induced toxicity, and analytical techniques for investigating PM morphology and chemical composition. A systematic literature search was performed using Scopus, Science Direct, Google Scholar, and PubMed databases. The keyword combinations for the literature search included: PM₁₀, coarse PM, fine PM, ultrafine PM, atmospheric particulates, urban aerosol, physicochemical characterization, toxicity, genotoxicity, ROS, oxidative stress, inflammation, A549 cells, inflammatory cytokines, health effect, pulmonary fibrosis, PM morphology, PM size, particle structure, single-particle analysis, PTE, heavy metals, trace

elements, destructive and non-destructive techniques, PM measurement instruments, PM monitoring, ICP-MS/AES, IC, XRD, XRF, EDS/EDX, TEM, SEM, and AFM.

The literature search resulted in over 1030 papers. The abstracts, methodologies, and major findings of the articles identified through the literature search were considered, and about 171 articles were found to be eligible for discussion in the present review. The scientific articles related to the toxicity mechanisms of PM exposure as well as to various analytical methods for PM characterization are complex and increasing rapidly, thus we included only articles published in peer-reviewed journals and official reports, published between 2000 and 2022, and written in English. We excluded studies published prior to 2000 because we focused on recent analytical methods and instrumentation available to date.

We excluded articles related to organic contaminants (except PAHs), biological pollutants, anthropogenic ions, and gaseous species. Similarly, studies on indoor pollution were beyond the scope of the present review. The process of article selection is described in Figure 1.

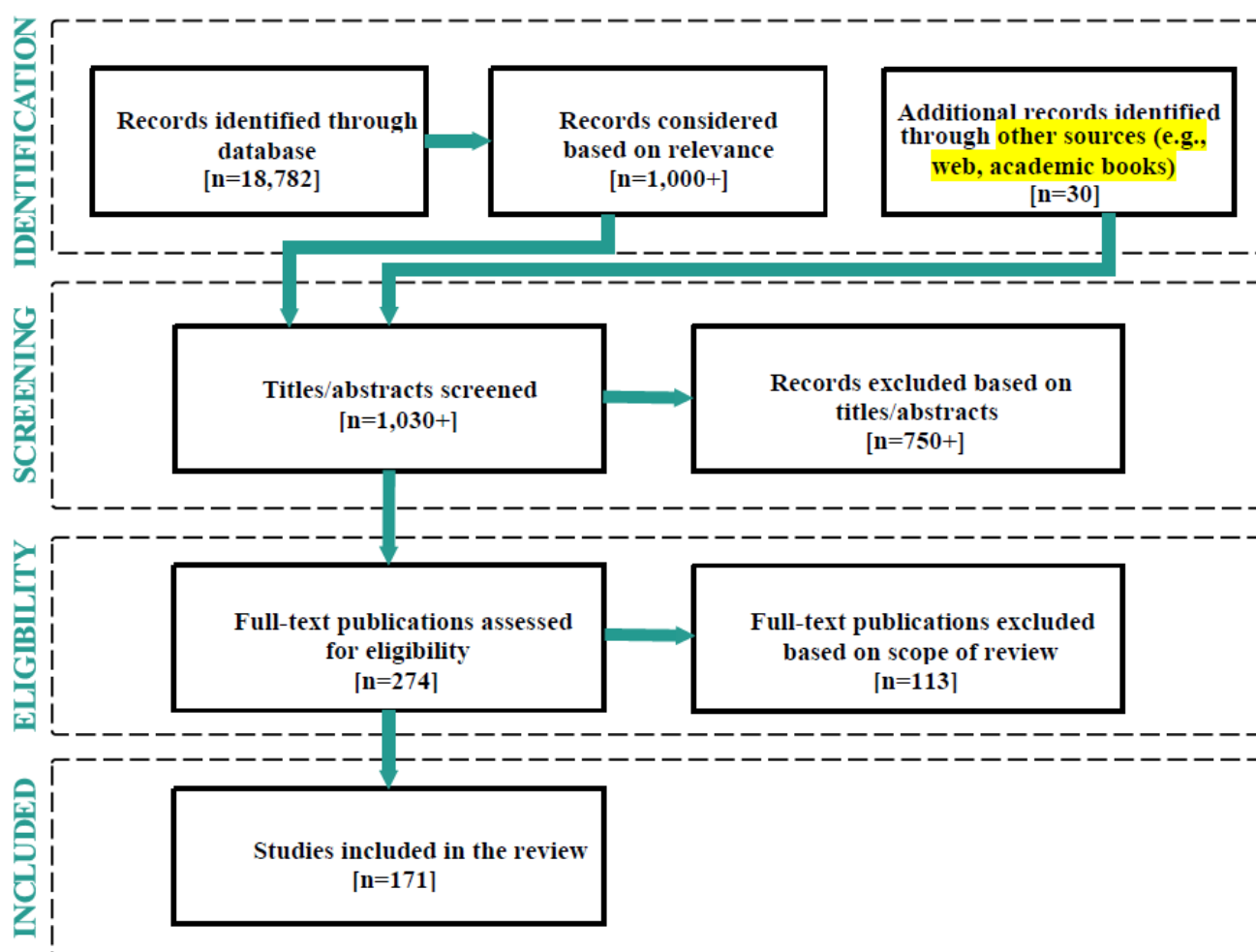


Figure 1. Flow chart of article selection process.

3. Physicochemical Characteristics of PM as Determinants of Toxicity

The current objective of epidemiological studies on the adverse effects of PM is to determine the cause and effect dynamics among the elemental composition of PM, cellular mechanism, and related disease progression [22]. Toxicology studies could complement epidemiological studies and elucidate the mechanisms underlying the observed health effects [29–31]. Toxicological investigations on PM have revealed the ability of airborne particles to increase the amount of ROS, disrupt the oxidative potential of cells, and induce oxidative stress [13–16]. Moreover, PM is also characterized by the accumulation of

inflammatory markers and inflammatory cells [32,33]. The suggested mechanism for the response to PM exposure is given in Figure 2. Overall, the Fenton reactions of transition metals (e.g., Fe) can produce highly reactive $\bullet\text{OH}$ radicals, whereas the activation of cellular signaling pathways increases the formation of H_2O_2 and $\text{O}_2^{\bullet-}$. Free radicals promote oxidative DNA damage, lipid oxidation, and protein carboxylation. The defense mechanisms include the activation of NAD(P)H quinone oxidoreductase 1 (NQO1) and cytochrome P450 (CYPs) proteins to reduce the free radical load [34]. Health risks from exposure to atmospheric particulates are associated with their physical characteristics and chemical composition [35–37].

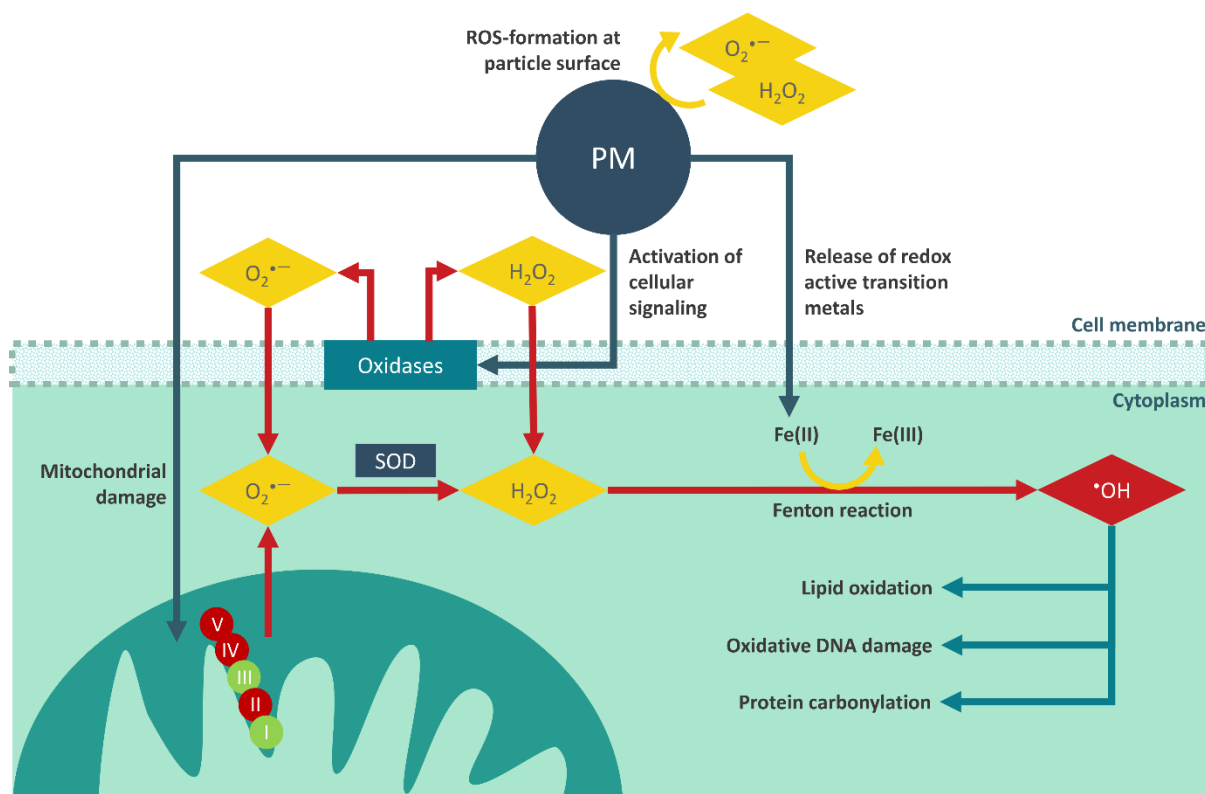


Figure 2. Suggested model of cellular response to PM exposure. PM-bound PTEs induce production of free radicals (via Fenton reaction) and activation of cellular signaling pathways resulting in cellular and mitochondrial damage. (Adapted from [34]). Overall, Fenton reactions of transition metals (e.g., Fe) can produce highly reactive $\bullet\text{OH}$ radicals, whereas the activation of cellular signaling pathways increases the formation of H_2O_2 and $\text{O}_2^{\bullet-}$. Free radicals promote oxidative DNA damage, lipid oxidation, and protein carboxylation. The defense mechanisms include the activation of NAD(P)H quinone oxidoreductase 1 (NQO1) and cytochrome P450 (CYPs) proteins to reduce free radical load [34].

3.1. Cytotoxic and Inflammatory Potential of Different Size Fractions of PM

It has been suggested that fine fractions of PM ($d < 2.5 \mu\text{m}$) are more toxic due to their ability to penetrate deeper into the pulmonary alveoli and their retention in the respiratory system [9,10,38]. Smaller particles contribute largely to the particle number count, whereas coarse particulates contribute more to the total particle mass [10,39]. Moreover, [40] showed that during the accumulation phase of PM, the number of fine PM particles ($d < 0.35 \mu\text{m}$) increased significantly compared to coarse particles, which indicates that fine particles tend to accumulate through particle number rather than particle mass. The aggregation of smaller fractions impairs the phagocytic function of alveolar macrophages, enhancing the penetration into the lower sections of the respiratory tract [35]. Fine particles also induce a greater inflammatory response due to a larger surface area to volume ratio, higher reactivity,

and presence of organic carbon and PAHs [41,42]. Moreover, the presence of primary and secondary chemical components in fine PM from anthropogenic sources (e.g., primary: OC, BC; secondary: SO_4^{2-} , NH_4^+ , and NO_3^-) is associated with an increased risk of premature birth and asthma [40,43]. Numerous studies have demonstrated the greater inflammatory potential of fine PM compared to the coarse fraction (e.g., [10,11,39]. For example, [44] reported an inflammatory response induced by $\text{PM}_{0.5-2.5}$ in the macrophage-like J774 cell lines. Moreover, acute and sub-chronic exposure to fine and ultrafine PM can lead to Nrf2 molecular pathway activation indicating oxidative stress, which was not observed for the coarse PM fractions [41].

Once inhaled, coarse PM tends to deposit in the upper parts of the respiratory tract and then are cleared primarily by mechanical clearance or dissolution [45], which explains the lower biological response to coarse PM exposure [41]. However, exposure to PM_{10} can cause a higher accumulation of $\text{TNF-}\alpha$ (an inflammatory mediator), compared to $\text{PM}_{2.5}$ exposure indicating a greater inflammatory response [9,17]. Moreover, the highest level of HO-1, antioxidant enzyme, which is a marker of cellular oxidative stress, was attributed to PM_{10} [41]. [46] reported a more distinct gene expression pattern following coarse PM fraction exposure, while the patterns from exposure to fine and ultrafine PM patterns were similar. Overall, both coarse and fine PM can induce toxicity and should be considered equally significant.

3.2. Particle Morphology as a Modular of PM Toxicity

Particle morphology is another essential factor affecting the level of induced cytotoxic effect. The internal structure of primary particles can be classified into: (a) purely turbostratic structures; (b) fullerenoid (onion-shaped) structures; (c) turbostratic structures with non-aligned basal planes; and (d) shell-core structures with multiple spherical nuclei oriented concentrically, making up the “outer core” with randomly oriented layers (Figures 3 and 4) [36,47]. Several studies have also reported the ability of particulates to exhibit certain shapes and form chain-like or grain-like structures (e.g., soot from diesel exhaust) [36,48,49].

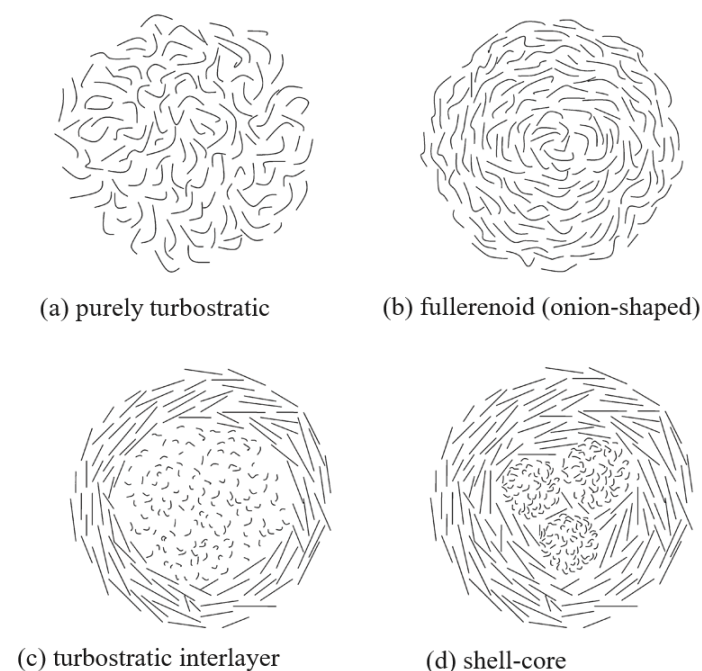


Figure 3. Schematic illustration of the internal structure of primary particles. Reproduced from [50] with permission from *Applied Energy*.

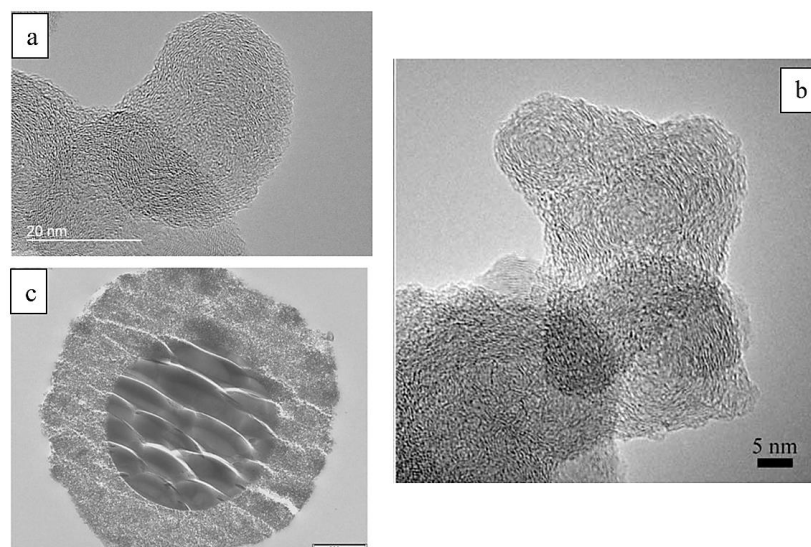


Figure 4. TEM micrographs of selected internal structures of primary particles: (a) purely turbostratic, (b) fullerene-like (onion-shaped), and (c) shell-core (Reproduced from [51] with the permission of *The Journal of Geophysical Research*; ref. [52] with the permission of *The Journal of Chromatography A*; ref. [47] with the permission of *Fuel*).

Commonly, high-temperature anthropogenic combustion processes (e.g., industrial combustion) produce particles that are spherical in shape [53]. A recent review [54] discussed the barrel-, disk-, and rod-shaped particle interactions with cellular structures, revealing that barrel- and disk-shaped micro/nanoparticles can disrupt the structure of the DPPC monolayer, which is the primary phospholipid of the pulmonary surfactant (Figure 5). Moreover, barrel-shaped particles can cause more damage to the structure of the lung surfactant due to their larger contact area. However, rod-shaped particles disrupt the alveolar structure by having greater penetration ability due to a higher length-to-diameter ratio.

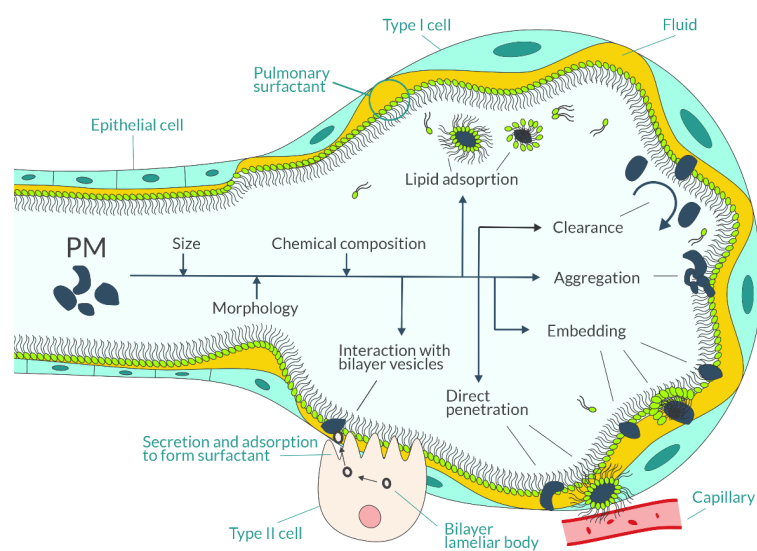


Figure 5. Structure of human alveolus. Type II alveolar cells produce proteins and lipids forming pulmonary surfactant. The major phospholipid of pulmonary surfactant is DPPC. The interaction of PM with alveolar surfactant depends on various factors including physicochemical characteristics (e.g., morphology, size, and elemental composition) of PM particles. PM can penetrate alveoli as a single particle or form particle aggregates. The cellular structure is compromised due to direct particle penetration or formation of particle–bilayer vesicle complex. After penetration, PM can also invade capillaries. (Adapted from [54]).

It is also suggested that capillary force is one of the determinants of particle dynamics and the disruption of the pulmonary surfactant. Morphological features (including sharp edges, surface defects, and fractures) increase the capillary force as well as determine the particle reactivity and potential toxic effect [55]. Cylindrical or cubical particles tend to exert a higher capillary force due to the pinning of the air–water interface line at the edges [56]. Mechanical action induced by the particulates also contributes to mitochondrial damage resulting in the initiation of a series of cellular pathways that can disrupt metabolic activity and inhibit ATP synthesis. Irregularly shaped particles impair the cellular structure by damaging cell membranes and other organelles [57]. Moreover, the accumulation of particles impairs the pulmonary clearance mechanism and may induce an indirect toxic effect due to a prolonged contact with toxic constituents of PM and corresponding cellular response, which will be described in detail in the following section.

3.3. Chemical Composition as a Determinant of PM Toxicity

The cytotoxicity of different PM fractions is linked to the size, morphological characteristics, and chemical composition of the particulates. The present review mainly focuses on the cytotoxic and inflammatory effects of PTEs, while also including PAHs as an important group of organic contaminants. It should be noted that there are also other fractions in PM (e.g., OC, BC, VOCs, SO_4^{2-} , and NO_3^-) that have the potential to induce significant toxicity. These are excluded from the present review; however, these contaminants along with their related biological responses have been described elsewhere, e.g., [58–61].

3.3.1. PTEs

Although the exact molecular mechanism of PM cytotoxic effects is still unclear, it has been suggested that the cell response to environmental stimuli involves the activation of complex cellular pathways and transduction processes [62]. PTEs cross the cell membrane through membrane proteins by cell entry mechanisms, including facilitated diffusion and transport [13].

Once in the cell, PTEs can implicate an inflammatory cell response [21,63,64]. Metal-induced inflammatory response is indicated by the accumulation of pro-inflammatory markers including IL-6, IL-1 β , TNF- α , and IL-8 [11,16,19,21]. Moreover, metal-induced oxidative stress following PM exposure is also related to a reduction in antioxidant capacity of dismutases (SODs), catalase, and Gpx [13,19,32].

Several studies have reported a negative correlation between cell viability and certain PTEs [11–13]. An elaborate description of PTE-induced toxic effects is summarized in Table 2. To exemplify, Pb induces a disruption of cellular functions by mimicking Ca [65]. Pb also inhibits enzyme activity due to its stronger affinity than Zn, which acts as an enzyme cofactor. Moreover, Pb is reported to have a significant positive correlation with an increased NO radical that can trigger cell toxicity [13,21]. Regarding Ni, the proposed mechanism of toxicity is also a higher binding capacity to enzymes and proteins, impairment of mitochondrial function, and induction of cell apoptotic mechanisms [17]. Cu in PM_{2.5} is reported to increase the expression of pro-inflammatory cytokine genes indicating a cellular response to ROS accumulation [12]. Furthermore, Cu and Ni have also been linked to the accumulation of HO-1 [63]. Fe-containing particles could demonstrate cytotoxic and genotoxic effects by disrupting DNA and mitochondrial function, producing NO and OH radicals in lung epithelial cells [17,66]. Among other PTEs, V, Cr, Mn, Cd, and Sb are reported to be responsible for the damage of the DNA plasmid [19,20]. As and Zn are associated with the production of IL-8, further indicating a pro-inflammatory response [19]. Disruption in Zn homeostasis is proposed to destabilize the endosomal membrane and cell apoptosis [65].

Table 2. Toxic effects, toxicity mechanisms, and major sources of selected PTEs bound to PM.

PTE	Mechanism of Toxicity	Reference Concentration (RfC) by U.S. EPA, IRIS (mg/m ³)	Non-Carcinogenic Toxic Effect	Carcinogenic Toxic Effect	Major Sources	References
Arsenic (As)	Induces pro-inflammatory response by production of IL-8, IL-6 Increases level of c-reactive protein (CRP) and vascular endothelial growth factor (VEGF)	1.5×10^{-5}	Skin and mucous membrane irritation Increased risk of spontaneous abortion and low birth weight	Association with lung, skin, liver, and bladder cancer Group A human carcinogen	Vehicle emissions Industrial activity Coal and oil combustion	[67–75]
Lead (Pb)	Induces disruption of cell function by mimicking Ca Inhibits enzyme activity by having a stronger affinity than Zn that acts as an enzyme cofactor Increases level of NO radical	Not provided	Disruption of CNS, blood pressure, kidneys, reproductive system, and vitamin D metabolism Impairment of cognitive development, growth reduction, and hearing loss in children Increased risk of spontaneous abortion and low birth weight	Potential carcinogenic effect Group B probable human carcinogen	Vehicle emissions Industrial activity Tire wear and brake abrasion Power plant emissions	[13,65,68,70,71,73,76]
Mercury (Hg)	Induces DNA damage by inhibiting mitotic spindle Decreases immune tumor response Increases accumulation of free radicals	3×10^{-4}	Disruption of CNS (e.g., paresthesia, erethism, irritability, tremors, and blurred vision), kidney functions, and reproductive system	Group D not a human carcinogen (elemental Hg) Group C possible human carcinogen (inorganic and methyl Hg)	Fossil fuel combustion Biomass burning Industrial emissions Coal combustion by power plants Incineration of medical waste	[68,77]
Cadmium (Cd)	Binds to metallothionein and transported from the liver to the kidneys Induces DNA damage by altering its repairing abilities	1×10^{-5}	Accumulation in kidneys causing kidney failure Disruption of liver, lung, immune systems, blood, and nervous system Softening of bones	Association with lung cancer Group B1 probable human carcinogen	Industrial activity Combustion of fossil fuels Incineration of waste Metal smelting and refining	[70,75,78]
Chromium (Cr (VI))	Induces DNA damage by altering its repairing abilities	1×10^{-4}	Respiratory conditions (e.g., septum perforations and ulcerations, decreased pulmonary function, and pneumonia, and asthma) Disruption of liver and kidney functions and immune system Increased risk of pregnancy and childbirth complications	Strong association with lung cancer Group A known human carcinogen (inhalation)	Industrial activity Road salt emissions Power plant emissions	[68,71,73,75]
Copper (Cu)	Increases expression of pro-inflammatory cytokine genes indicating cellular response to ROS accumulation Increases accumulation of HO-1	Not provided	Disruption of liver and kidney functions Anemia Wilson's disease due to accumulation of Cu	Link to carcinogenicity is not fully understood Group D not a human carcinogen	Vehicle emissions Road dust resuspension Industrial activity Tire wear and brake abrasion	[12,63,68,70,71,76]
Cobalt (Co)	Disrupts enzymatic activity of catalase, amino levulinic acid synthetase, and P-450 Inhibits Krebs cycle Interferes with Zn and iodine metabolism	6×10^{-6}	Respiratory conditions (e.g., coughing, wheezing, asthma, pulmonary fibrosis, and pneumonia)	Link to carcinogenicity is not fully understood due to limited data available	Vehicle emissions Coal and oil combustion	[68,71]
Iron (Fe)	Induces cytotoxic and genotoxic effects by disrupting DNA and mitochondrial function, production of NO and OH radicals in lung epithelial cells	Not provided	Eye discoloration Pneumoconiosis (<i>Siderosis</i>) (symptoms include coughing, shortness of breath, structural changes in lungs)	Association with cancer in animal studies	Soil emission and mineral dust Combustion of fossil fuels Tire wear and brake abrasion Road salt emissions Steel manufacturing industries, cement mills	[72,79,80]

Table 2. Cont.

PTE	Mechanism of Toxicity	Reference Concentration (RfC) by U.S. EPA, IRIS (mg/m ³)	Non-Carcinogenic Toxic Effect	Carcinogenic Toxic Effect	Major Sources	References
Zinc (Zn)	Induces pro-inflammatory response by accumulation of IL-8 Disruption in Zn homeostasis is proposed to contribute to destabilization of endosomal membrane and cell apoptosis	Not provided	Anemia Decreased level of HDL cholesterol Anosmia (loss of smell) caused by disruption of nose nerve receptors	Link to carcinogenicity is not fully understood Group D not a human carcinogen	Vehicle emissions Industrial activity Road dust resuspension Tire wear and brake abrasion Coal and oil combustion Combustion of fossil fuels	[19,65,68,70,71,76]
Manganese (Mn)	Disrupts DNA by interfering with DNA polymerase Disrupts mitochondrial function Activates MAPK cell signalling cascades increasing likelihood of cancer	5.00×10^{-5}	Disruption of CNS Respiratory condition Manganism	Link to carcinogenicity is not fully understood Group D not a human carcinogen	Vehicle emissions Road dust resuspension	[68,71,76]
Vanadium (V)	Induces oxidative stress by increased accumulation of 4-hydroxy-2-nonenal (4-HNE) Induces damage of DNA plasmid	1.00×10^{-4}	Respiratory conditions (e.g., coughing, wheezing, chest pain, and sore throat) Increased accumulation of neutrophils in nasal mucosa	Association with lung cancer in mice Group D not a human carcinogen	Combustion of fossil fuels Power plant emissions	[68,70,71,74,81,82]
Antimony (Sb)	Inhibits enzymes activity (e.g., enzymes involved in cellular respiration and carbohydrate and protein metabolism) Disruption of DNA plasmid	Not provided	Respiratory conditions (e.g., lung inflammation, chronic bronchitis, inactive tuberculosis, and emphysema) Disruption of cardiovascular system	Association with lung tumors in animal studies Group D not a human carcinogen	Vehicle emissions Tire wear and brake abrasion Combustion of fossil fuels	[68,70,71]
Nickel (Ni)	Has higher binding capacity in enzymes and proteins Impairs mitochondrial function and induces cell apoptotic mechanisms Increases accumulation of HO-1 Induces DNA damage by altering its repairing abilities	9.00×10^{-5}	Respiratory conditions (e.g., asthma, allergy, and breathing difficulties)	Association with lung and nasal cancer Group A known human carcinogen (Ni refinery dust and Ni subsulfide) Group B2 probable human carcinogen (Ni carbonyl)	Vehicle emissions Industrial activity Coal and oil combustion Power plant emissions	[17,63,68,71,73,74,81,82]
Nickel (Ni)	Has higher binding capacity in enzymes and proteins Impairs mitochondrial function and induces cell apoptotic mechanisms Increases accumulation of HO-1 Induces DNA damage by altering its repairing abilities	9.00×10^{-5}	Respiratory conditions (e.g., asthma, allergy, and breathing difficulties)	Association with lung and nasal cancer Group A known human carcinogen (Ni refinery dust and Ni subsulfide) Group B2 probable human carcinogen (Ni carbonyl)	Vehicle emissions Industrial activity Coal and oil combustion Power plant emissions	[17,63,68,71,73,74,81,82]

3.3.2. PAHs

Organic compounds constitute a major fraction of PM including PAHs, phenols, and atmospheric humic-like substances [13]. PAHs and their atmospheric oxidation products (NPAHs and OPAHs) are well known for their carcinogenic and mutagenic effects [19,83–85]. The U.S. EPA recognizes 16 priority PAHs, among which benzo[a]pyrene expresses a strong mutagenic activity and overall toxicity [14,19,86]. PAHs originate from both natural (e.g., volcanic eruption and biomass burning) and anthropogenic sources (e.g., vehicle exhaust, oil manufacturing, waste incineration, and coal burning) [84]. Thermal processes occurring at lower temperatures (e.g., biomass burning) produce lighter PAHs, whereas high-temperature activities (e.g., thermal power plants) tend to generate PAHs with greater molecular weights [84,87].

The toxicity of PAHs is related to the reduction of the mitochondrial membrane potential, disruption of cellular metabolic processes, exertion of the genotoxic effect, and induction of oxidative stress by ROS generation [83]. PAHs can cross the cell membrane due to their lipophilic characteristics. Inside the cell, PAHs are metabolized into quinones and further into semiquinones as a part of the cellular defense mechanism. The accumulation of ROS increases as semiquinones are reduced back to quinones via redox cycling. Exposure to PAHs also induces an accumulation of pro-inflammatory markers, including IL-6, IL-1 β , TNF- α , and HO-1. Moreover, the PAH-induced activation of Nrf2 further indicates oxidative stress. Finally, in vivo studies reported the proliferation of proinflammatory T cells and dendritic cells [13].

Chromatography-based techniques are the most commonly used methods for quantifying PAHs [86,88]. A combination of gas/liquid chromatography and mass spectrometry is suggested to be the preferred method for PAH characterization [27].

4. Analytical Methods for Physicochemical Characterization of PM

Over the decades of air pollution research, various methods have been developed to study the chemical composition and morphological properties of atmospheric particulates. Table 3 summarizes in detail the key aspects of the commonly used analytical methods for PM characterization. These laboratory techniques are conventionally classified as destructive or non-destructive based on whether the reproducibility of the analysis is possible on a given sample. They can be further classified based on the operating principle (Figure 6). The present section focuses on the off-line analytical methods commonly used for PM characterization by aiming to present: (1) the output of these methods (e.g., images, spectra, and composition); (2) the significant technical aspects; (3) their strengths and weaknesses; and (4) sample requirements (e.g., preparation procedures, filter types, and volume/mass requirements).

Table 3. Summary of analytical techniques/assays for physicochemical characterization of PM.

Technique	Brief Description	Advantages	Disadvantages	Unique Features	Remarks	References
Inductively coupled plasma analysis (ICP)	A method performing simultaneous analysis of a wide range of elements at sub- $\mu\text{g/L}$ elemental concentrations	High sensitivity Wide range of analyzed elements Flexibility in targeting specific elements	Destructive Extensive sample preparation and QA/QC procedure Possible interference from filters and laboratory procedures Accuracy is limited by sample mass if analytes are at trace concentrations	Possibly the most sensitive method for bulk elemental characterization, especially for metals	Invaluable for precise determination of elemental composition and human toxicity studies	[26,89,90]
Ion chromatography (IC)	A method used to determine the ambient concentration of gaseous pollutants, anionic, and cationic species	Analysis of several ions simultaneously Relatively quick and simple procedure	Destructive Cannot provide data on constituents other than water-soluble fractions	Speciation of bulk water-soluble compounds	Can play a crucial role in studying secondary aerosol particles and human toxicity Available in most laboratories	[91–95]
Scanning electron microscopy (SEM)	A technique emitting electron beams and receiving signals describing surface topography, electrical conductivity, and other characteristics of scanned samples	Provides 2-D images featuring particle shape and surface texture Quick and simple procedure An automated mode may produce statistically significant data, such as size distribution and morphology groups Non-destructive	Cannot provide data on volume or mass Operates under vacuum conditions Possible sample alteration/deterioration at high magnifications The automated mode cannot be reliably applied to particles smaller than 0.1 μm Requires use of conductive substrates or sample coating	Ability to provide statistically significant morphological and, if coupled with chemical analysis instruments, elemental composition data	Often coupled with energy-dispersive X-ray spectroscopy (EDS), which allows rapid elemental data acquisition along with imaging	[23,24,53,96–99]

Table 3. Cont.

Technique	Brief Description	Advantages	Disadvantages	Unique Features	Remarks	References
Transmission electron microscopy (TEM)	A technique passing electron beams through the sample and providing data on morphological structures and mixing state of particles	Provides 2-D images featuring particle shape and cross-sections Can visualize the internal structure of particles revealing their mixing states Higher resolution compared to SEM Non-destructive	Requires particle collection on TEM grids or sample transfer and preparation Cannot provide data on volume or mass Cannot be automated; therefore, it is unsuitable for analysis of a large number of particles Operates under high vacuum conditions Possible sample alteration/deterioration at high magnifications	Ability to provide data on particles' internal structure at high resolutions	Often coupled with energy-dispersive X-ray spectroscopy (EDS), which allows rapid elemental data acquisition along with imaging	[97,100,101]
Atomic force microscopy (AFM)	A technique using a nanoscale cantilever tip traveling across the surface of the sample to map its 3-D topography and used to study mechanical properties of particles	Able to generate 3-D particle models Vertical and lateral resolutions of around 0.1 and several nm, respectively Can operate in ambient conditions Non-destructive Little to no sample preparation	Severely affected by surface roughness of the sample substrate Cannot be automated; thus is unsuitable for analysis of a large number of particles	Ability to generate 3-D models and study properties, such as mass, volume, hygroscopicity, surface roughness, adhesion to other particles and surfaces	Can be coupled with Raman spectroscopy for simultaneous chemical characterization of particles Suitable for analysis of biological samples	[102–107]
X-ray diffraction (XRD)	A method utilized for bulk chemical speciation of mineral PM by using existing mineral databases	Can identify and quantify chemical compounds in the sample Quick and simple procedure for identification of minerals in PM Direct analysis on substrates, such as PTFE, quartz, and glass fiber filters Non-destructive	Limited to mineral compounds Sophisticated quantification procedure Accuracy affected by sample crystallinity, particle size resolution, and relative abundance of constituents Requires greater sample mass for adequate analysis (>few mg) Requires access to mineral databases Possible background interference from substrates	Bulk chemical speciation of mineral fractions of PM	Cannot be used as a standalone method for PM chemical analysis since it does not provide data on organic fractions Commonly applied to studying materials such as minerals, ores, and soils Available in most laboratories	[108–114]
X-ray fluorescence (XRF)	A technique used for the determination of the bulk elemental composition of PM	Flexibility in targeting specific elements, some even at trace concentrations Relatively high accuracy with detection limits down to 1–2 ng/m ³ for specific elements Quick procedure Non-destructive Little to no sample preparation	Difficulties in quantifying elements with small atomic masses or low concentrations Extensive QA/QC and calibration procedure Possible background interference from glass and quartz fiber filters	Rapid acquisition of bulk elemental composition of PM	Recommended as a quick and non-destructive method to detect and quantify elements of interest in PM as an alternative to more tedious techniques such as ICP	[115–121]
X-ray photoelectron spectroscopy (XPS)	A method applied to characterize the surface chemistry of atmospheric particulates by providing the chemical composition of shallow particle regions (<10 nm)	Provides elemental composition and speciation of particle surface Can produce semi-quantitative data with accuracy down to 0.1 at. % Can detect and quantify low-Z elements, such as C, N, and O Quick procedure Non-destructive No sample preparation Can be applied to small sample masses	Requires high vacuum conditions Issues related to sample charging and need in charge compensation Requires access to spectrum databases Possible background interference, especially for studying C content on C-containing substrates	Determination of surface chemistry of particles, especially C-containing compounds, as most of the other techniques struggle to quantify low-Z elements	Cannot be used as a standalone method for PM chemical characterization, but can contribute to studying particle heterogeneity and formation mechanisms	[122–127]

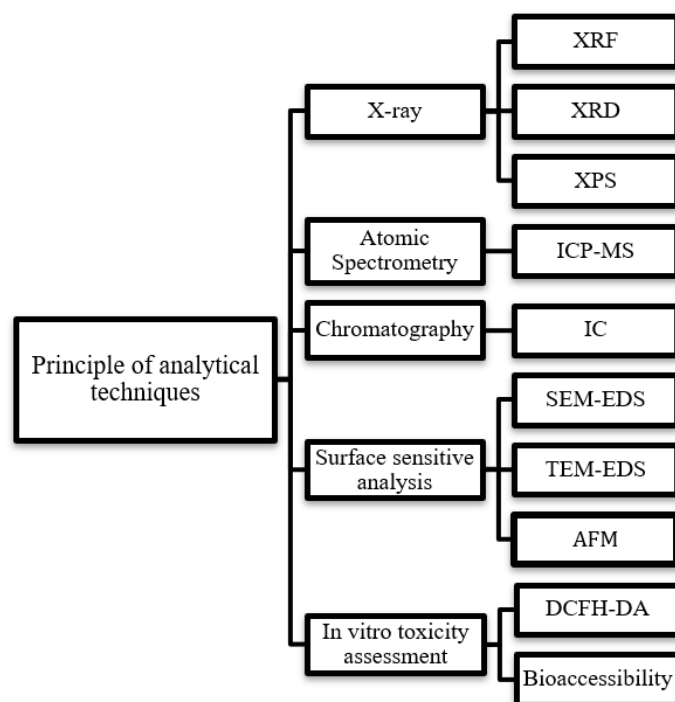


Figure 6. Classification of reviewed analytical techniques for PM characterization.

4.1. Destructive Techniques for PM Analysis

4.1.1. ICP

ICP is a tool for trace element analysis that can be described as a hard ionization method, as most of the analyzed sample molecules undergo complete atomization. A sample is introduced into the instrument through a nebulizer and spray chamber, transforming it into a fine aerosol. Other system components include torch and argon plasma generating radiofrequency coil (ion source), which contains positively charged ions and unbound electrons that ionize the introduced sample [89]. Ions are quantified based on their mass–charge (m/z) ratio. Internal standards used for analysis include ^6Li , ^{45}Sc , ^{89}Y , ^{103}Rh , ^{115}In , ^{159}Tb , ^{165}Ho , and ^{209}Bi , and only the elements not expected to be present in the sample matrix should be used to prevent internal standard recovery bias [90].

The major types of ICP include ICP-MS and ICP-OES (or ICP-AES). Choosing the appropriate instrument for environmental analysis depends on the sample matrix and regulatory limits: ICP-MS is precise, provides low DLs, and may be preferred when low regulatory limits are required [90]. Moreover, collision cell technology in ICP-MS reduces polyatomic spectral interference. Regulatory methods for the determination of trace elements in PM by ICP-MS include EPA 6020 and Method IO-3.5.

ICP-OES is more robust for samples with high regulatory limits and can be used for the analysis of soil, solid waste, groundwater, and wastewater. ICP-OES is also a more cost-effective option if low DLs are not required. Accordingly, ICP-OES is not preferred for As and Hg (or PTEs with low regulatory limits). For the determination of the total As concentration in PM, it is recommended to use ICP-MS [63,128,129] or AAS [128,130]. The measurements of the total Hg content in PM can be performed via ICP-MS [131], AAS [132], cold vapor AFS [133], or via a direct mercury analyzer [134,135]. Regulatory methods for metals identification in PM by ICP-OES include EPA 6010 and Method IO-3.4 [90,136].

Overall, the main advantage of ICP is its ability to perform a multi-element analysis with lower DLs allowing to determine sub- $\mu\text{g/L}$ concentrations of a wide range of elements simultaneously in a single run. However, the cost of ICP systems limits their use in lower volume laboratory settings, for which more cost-effective options including flame AAS may be suggested.

For ICP analysis, airborne samples are collected on filter papers (e.g., PTFE or quartz fiber filters). The main issue to consider is sample extraction from the filter, since ICP processes liquid samples. One way to extract a sample mass from the filters is via methanol or ultrasonication in organic solvents, which presents several issues, as dissolving PM in aqueous solvents can alter its properties, including chemical composition and size distribution [26]. Numerous studies suggest the digestion of a portion of a filter after cutting it using a ceramic blade [74,92,137–139]. However, that assumes a homogeneous deposition of PM on the substrate [137], which may lead to significant uncertainty and error. It is possible to avoid sample extraction if solid samples can be analyzed in case ICP is employed with electrothermal vaporization or laser ablation [89]. The most common digestion acids include HNO_3 , HCl , HF , and perchloric acid HClO_4 . HNO_3 and HCl are more prevailing and have relatively lower safety issues. It should be noted that HF is highly dangerous, and its use must be exercised with extreme caution, as it causes tissue necrosis by hydration and reacting with calcium ions [90].

An analysis of aerosols collected on a filter could be challenging given the low concentrations of analytes and often limited sample mass. The mass requirements for ICP analysis are specified in [26]. Furthermore, some digestion acids are known to cause interferences for certain elements. Therefore, choosing an appropriate combination and amount of acids for sample digestion is crucial to minimize interference and achieve low detection limits [140]. The most commonly used acid mixture for environmental analysis is aqua regia ($\text{HNO}_3 + \text{HCl}$ at 1:3 ratio) [141]. However, the presence of certain acids is required for the detection of specific elements. For instance, elements from the aluminosilicate matrix require HF in the digestion mixture, and HCl is used for platinum group elements (PGE) [140]. Finally, digestion in closed vessel systems is preferable, as it reduces sample loss due to volatilization and prevents airborne contamination [142].

4.1.2. IC

IC is used to simultaneously determine several anionic and cationic species in aqueous samples in a short time [91], including SO_4^{2-} , NO_3^- , NH_4^+ , Ca^{2+} , Cl^- , Mg^{2+} , Na^+ , K^+ , and F^- .

Moreover, a speciation analysis in IC allows the determination of different oxidation states of the same element [95]. The water-soluble fraction of particulates that contains ionic species is linked to potential health effects of PM, and water-soluble forms of PTEs that can freely pass the air–lung fluid interface [94].

In source apportionment studies, ionic concentrations from IC along with statistical analyses allow the identification of pollution sources. In more detail, the secondary formation of SO_4^{2-} via the oxidation of SO_2 indicates a coal combustion source or biomass burning [143]. Agricultural activity leads to high concentrations of NH_4^+ resulting from the reaction between NH_3 and acidic species [144]. SO_4^{2-} and NH_4^+ also originate from vehicle exhaust [92]. An elevated Ca^{2+} to Mg^{2+} concentration ratio suggests that ions come from dust of soil origin, while a high Mg^{2+} to Ca^{2+} concentration ratio indicates anthropogenic sources (e.g., industrial coal combustion) [143,145]. Ions, such as Cl^- and K^+ , can originate from biomass burning, coal combustion, and sea salt [93].

Prior to the IC analysis, ambient samples collected on a filter are extracted using deionized water and ultrasonication, which allows the extraction of water-soluble inorganic species. The leachate is then filtered using a filter paper (e.g., PTFE and nylon) [92,146–149]. The method also requires the injection of the analyte into detection eluents (e.g., solutions of Na_2CO_3 , NaHCO_3 for anions, and HNO_3 for cations), which carry the ions through the chromatograph column [150].

4.2. Non-Destructive Techniques for PM Analysis

4.2.1. SEM

Electron microscopy-based techniques can be used for single-particle analysis to investigate the physical, chemical, and morphological characteristics of individual particles [151,152].

The most commonly used electron microscope-based techniques include SEM and TEM, and their application for PM characterization has been extensively reviewed in other studies [24,96,99]. A review of selected studies that used SEM for particle characterization is also presented in Table 4. SEM operates by emitting high-energy electron beams at a particle location in a raster scan pattern and then receiving signals describing surface.

Table 4. List of articles on PM characterization using SEM.

Reference	Sample	Instruments and Techniques Used	Investigated Features	Remarks
[153]	PM samples collected in the Sartenejas Valley, Venezuela	SEM-EDS	Particle morphology and elemental composition (C, O, Si, Na, Mg, Al, Cl, K, Ca, Fe, and Ti)	-PM particles were classified as a function of particle size and elemental composition -Relationships between different PM fractions were analyzed -Morphological features of deposited particles were characterized considering the origin of PM
[154]	PM samples collected in rural residential area of Tezpur, India	SEM-EDS	Particle morphology and elemental composition (C, O, Si, Al, Fe, Ca, Na, Ti, Mg, K, S, Fe, Mn, Ni, V, and Zn)	-PM particles were classified based on morphological features considering the origin of PM
[155]	PM collected in Ballari, India	SEM-EDS	Particle morphology and elemental composition (C, O, Na, Mg, Al, Si, S, Cl, Mo, K, Ca, Ba, Ti, Fe, Zn, Co, Hf, and Br)	-Deposited particles exhibit oval or spherical shape with smooth surfaces containing aluminosilicate group of elements
[114]	PM collected in different locations at Jeddah, Saudi Arabia.	FE-SEM-EDS	Particle morphology and elemental composition (C, O, Si, Na, Mg, Al, N, S, Cl, and Ca)	-Particle aggregates are more typical to industrial site than residential areas -Elemental composition determined by EDS analysis was confirmed by XPS results.
[53]	TSP and PM _{2.5} collected in Monterrey, Mexico	SEM-EDS	Particle morphology, elemental composition (Ca, Si, O, Al, K, Fe, Zn, Mn, Cu, Mo, and Pb), and size distribution	PM particles were classified as a function of particle size and elemental composition -Morphological features of deposited particles were characterized considering the origin of PM

Various types and operation modes of SEM can enhance PM characterization. Two alternatives to traditional SEM used in ambient aerosol analysis are ESEM (see [98]) and FE-SEM (see [114,156]). ESEM has sample chambers with partial water vapor pressure that facilitates studying wet samples including biological specimens. FEG-SEM offers a 3–6 times higher resolution (up to 300,000× magnification) with greater analytical depth enabling to see individual micron-size particles (Figure 7), resulting in clearer images with less electrostatic interferences [151]. CC-SEM is an increasingly popular mode of SEM operation that enables a quantitative analysis providing statistically significant data on sampled particulates [23,99]. In this mode, images (50–100 images per substrate) are taken at random locations throughout the sample at fixed magnifications, and then a software classifies and counts particles based on their morphology and elemental composition [23]. In contrast to operator-controlled SEM, an automated analysis cannot provide detailed data, such as internal mixing states, and may misread particles with intricate morphologies, such as soot, which should be considered during result interpretation [157]. Although

automated SEM is utilized effectively in examining surface information in short durations (around 10,000 particles per hour), it can rarely be applied to the characterization of particles $<0.1\ \mu\text{m}$ [23,99].

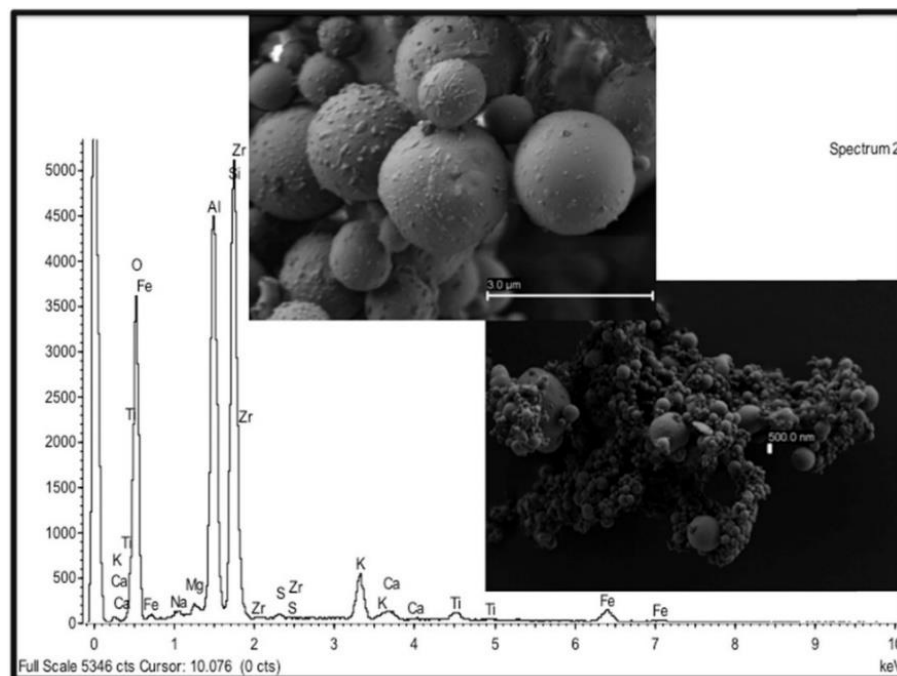


Figure 7. FEG-SEM images and a respective EDS spectrum of coal fly ash particles obtained using field emission SEM. Reproduced from [158] with permission of Environmental Research..

SEM generates only 2-D images of particle surfaces, which is insufficient for studying the inner structure or determining the volume and the mass of the particles [24]. A higher magnification imaging requires a high-energy electron beam, which alters and/or deteriorates the analyzed particles [98,99]. Moreover, the SEM analysis under vacuum conditions prevents a reliable analysis of the volatile components in the sample [99].

Prior to the SEM analysis, the specimen should be clean from possible contamination, such as hydrocarbons, due to prolonged air exposure as well as contaminants from fingers as the quality of SEM image will be affected by these [159]. Non-conductive samples should be coated with a thin layer (e.g., 20 nm, [23]) of a conductive material, such as Au [23,93], C (RTI protocol), and Pt [156]. It is possible to re-analyze the same material repeatedly using SEM, but the coated samples might no longer be suitable for other analytical techniques. The analysis can also be performed on conductive substrates, such as an Ag plate, without coating to minimize possible interferences [160].

Coupling electron microscopes with EDS enables the simultaneous study of the morphology and the chemistry of the particles [96]. SEM is often equipped with EDS that allows to study the bulk elemental composition of particles. EDS is preferred due to its simplicity and convenience; the technique is relatively easy and fast (analysis duration ranging from 30 s to 2 min), and the tool usually has a pre-installed software that instantly identifies peaks. EDS provides an opportunity to correlate morphological characteristics of a certain group of particles with their chemical composition (Figures 8 and 9). An EDS analysis also allows to visualize the chemical composition of an individual particle in the form of elemental distribution maps (Figure 10) [161,162] of the scanned region. A comparison of the distribution maps allows to find a correlation between certain elements indicating the presence of specific compounds or hinting at the common sources [163]. Figure 10 further shows particles' elemental composition typical for combustion sources of traffic emissions, indicating the use of EDS in the source apportionment.

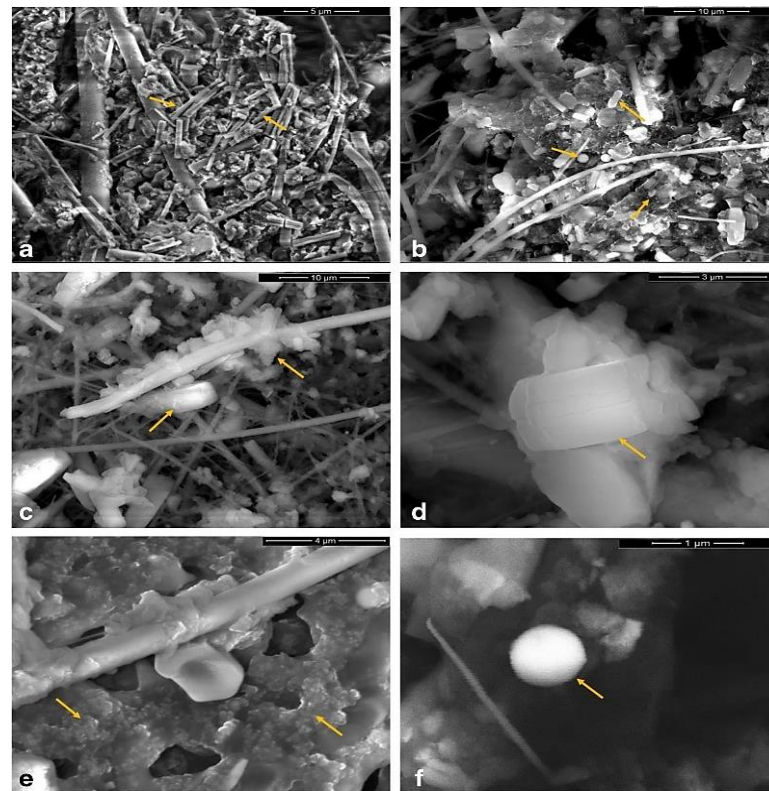


Figure 8. SEM images of (a) S-rich, (b,c) mineral, (d) aluminosilicate, (e) $PM_{0.1}$ of organic carbon or soot (f) tar ball. Reproduced from [149] with permission of *The Journal of Atmospheric Chemistry*.

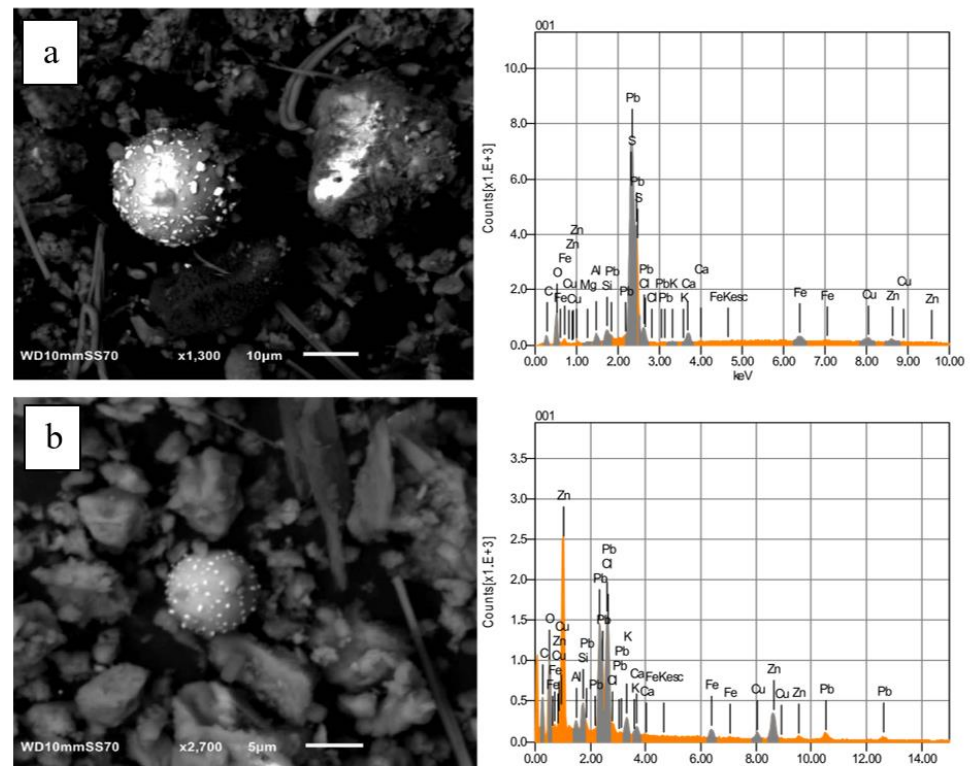


Figure 9. SEM images and respective EDS spectra of two lead oxide particles with different elemental content. (a) Trace elements possibly associated with power plant emissions; (b) various elements associated with the ceramics industry. Reproduced from [53] with permission of *Atmospheric Research*.

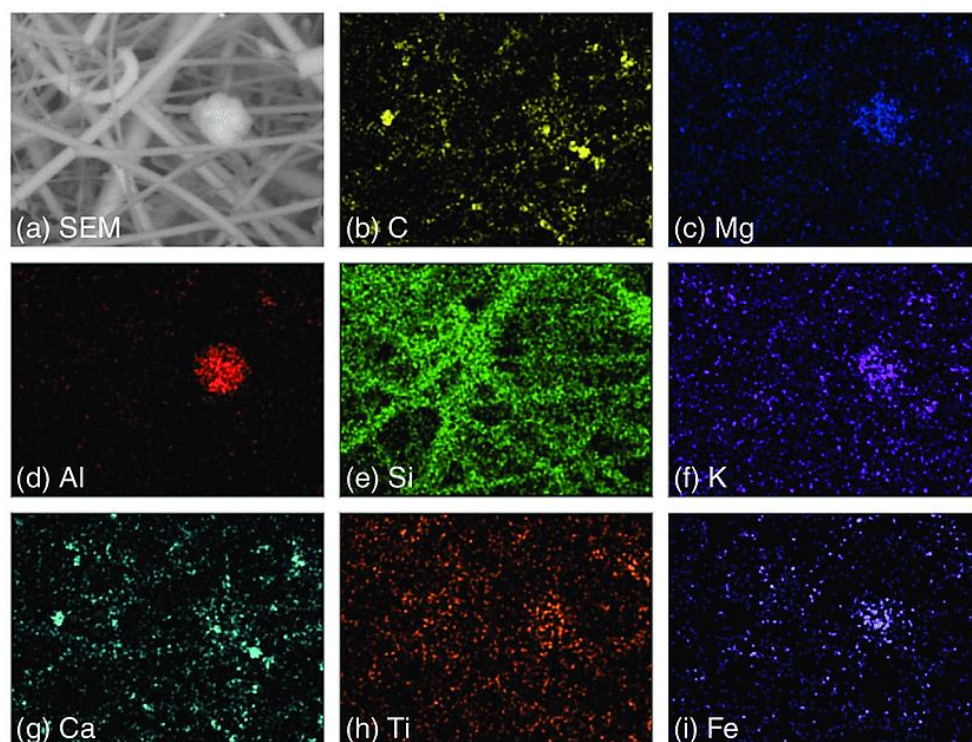


Figure 10. Single-particle SEM-EDS map. (a) SEM image; (b–i) EDS elemental analysis for C, Mg, Al, Si, Ca, Ti, and Fe. Reproduced from [164] with the permission of *Remote Sensing*.

EDS can sometimes show the chemical composition of the substrate or the background instead of the particle, if the particle size is too small or its density is low, which is the drawback of this technique. For example, interferences for C, O, and/or F from Teflon/PTFE and quartz filters [164] inhibit the quantification of elemental data from the EDS analysis and result in relative abundance reports. Figure 8 shows the background interference for Si spectra from the quartz filter affecting the EDS signal.

Moreover, inhomogeneity of particles at the point of analysis may lead to false spectra, as particle chemistry at a location may not represent the bulk chemistry. Studying a greater number of particles out of sampled aerosol and performing a statistical analysis of the acquired results helps improve the accuracy of the technique [96].

Despite certain disadvantages, SEM coupled with EDS is by far the most commonly used technique for single-particle characterization and is strongly recommended for routine PM monitoring procedures as a relatively practical tool to study PM physicochemical properties.

4.2.2. TEM

Another valuable technique for the assessment of airborne particulates is TEM that provides insights on particle morphology and structure, size distribution, and mixing state at a nanosize scale [165,166]. Selected studies that used TEM for particle characterization are summarized in Table 5.

The use of TEM is higher than SEM and ranges from 80–300 kV to enable electron penetration through the specimen. The voltage of 200–300 kV is applied for routine TEM imaging, while for the analysis of light elements (e.g., C), voltage as low as 100 kV can be sufficient [159]. The TEM analysis provides a high magnification power (i.e., up to $\times 1,000,000$) [167] and resolution, enabling to visualize PM particles smaller than 100 nm (Figure 11). Moreover, it is possible to differentiate airborne particles based on the morphological structures typical to particular emission sources (Figure 12). Finally, TEM can also be equipped with EDS (Figure 13), providing information on the chemical constituents of individual particles (e.g., metals and organic and inorganic species) [168].

Table 5. Summary of selected studies on PM characterization using TEM.

Reference	Sample	Instruments and Techniques Used	Investigated Features	Remarks
[75]	PM ₁₀ and PM _{2.5} samples particles collected from six different sources	TEM	Particle morphology	-PM particles were compared according to size fraction and physicochemical characteristics
[100]	Soot particles collected in the North China Plane	TEM-EDS	Particle morphology, elemental composition (C, O, Si, Na, Cl, Al, Ca, Fe, Zn, Pb, Mn, S, and K), and mixing state of soot particles	-PM morphology was investigated -Morphological changes of PM particles in the atmosphere were thoroughly discussed -Fractal dimensions (D_f) of ambient soot particles were calculated
[97]	PM collected in different locations in China	TEM-EDS	PM morphology and mixing state of particles	-New insights in morphology of mixing structures of individual aerosol particles were provided
[165]	PM collected in residential area in Al-Ain city	STEM	Particle morphology	-Health effect from PM was assessed considering MP morphology
[147]	PM _{2.5} in industrial and urban sites in eastern China	TEM-EDS	Particle morphology, elemental composition (Si, Na, K, O, S, Al, Fe, Ca, Ti, Co, and Pb)	-Dependence of PM-induced cytotoxic and mixing state of ambient particles was suggested

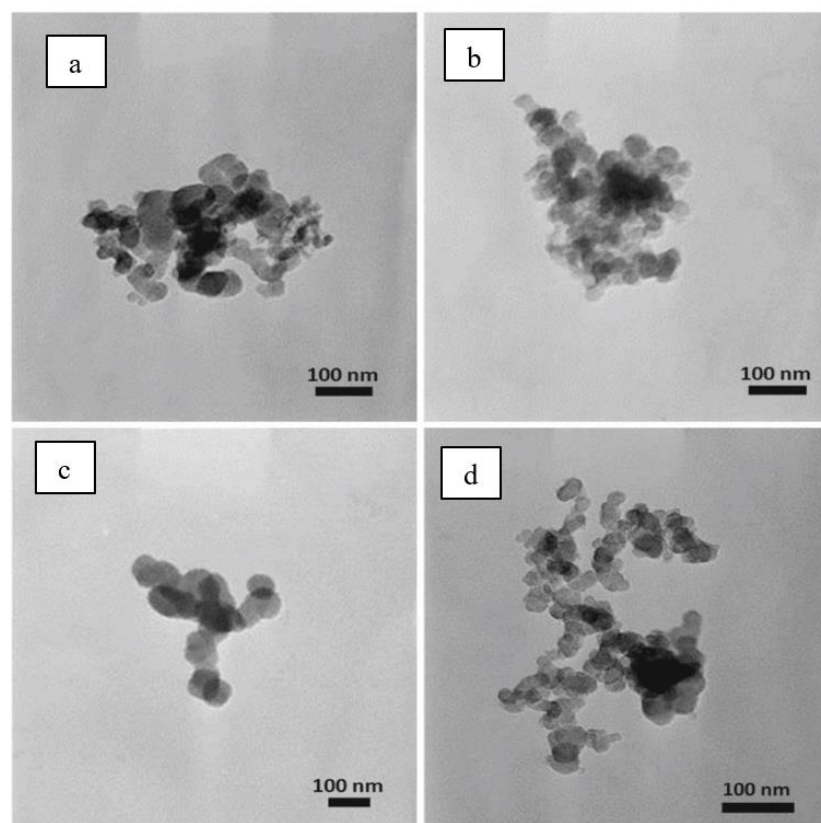


Figure 11. TEM image of airborne particulate aggregates collected on a residential area. Particle size range in (a,b,d) is 30–115 nm and in (c) is 80–112 nm. Composition of spherically shaped particles in (a,b) includes amorphous sulfate and silicates. Tetrahedral particles in (c,d) contain crystalline silicates (reproduced from [165] with permission from *Air Quality, Atmosphere, and Health*).

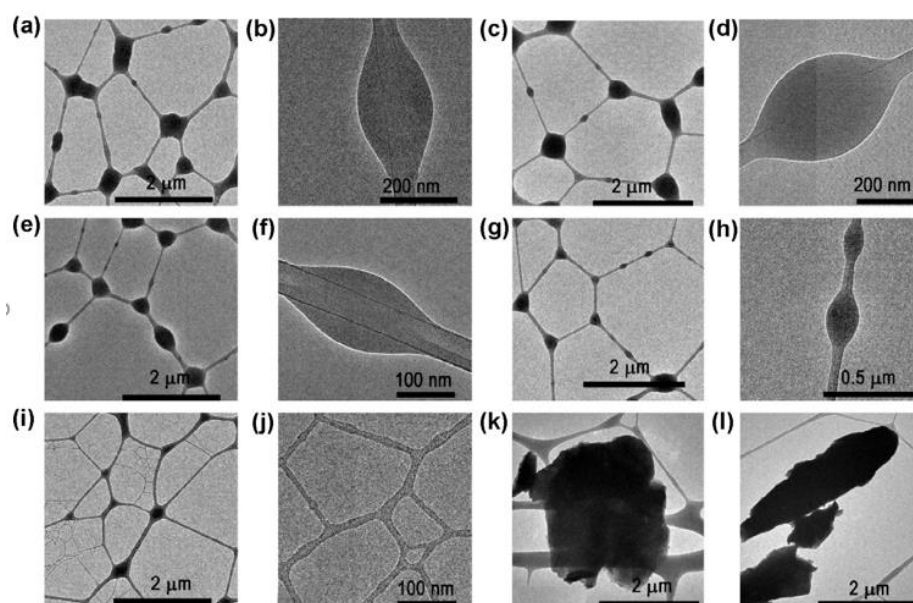


Figure 12. TEM structural image of PM_{2.5} particles from (a,b) barbecue smoke, (c,d) cigarette smoke, (e,f) incense smoke, (g,h) wood smoke, (i,j) car exhaust, and (k,l) soil dust (reproduced from [75], with permission from *Nano Research*).

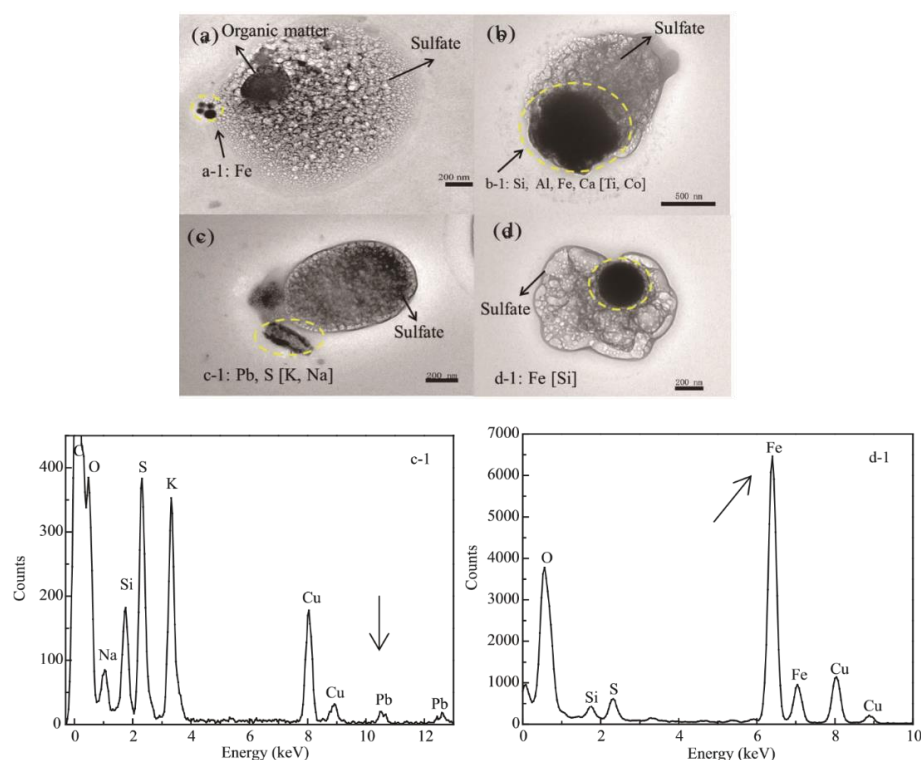


Figure 13. TEM images of particulate-bound PTEs internally mixed with other inorganic and organic materials in the samples collected at the industrial site. (a,d) Fe-containing; (b) mineral-containing; and (c) Pb-containing. Circles show area examined by EDS and corresponding EDS spectra (only (c-1) and (d-1)). Cu and C in the EDS spectra correspond to copper TEM grid with carbon film (reproduced from [147], with permission from the *Journal of Environmental Science*).

For an electron signal to pass through, the sample should be within 100 nm thickness, especially for those containing heavy elements [159]. Sample characteristics, such as density, can hinder electron transmission in the case of high-density materials. TEM operates in a

high vacuum (from $<10^{-6}$ Torr in conventional TEM to 10^6 Torr in environmental TEM) as electrons are unable to pass through air molecules [169]. That, however, can lead to the evaporation of volatile components of PM [103].

Despite its useful features, it is time-consuming to obtain statistically robust information via TEM on particle morphology and size distribution for air samples. Moreover, a resolution of a few tens of nms is sufficient for airborne sample characterization. Although TEM is a comprehensive technique for the visualization of internal structures of a single particle, it shows only a part of the sample because of its high magnification. Moreover, the detection of secondary aerosol species and the differentiation of species in the homogeneous particles is challenging [97].

A major challenge in the TEM analysis is sample preparation. Air samples collected on filters require dissolution in a solvent prior to TEM analysis, which may alter the chemical composition. Sample preparation may also involve drying, freezing, or applying a conductive coating material [75,96]. Individual aerosol particles can be collected directly on carbon-coated TEM grids to avoid undesirable effects from the sample preparation [92,97,100,165]. However, particles collected on a grid may not be uniformly distributed [97,100]. Moreover, the sampling time should be carefully considered as longer times may result in particle agglomerates rather than single particles, whereas a shorter sampling time would not give statistically significant data [96]. Considering its limitations, the TEM analysis could be recommended as a complementary technique for particle characterization.

4.2.3. AFM

AFM utilizes a nanoscale cantilever tip traveling across the surface of the analyzed sample to map its 3-D topography [170]. This ability to generate 3-D particle models at a high spatial resolution and a vertical resolution of ≤ 0.1 nm are among the significant advantages of AFM [102,104,105,171]. AFM has been implemented to study particle properties including size, shape, mass, volume, hygroscopicity, surface roughness, and adhesion to other particles and surfaces [102,104,106,107,172]. Selected studies using AFM for particle characterization are summarized in Table 6.

Table 6. Summary of selected studies on PM characterization using AFM.

Reference	Sample	Instruments and Technique Used	Investigated Features	Remarks
[173]	Reference material NBG18, by the SGL Carbon Group (Germany) (dust particles)	AFM	Adhesive force between micron size particles and commonly used indoor surfaces	-The adhesive force between dust particles and different surfaces was assessed -Major factors affecting the adhesive force were reviewed
[174]	Soot particles collected from the flame at a height above the burner (HAB)	STM/AFM	Molecular and structural composition of soot particles	-Aromatic and non-aromatic compounds contributing to the formation of soot particles were identified -Results of AFM on chemical and structural composition of soot particles were compared with Raman spectroscopy
[107]	PM _{2.5} collected in Beijing, China	AFM	Mechanical properties of fine PM	-Morphological features of PM _{2.5} , such as adhesion, deformation, elasticity, rupture, indentation, diameter, and area were discussed
[104]	Candle soot particles produced in a collision atomizer	AFM	Particle morphology	-The heights and particle deformations of sub- μ m soot particles were determined
[103]	Particles from five different aerosols	TM-AFM	Particle morphology, solubility, and internal structures	-Organic aerosol particles showed mostly shell-core structures with varying solubility

AFM enables the specification of particle nanosurface features that are not visible in SEM or TEM (Figure 14). AFM coupled with Raman spectroscopy can also provide detailed chemical spectra of the analyzed particles [105,106]. In a single-particle analysis, AFM is often operated in tapping [103,105,106] and non-contact [104,105] modes suitable for scanning soft materials in ambient conditions, reducing the volatilization of organic compounds in PM during scanning [103]. In the non-contact mode, the instrument measures attractive forces between the probe and the sample to deduce its surface topography without tip-sample contact at a resolution limited by probe-to-sample distance, whereas in the tapping mode, the cantilever oscillates vertically, coming in direct contact with the sample in short intervals, yielding a higher resolution [175]

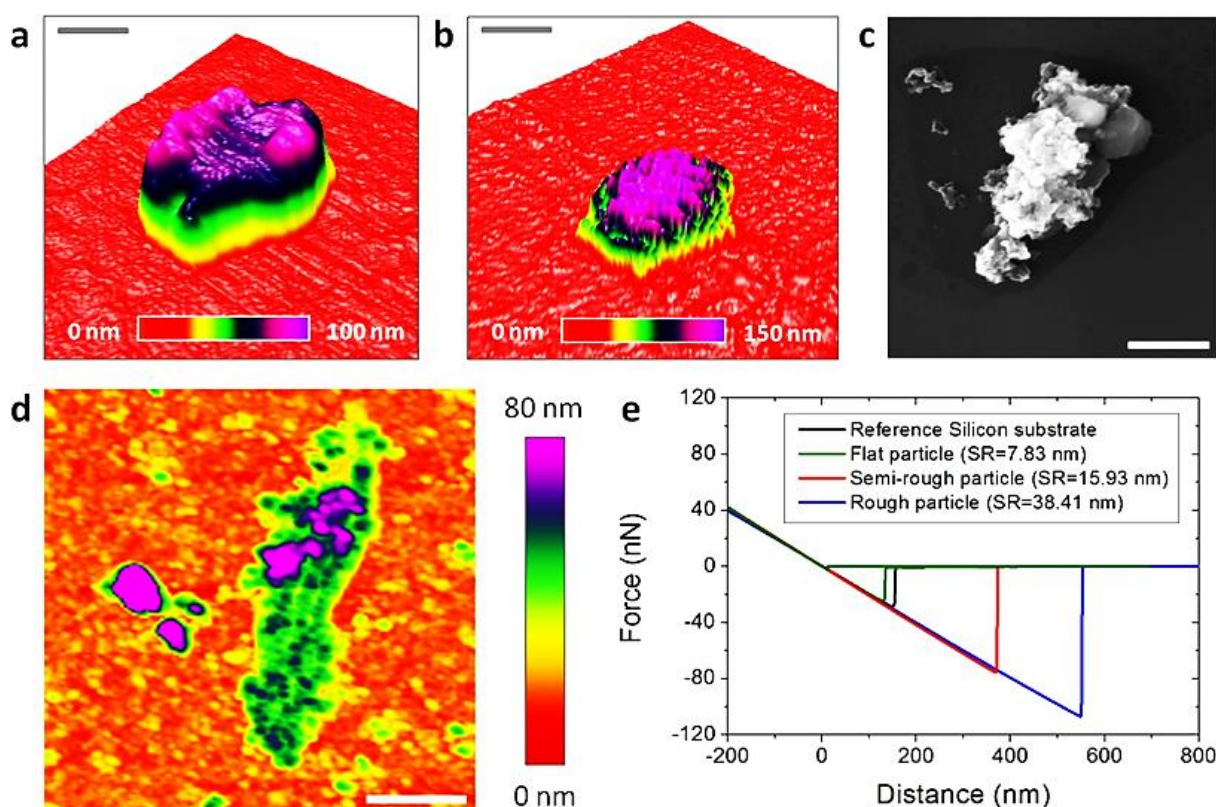


Figure 14. Examples of 3D models (a) smooth [scale bar = 0.3 μm] and (b) rough [2.5 μm], (d) a topographic image [3 μm], and (e) a graph of tip-particle adhesion force vs. distance produced for different fine particles using AFM. (c) shows a topographic micrograph [1.1 μm] of a soot particle acquired using SEM. Reproduced from [107] with permission of *Scientific Reports*.

The AFM analysis requires little to no sample preparation and can be performed on non-conductive materials, limiting sample deformation and alteration [102,171]. It also enables an analysis of the liquid samples, making it suitable for biological sample imaging [170]. A reliable AFM analysis on PM collection substrates, such as polycarbonate or quartz, is substantially hindered by the filter surface roughness and might need a particle transfer [107]. Although obtaining volumetric particle images is an advantage, it has more of a complementary role in the PM characterization process as it cannot be automated and requires substantial efforts to produce statistically significant data [102,104].

4.2.4. XRD

In air quality research, XRD is used to determine the chemical speciation of mineral PM [26]. In the XRD analysis, major compounds present in PM are identified based on interplane distances and the relative intensity of their peaks at a preferred orientation [108,111]. Some minerals found in PM are of geological origin [45], while anthropogenic sources can add

other mineralized matter, such as soot and fly ash. Finally, a third group of mineral compounds could be formed in the air from primary pollutants as secondary aerosol particles; these secondary compounds can modify the toxicity of the original pollutants [163]. Identifying major compounds constituting the sample as well as their common origin may help in source apportionment.

In a simple qualitative XRD analysis (e.g., performed by [109,111,137,148,163,176,177]), the diffractogram peak values are checked against existing mineral databases to identify the most abundant mineral types. In a semi-quantitative analysis, the reference intensity ratio method is applied to evaluate the XRD peaks [108] in which the reference intensity values of PM given in various databases are used to estimate the relative content of each component in percent (e.g., [110,112,113,178,179]). Finally, a quantitative evaluation of the XRD results could determine weight proportions of various minerals within the sample and is by far the hardest stage in the XRD analysis. It requires either a concurrent analysis of the source samples, an elaborate set of assumptions to reduce uncertainties [108,180], or focusing on quantifying highly crystalline phases, such as quartz [181]. Selected studies that used XRD for particle characterization are summarized in Table 7.

Table 7. Summary of selected studies on PM characterization using XRD.

Reference	Sample	Instruments and Technique Used	Investigated Features	Remarks
[178]	TSP and PM _{2.5} from Monterrey, Mexico	XRD	Semi-quantitative mineral composition (CaCO ₃ , SiO ₂ , and CaSO ₄ (H ₂ O) ₂ , iron oxides, halite, aluminosilicates, and TiO ₂)	-PM composition and morphology were assessed by three methods -Potential PM emission sources were identified using PCA
[113]	TSP, PM ₁₀ , and PM _{2.5} from two meteorological stations, Iran	XRD	Semi-quantitative mineral composition (quartz, calcite, gypsum, hematite, halite, sulfur, barium chlorite, magnetite, biotite, and clay minerals)	-Sample preparation and handling are given in detail -Seasonal variation of PM composition was discussed -Comparison of normal and dusty day impact on PM compositions was provided
[112]	PM _{2.5} from Pune, India	XRD	Semi-quantitative mineral composition (quartz, wollastonite, vermiculite, kaolinite, calcium aluminum silicates, calcium iron oxide, magnetite, wuestite, gypsum, kokaite, magnesium phosphate, silicon phosphates, dolomite, iron-zinc, aenigmatite, and halite)	-20 minerals were identified -Sources of PM emissions were identified incorporating XRD results -Comparison of particle groups found in different studies
[108]	Soil and PM ₁₀ from Seoul, South Korea	XRD	Quantitative mineral composition (illite-smectite, illite, chlorite, kaolinite, smectite, quartz, plagioclase, K-feldspar, and calcite)	-Description of quantitative XRD analysis of PM using set of assumptions and soil composition -Comparison between bulk and single-particle mineralogy
[180]	PM ₁₀ from Beijing, China	XRD	Semi-quantitative mineral composition (clay minerals, quartz, plagioclase, K-feldspar, calcite, dolomite, hematite, pyrite, magnesite, gypsum, laumontite, K(NH ₄)Ca(SO ₄) ₂ ·H ₂ O, NH ₄ Cl, and As ₂ O ₃ ·SO ₃)	-Results of mineral composition -Comparison between semi-quantitative mineral compositions found using XRD and ESEM-EDS as well as between urban and satellite sites

There are two main approaches to sample handling for the XRD analysis: (1) transfer of the sampled material from the collecting substrate onto a supporting surface and (2) direct examination of the loaded substrate. Using glass slides [108] or other sample holding bases (e.g., silver membranes [181], amorphous silicon [178]) minimizes issues related to sample placement (redistribution over a smaller area) and background interference [182]. They also allow flexibility in selecting sampling substrates, which might be influenced by available sampling options and other laboratory analyses requiring particular filter types. Qualitative and semi-quantitative XRD data have been reported from a direct analysis of PTFE (e.g., [112,137,163]) and quartz (e.g., [113,148,176]); however, a high quartz background had to be offset by subtracting blank filter measurements from diffractograms [137,176]. Moreover, these fiber filters are prone to ‘masking’ smaller particles stuck in the filter interior [182]. Depending on the study scope, both sample handling approaches can be further extended by heating the substrates to 300–550 °C to remove volatile organic compounds [108], and glycosylation to enhance the quality of the clay mineral analysis [108,137].

In combination with mineral databases (e.g., JCPDS) [110,112,176,177,180]), software is used to analyze the XRD output and/or perform the quantification of the obtained mineral compositions, e.g., EVA for peaks analysis [113]; SIROQUANT 3.0 for mineral quantification [113]; and X’Pert HighScore for qualitative and semi-quantitative analysis [110,178] (MATMEC VI.0 for diffraction analysis [183]).

Although identifying the chemical compounds and elemental compositions of a sample is a superior advantage of XRD, its accuracy is limited by crystallinity and the relative abundance of the sample constituents, sample mass, and particle size resolution. More crystalline structures (measured by crystallinity index) produce more pronounced peaks, which makes signals from partially crystalline and amorphous materials less detectable for XRD [179,184]. Moreover, if the abundance of major compounds is very high, the other compounds present in the sample may become undetectable [163,177], particularly minor phases with concentrations less than 5% wt. [109].

The mass of the sample is also crucial to the reliable analysis, which is often difficult to collect in adequate amounts [26,110,180]; i.e., a few mgs of sample might not be sufficient for a quantitative analysis [108]. The reliability of the XRD analysis might be increased by analyzing directly on the substrate instead of transferring the sample onto slides [113]. The size of the particles is also important to the analysis output as smaller particles produce minimal peaks [113], which could be resolved by using specialized techniques, such as micro-XRD [26] or 2-D XRD [185]. Due to these limitations and the unsuitability of XRD to produce good quantitative compositional data of PM, this technique is recommended as a complementary tool for PM characterization.

4.2.5. XRF

XRF is a rapid, non-destructive technique for the characterization and quantification of elemental composition with adequate sensitivity, inferior only to more resource-intensive and time-consuming techniques, such as ICP-MS [26,163]. Some XRF devices may offer flexibility in targeting specific elements of interest (e.g., tracers of potential PM sources or PTEs), which can be simultaneously quantified. The technique has a wide range of targetable elements, and two or more irradiation conditions can be set to optimize the analysis for low-Z (Na to Si/P) and medium-to-high-Z elements (e.g., S to Pb) [116,127,186]. XRF is a quick and straightforward tool for gathering chemical data on PM macrocomponents [115]. Selected studies using XRF for particle characterization are summarized in Table 8.

Table 8. Summary of selected studies on PM characterization using XRF.

Reference	Sample	Instruments and Technique Used	Investigated Features	Remarks
[121]	PM ₁₀ and PM _{2.5} from Rio Claro, Brazil	SR-XRF	Elemental composition (Si, S, Ca, K, Ti, Cr, Mn, Fe, Cu, and Zn)	-Emission sources were determined using enrichment factors (EF) and PCA -Effect of precipitation on PM composition was studied
[117]	Size-segregated PM (0.05–10 µm) from Genoa, Italy	ED-XRF	Elemental composition (Na, Mg, Al, Si, P, S, Cl, K, Ca, Ti, V, Cr, Mn, Fe, Ni, Cu, Zn, Se, Br, Sr, Zr, Mo, Ba, and Pb)	-Particle chemistry was characterized for size-resolved PM -Size-segregated source apportionment was performed using PMF
[120]	PM ₁₀ and PM _{2.5} from Ile-Ife, Nigeria	ED-XRF	Elemental composition (Na, Mg, Al, Si, S, Cl, K, Ca, Ti, V, Cr, Mn, Fe, Ni, Cu, Zn, As, Br, Rb, Sr, and Pb)	-Source apportionment and particulate transport study based on XRF results (PMF, CPF, and backward trajectories)
[119]	TSP from Turin, Italy	WD-XRF	Elemental composition (Ba, Br, Ca, Cl, Cr, Cu, Fe, K, Mg, Mn, Ni, Pb, S, Ti, and Zn)	-Temporally extensive PM data (25 years) revealed clear compositional differences in PM and source influences from 1976 and 2001 -Comparison of XRF and ICP-AES results demonstrated higher sensitivity and analysis speed of XRF
[116]	PM ₁₀ , PM _{2.5} , and PM ₁ from Genoa, Italy	ED-XRF	Elemental composition (Na, Mg, Al, Si, P, S, Cl, K, Ca, Ti, V, Cr, Mn, Fe, Ni, Cu, Zn, As, Se, Br, Rb, Sr, Zr, Mo, Ba, and Pb)	-Extensive daily PM sampling was performed (1600 samples in total) -Sources were identified via PMF

The quantitative XRF output is obtained in elemental concentrations in ng/m³ by calculating the sensitivity factor for each element using standard reference materials, mass concentration in mass/area (also known as elemental thickness) from the XRF measurements, analyzed filter area, and sampling volume rate [110,118,120,121,163,186–191]. Uncertainties in the XRF measurements generally lie within the 5–15% range for most elements except for those with small atomic masses [120] or with low concentrations near instrument DLs [116]. Low-Z elements are also prone to cause X-ray self-attenuation and might require correction factors during quantification [116,186,190]. Generally, MDLs as low as 1–2 ng/m³ for a selected number of elements have been reported [116,117,120,127,192,193].

Instrument calibration and routine calibration checks are important steps of quantitative XRF analysis procedures. During calibration, the sensitivity curve for each targeted element is developed using standard reference materials; the most commonly used ones being MicroMatter thin-film, single element and compound reference materials [116,117,127,163,186,189,190]. Other options include preparing a mix of different salt standards containing targeted elements [110] and analyzing additional samples concurrently with more reliable methods, such as ICP, to develop a custom calibration [115].

As part of quality assurance and control, an XRF calibration check is performed by analyzing standard materials, where elemental recovery percentages reveal how well the instrument is calibrated [115,118]. Quality control of the XRF measurements can be performed by confirming the repeatability and reproducibility, i.e., the consistency of the measurement results of the same standard on the same day and different days, respectively [118]. NIST SRM for PM on PC filters is regularly used as either a calibration standard or a calibration check material.

Different types of XRF have been applied to the chemical characterization of PM. The most widely employed type of XRF is an ED-XRF [115,116,118,120,127,186,188,193–195], followed by WD-XRF [119,187,196] (and SR-XRF [121,191]). While these types share the typical assets of XRF, SR-XRF is evidently more sensitive than other traditional XRF techniques enabling a trace elemental analysis [121,197]. In the ED-XRF analysis, one of the major concerns is the sample amount rendering it less suitable for time-resolved or size-segregated measurements but possible for the samples collected by a multi-staged impactor with a proper setup [117]. On the other hand, WD-XRF has limitations similar to XRD with overlapping

peaks and the matrix effect and, on top of that, requires a wider range of crystals to analyze more elements [119].

One advantage of XRF is little to no sample preparation allowing for an analysis of atmospheric particulates at their unmodified state, avoiding dilution of already low amounts of trace elements and simplifying procedures [26,119,121]. Generally, Teflon and PC filters are the recommended substrates for an XRF analysis [96,198], and Teflon filters, in particular, are the filters of choice in the official SOPs [199,200]. Though other collection substrates, such as glass fiber [110,119,187] and quartz fiber filters, [187] can also be directly analyzed, interferences from the filter blank contributions (Na, Sr, Al, Si, and P for glass fiber; Zn and Sb for quartz fiber) were reported [119,189]. Given the non-destructive nature of the XRF method, the samples may be stored for re-analysis or analyzed by other techniques [119].

4.2.6. XPS

Atmospheric chemical reactions mostly occur at particle surfaces; thus, it is typical for their surface composition to differ from their bulk chemistry [124,125]. Components on the PM surface are the first to contact physiological fluids following PM inhalation, signifying interest in the surface characterization from a toxicological point of view [127]. XPS can be applied to determine the surface chemistry of atmospheric particulates by providing the chemical composition of shallow particle regions (detection depth < 10 nm) [24,75,122]. The instrument generates energy spectra of intensity versus binding energy characteristic to elements and their oxidation states, later converted to atomic percentage [126,127]. XPS can be operated to produce survey and high-resolution spectra, where the former is often used to determine elements present at the particle surface and the latter provides more detailed data required for the speciation by the deconvolution of signal peaks [53,127]). Selected studies that used XPS for particle characterization are summarized in Table 9.

Table 9. Summary of selected studies on PM characterization using XPS.

Reference	Sample	Instruments and Technique Used	Investigated Features	Remarks
[127]	PM _{2.5} from Sardinia, Italy	XPS	Particle surface chemistry (elements: C, O, N, S, and F; chemical states: C, O, N, and S)	-Detailed quality assurance and control procedure for XPS analysis was provided -A flood gun neutralizer was used to compensate for sample charging -C, O, N, and S species were identified and measured using XPS
[124]	Size-segregated PM (0.01–10 µm) from Beijing, China	XPS	Particle surface chemistry (elements: Al, Si, S, Cl, C, Ca, N, and O; chemical states: C, O, N, and S)	-Size-resolved surface elemental composition carried out with data on chemical states of selected elements (S, N, and C) and ammonium
[125]	Size-segregated PM (0.05–18 µm) from Lecce, Italy	XPS	Particle surface chemistry (elements: N, S, Cl, Si, Na, Ca, Fe, Cr, Cu, and Mg; chemical states: C, O, N, S, Na, and Cl)	-Detailed XPS analysis procedure including accounting for substrate interferences was provided -Elemental composition and speciation of C, N, S, Na, and Cl were determined
[123]	Size-segregated PM (0.05–18 µm) from Hong Kong	XPS	Particle surface chemistry (elements: F, C, O, N, S, Si, Ca, Na, and Mg; chemical states: C, O, N, and S)	-Size-resolved surface elemental composition and speciation of selected elements (C, N, and S) was presented
[122]	TSP from Guangzhou, China	XPS	Particle surface chemistry (elements: C, O, N, S, Si, Na, Ca, Cl, Fe, K, Al, and Cu; chemical states: C, O, N, and S)	-Elemental composition and speciation of C, O, S, and N were carried out -Surface chemistry was compared to bulk chemistry obtained using IC and elemental analyzer

XPS produces semi-quantitative data on both elemental and chemical state compositions with an accuracy of up to 0.1% [24,123,124]. The sensitivity of the technique allows detecting and quantifying various elements (including low-Z elements, such as C, N, and

O) at concentrations as low as 0.1% [53,124]. Moreover, it offers a possibility to study various C functional groups present at the particle's surface but often requires utilizing collection substrates without C, such as Al foil, to avoid background interference [123,125]. A procedure for XPS analysis, including the speciation of C functional groups of particles collected on PTFE, is described in detail by [201].

An XPS can examine samples without sample preparation [24,126,201]. In addition, the method is quick and does not require a substantial sample amount [124]. However, an XPS analysis is performed under a high or an ultrahigh vacuum [53,127,202], facilitating the evaporation of semi-volatile organic compounds. Though XPS has a few drawbacks involving the need for charge compensation, sophisticated spectral deconvolution, and access to databases containing reference spectra of analyzed elements [24], recent studies offer a variety of solutions. Flood gun neutralizers [127] or hot cathodes [202] could be used to solve the sample charging issue. A spectrum analysis is usually performed via software such as Multipak [203], NewGoogly [125], Kratos [123], and XPSPEAK 4.1 [122]. Finally, NIST Standard Reference Databases can be referred to for peak assignment [125].

Since XPS provides compositional data from the analysis depths of a few nms in contrast to methods, such as EDS and XRF, of around a μm , respectively, the result compositions may differ. This might be used to speculate on differences between bulk and surface chemistries [127] as well as particle heterogeneity and formation mechanisms [122]. XPS is a powerful complementary method to bulk chemistry analysis techniques, particularly due to its speciation capability [202]. It could be advised to use it complementarily with methods, such as XRF, to provide a full chemical characterization [201].

Figure 15 displays a decision tree diagram, which can help choose analytic techniques to apply to PM characterization from a pool of common methods. The diagram contains general information to key questions that can guide the selection process, including investigated PM characteristics, sample pretreatment requirements, automation capabilities, spatial resolution, and instrument limitations. This tool may aid the preliminary study planning and help search for alternative techniques.

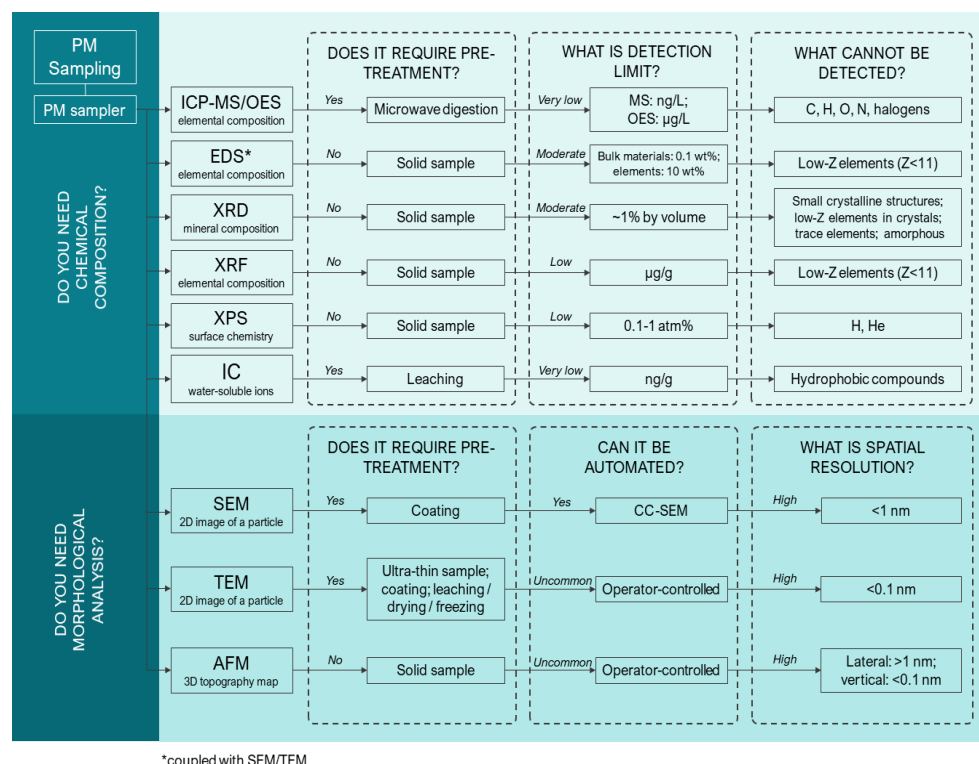


Figure 15. Decision tree diagram for choosing appropriate PM characterization techniques.

4.3. Determination of Intracellular and Mitochondrial ROS Production

The cytotoxic effect of PM exposure can be assessed using various techniques and assays depending on the toxicity mechanism and oxidative potential. The most commonly used technique for assessing the PM cytotoxic effect is the detection of the cellular ROS level by DCFH-DA. DCFH-DA is a cell-permeable ester used for the assessment of the cellular H_2O_2 level [14,15,17,21,33,204]. In the cell, esterases hydrolyze it to form a stable fluorescent product (DFC) if ROS are present [65]. Although being a popular, relatively inexpensive, and reliable fluorescent probe [205], this technique has limitations including an increased concentration of superoxide radical formation due to the conversion of DCFH-DA into DFC, which can affect the quantification of the ROS level. Moreover, DCFH-DA does not directly react with H_2O_2 and can be oxidized to DFC by other oxidizing species [206].

Another method for mitochondrial ROS detection is the DHE fluorescent probe that exhibits strong red fluorescence after being oxidized. DHE is highly sensitive for superoxide detection; however, it can be affected by changes in the mitochondrial membrane potential [205,206]. One of the suggestions on how to increase specific mitochondrial localization is to use mitoSOXTM Red, which is a derivative of DHE. Moreover, to indicate both cytosolic and mitochondrial superoxide levels, it is proposed to use a combination of DHE and mitoSOXTM Red [205]. It is suggested to use mitoSOX at concentrations of 2 μ m or less to avoid an increased accumulation of mitoSOX in the cytoplasm and disruption of the mitochondrial specificity for superoxide detection [206]. Fluorescence produced by the probes can be then measured by flow cytometry [15,33]. For the reader's reference, a comprehensive review of the most recent analytical techniques for the measurement of the PM oxidative potential as well as the chemical and physical determinants of the PM oxidative potential was provided by [207].

Using the cell culture as an exposure model can elucidate the mechanism of particle-cell interaction. The most commonly used in vitro human cell model to study the effect of PM following inhalation exposure includes the human lung adenocarcinoma cell line A549 [12,17,21,204,208,209]. The human A549 cell line is used as a model for alveolar type II cells responsible for surfactant production. Although A549 cells have some characteristic features of alveolar type II cells, the drastic difference is in the inability of A549 to express an alveolar type I phenotype through transition [210]. Other cell cultures used as exposure models include the murine macrophage cell line RAW 264.7 [33,63], the human bronchial epithelial (HBE), and the proliferating, single-cell type bronchial epithelial cell line (BEAS-2B) [211]. A decision tree diagram, which can assist the selection of appropriate methods for toxicity assessment is presented in Figure 16.

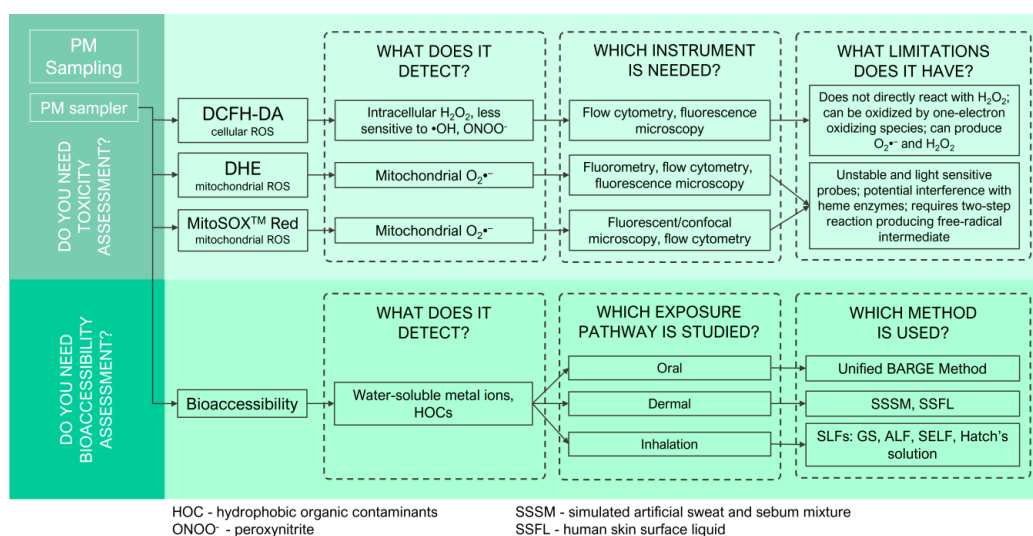


Figure 16. Decision tree diagram for choosing appropriate PM characterization method for toxicity/bioaccessibility assessment.

4.4. Assessment of PTE Bioavailability via Bioaccessibility Testing

Evaluating toxicity and subsequent health risks from human PM exposure is commonly based on the total elemental concentration of PTEs in airborne particulates. However, this approach can overestimate the toxicity and risks, and hence lead to inaccurate conclusions, as not all fractions of PTE are soluble in human physiological fluids [212]. Recent studies suggest utilizing a new approach in the health risk assessment by studying the effect of the bioavailable fraction of airborne pollutants in a simulated lung medium. They are commonly referred to as lung bioaccessibility methods [45].

It has been reported that inorganic and metallic ions are the main constituents of water-soluble PM fractions [213]. Water-soluble metal ions are bioavailable and can readily diffuse through the cell membrane, inducing ROS production. Xiao et al. [20] has reported that water-soluble Cu, Zn, As, and Mn in high concentrations in the coarse PM change the oxidative potential of the cell, reducing its viability. Moreover, it has been suggested that metal particles in atmospheric acidic sulfate can undergo heterogeneous reactions and become soluble [214,215].

The main routes of human exposure to pollutants include ingestion, inhalation, and dermal contact. Oral exposure has been a focus of many environmental studies [57,216–218]. It was the first incorporated pathway to the bioaccessibility studies, and oral bioaccessibility tests are the most commonly used bioavailability estimation method for studying oral exposure to contaminants and performing subsequent health assessments. More recently, the concept of bioaccessibility has been incorporated to the investigation of lung and dermal exposure to various contaminants and related health risks (e.g., [45,219–221]). While oral bioaccessibility testing protocols are well established (e.g., UBM) and validated by *in vivo* studies using animal models [222], protocols for lung bioaccessibility exhibit disparity in composition and physiological parameters of SLFs and physicochemical characteristics of the sample. Moreover, the lack of *in vivo* validation for lung bioaccessibility studies remains a major issue.

The inhalation of airborne contaminants can pose a greater risk for human health when compared to oral or dermal exposure pathways [223]. When studying inhalation exposure, older studies measured the release of PTEs from PM by dissolving them in relatively simple chemical solutions (containing, e.g., H_2O , NaCl , $\text{NH}_4\text{CH}_3\text{CO}_2$, and $\text{C}_6\text{H}_{11}\text{NO}$) following the notion that PTEs dissolve in human lung fluid in the same manner. However, in more recent work, these approaches are considered inaccurate because they do not represent the complex composition of the human lung along with its physiological parameters [224].

Physiologically based SLFs mimic the physiological conditions in the human lung and have recently been used for the measurement of lung bioaccessibility. SLFs include GS (original and modified), ALF, SELF, and Hatch's solution [224,225]. Variability in the composition of SLFs would be expected to greatly affect the release of contaminants from particulates. GS and ALF are among the most used physiologically based SLFs. The composition of GS includes cations (e.g., Mg^{2+} , Na^+ , Ca^{2+} , and K^+); anions (e.g., proteins, HCO_3^- , SO_4^{2-} , organic acids, Cl^- , and $[\text{PO}_3(\text{OH})]^{2-}$; non-electrolytes (e.g., amino acids, glucose, and products of protein metabolism); and carbonic acid [226], mimicking the interstitial fluid in the lung. A recent modification of GS includes additional proteins and amino acids, modification with a serum simulant, and lung surfactant [224]. ALF represents the acidic environment of alveolar macrophages during phagocytosis [227]. ALF has a composition similar to that of GS; however, the alternation of pH was reached by the addition of HCl or buffer. Studies reported higher elemental solubility in ALF compared to GS indicating acidity as a major factor [220,228–230].

Apart from various SLF compositions, lung bioaccessibility studies propose different parameters for simulating contaminant release from the particulates (e.g., pH, extraction time, temperature and procedure, solid to liquid ratio (S/L ratio), and agitation) meaning that there is no universally accepted procedure [224,225]. Internal factors affecting the bioaccessibility levels include the physicochemical characteristics of the sample, as the release of contaminants is influenced by parameters, such as the presence of various PM

matrices and particle sizes. Results on the bioaccessibility of PTEs obtained by various studies differ due to varying particle sizes and utilized simple chemical solutions [231]. A high variability in contaminant mobilization factors establishes the current research need for a unified bioaccessibility protocol to measure elemental solubility in SLFs. Furthermore, the composition of SLFs and physiological parameters should be optimized to obtain values that better approximate in vivo bioaccessibility results. In addition, elemental solubility is not a common tool used for risk assessment; therefore, bioaccessibility results should be incorporated for more accurate risk values and a better prediction of toxicity associated with PTE exposure. A decision tree diagram shown in Figure 16 can inform the selection of a suitable method for bioaccessibility assessment.

5. Characterization of Human Health Risks

A human health risk assessment is crucial for identifying hazardous substances, characterizing human exposure including inhalation, and proposing management strategies to reduce adverse health outcomes [224]. The human health risk assessment approaches, along with the tools developed by the U.S. EPA to estimate inhalation exposure and associated health risks, are commonly adopted throughout the world. Whether directly adopted or with modifications, this framework can be used as guidance in the risk assessment of the carcinogenic and non-carcinogenic effects of various contaminants [232]. It estimates risks based on the results of hazard identification, dose–response assessment, exposure assessment, and risk characterization.

Exposure assessment consists of a numerical estimation of the exposure/dose, including magnitude, duration, and frequency of exposure, and risk characterization is a final step that uses cumulative information about the hazard obtained from previous steps to the implement policy [38]. It must be emphasized that complex relationships exist between humans and their environments. As a result, it may be necessary to integrate environmental, socioeconomic, and behavioral contextual factors to the exposure assessment. Although these factors have been mostly excluded from the present review due to scope restraints, we invite interested readers to explore further the up-to-date literature (e.g., [26,233]).

In an exposure assessment, it is essential to estimate the duration of the potential exposure (e.g., acute, sub-chronic, and chronic). Toxicological studies have revealed distinctive effects of short and long-term exposures [232]. A short duration of exposure to relatively high concentrations of contaminants (e.g., minutes, hours, and days) could be classified as acute, whereas sub-chronic exposure lasts for weeks to years (e.g., 6–8 hrs/day, 5 days/wk) and a long-term exposure can last for many years and as such, is defined as chronic [232]. For an exposure assessment, ideally it is recommended to consider the complex nature of biological responses in the human body (e.g., contaminant accumulation and transport, clearance mechanisms, and potential irreversible effects) to define the duration of a site-specific exposure scenario. In a site-specific exposure assessment, the exposure duration should be similar to the exposure duration represented by a specific toxicity value. However, it may not be always plausible for human exposures influenced by factors, such as meteorological conditions (e.g., temperature, seasonal variations), that effect the intensity of the exposure for those living in close proximity to the source of emissions. Risk assessors should rely on professional judgment to apply exposure duration for a selected scenario that is consistent with the duration associated with a corresponding toxicity value. Moreover, uncertainties related to the application of a chosen toxicity value should be addressed in the risk characterization part. The present review article focuses on the estimation of a health risk following a chronic exposure scenario [232], which covers the relevant duration for PM exposure. In the chronic exposure assessment, the average daily dose of a contaminant following inhalation exposure is estimated using the following equation:

$$ADD_{inh} = (C \times IR \times ED \times EF) / AT \times BW \quad (1)$$

where ADD_{inh} is the average daily dose (mg/kg/day); C is the contaminant concentration in the air (mg/kg); EF is the exposure frequency (d/a); ED is the exposure duration (a), and AT is the average time (lifetime in years $\times 365$ d/a $\times 24$ h/d), and BW is the body weight (kg) [232]. In risk characterization, non-carcinogenic risks are estimated via hazard index (HI) calculations using the following equation:

$$HI = ADD_{inh} / RfC \quad (2)$$

where RfC is a reference dose for non-carcinogenic pollutants (mg/kg/day). A $HI \geq 1$ suggests an unacceptable non-carcinogenic health effect on the exposed population [234]. Carcinogenic risks are estimated via life-time cancer risk (LCR) calculations using the following equation:

$$LCR = ADD_{inh} \times CSF_{inh} \quad (3)$$

where CSF is the cancer slope factor ((mg/kg/day) $^{-1}$). Exceeding a threshold ranging from a target range of a one-in-a-million (10^{-6} risk) to a one-in-ten-thousand risk (10^{-4} risk) (exact threshold depending on the substance as well as the regulating health authority) for exposed individuals is considered unacceptable.

In most studies, the estimation of health risks from airborne pollutants is mainly based on the potential dose or the amount of inhaled chemical [232]. This works on the assumption that the potential dose and applied dose or amount that reaches the target organs are equal. This can lead to the overestimation of health risk because the amount of the absorbed/bioavailable contaminant is generally only a fraction of the potential dose. Therefore, the risk assessment framework may be enhanced by incorporating bioaccessibility as an estimation of bioavailability of the contaminant to the chemical daily intake equation (Equation (1)).

For most contaminants, the toxicity to human organisms comes from its solubility and the ability to cross the cell boundary to reach biologically active sites. However, recent evidence also suggests that bioavailable fractions are not the only ones expressing toxicity. Ref. [235] showed that redox-active metals, such as Cu and Fe, bound to the insoluble fraction of PM can induce oxidative stress, cytotoxicity, and DNA damage. Moreover, insoluble fractions of PM are responsible for the disruption of the cell membrane by forming particle agglomerates and generating phagocytic vesicles [213]. Therefore, there is a current need to investigate the toxicity profile of both soluble and insoluble PM fractions. Moreover, some physical characteristics of airborne pollutants, including particle size, shape, and deposition mechanisms, are rarely incorporated into the estimation of inhalation risks [224]. Therefore, extensive research is needed to understand the mechanism underlying PM toxicity to better predict health risks.

The previously described framework uses a deterministic method for calculating health risk meaning that a single-point value (e.g., average or highest value) is selected for each variable. However, this approach does not account for the uncertainties of contaminant concentrations and other exposure parameters. A probabilistic risk assessment is another method for calculating risk by estimating the likelihood and the extent of human adverse health outcomes due to inhalation exposure [236]. A sensitivity analysis is a component of a probabilistic risk assessment that identifies variables that have the most effect on risk assessment outcomes [234,237]. The Monte Carlo simulation is an example of a computational technique applied for a probabilistic risk assessment. It is used for random sampling and statistical modeling for the estimation of mathematical functions and to mimic the behavior of population samples [238,239]. It performs multiple trial runs (10,000 or more) [234,240] and presents risk factors that have uncertainty as to the probability distribution of randomly selected variables that create a range of possible outcomes [238]. The benchmark for health risk is most commonly set to the 95% percentile [240–242] that acts as a conservative upper threshold.

6. Conclusions and Recommendations

The present article reviews the significant determinants of particulate matter (PM)-induced cytotoxic effects and the subsequent implementation of analytical techniques for the characterization of airborne particles. A brief description on assessing human health risks is also provided. Adverse health outcomes are associated with a biological response due to the particulates' size, morphological properties, and elemental composition. The PM-induced cytotoxic effect includes systemic inflammation, increased accumulation of reactive oxygen species (ROS), oxidative stress, and changes in cell oxidative potential. It has been proposed that fine fractions of PM have higher toxic potential than coarse particles; however, the health effects of coarse PM may also need to be considered for a more comprehensive assessment of the human health risk. Morphological features and chemical constituents of PM are the primary determinants of the biological response following inhalation exposure.

The analytical methods for PM characterization are often utilized in combination since it is challenging to provide an insightful analysis of the collected airborne PM using one method. Studying only the bulk chemistry of PM can neglect the contribution on the individual particle level. Therefore, it is essential to select and recommend a set of analytical methods that complement each other to provide essential information on the critical parameters of PM. Furthermore, recommended analytical methods should be robust and require as little resources as possible. Thus, implementing the most appropriate method complying with the examined specific PM feature is of great importance.

Scanning Electron Microscope with an Energy Dispersive X-ray (SEM-EDS) is the most commonly used non-destructive technique for the single-particle analysis of PM. SEM can produce accurate size-resolved and statistically significant data on 2-D PM morphology with less resources (e.g., time and expertise) compared to other imaging methods, such as Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM). SEM coupled with EDS can also provide an average elemental composition of individual particles. Therefore, it is strongly recommended for routine monitoring procedures for both fine and coarse fractions. Other microscopy techniques, such as TEM and AFM, can be suggested as complementary analyses to study a region of interest, which can be determined via a preliminary SEM examination; the former can provide data on the internal structure of particles and particle formation, and the latter can characterize particle volumes and the hygroscopicity at high resolutions. Furthermore, EDS can also be coupled with TEM to characterize the elemental composition of PM particles, but it is limited in its detection and quantification capabilities. SEM-EDS or TEM-EDS cannot supply information on the oxidation states of identified elements or detect elements at trace concentrations and, therefore, cannot replace more sensitive chemical analysis techniques (e.g., Inductively Coupled Plasma (ICP) analysis), serving as rather rapid methods of linking the elemental composition of single particles to their morphology. Overall, future research using the analytical methods discussed in the present review is expected to increase to better characterize the physicochemical properties and toxicity of PM.

In addition to particle morphology, it is recommended to investigate the bulk chemistry of sampled PM using either dry analysis methods, such as XRF, or wet analysis techniques including ICP and ion chromatography (IC). XRF is a quick and straightforward method with an adequate sensitivity level for gathering bulk elemental data on PM, which can be utilized as a preliminary assessment tool prior to the more sensitive and resource-intensive ICP. It may be advised to include IC analyses in any regular PM monitoring, as it is the best tool for measuring water-soluble components of PM, which are of greater significance to health risk assessment frameworks. Although X-ray photoelectron spectroscopy (XPS) is not the most common technique for PM characterization, researchers can utilize XPS as it is a powerful surface chemistry analysis method complementary to the mentioned techniques, mainly due to its speciation capability. On the other hand, X-ray diffraction (XRD) allows the characterization of mineral fractions of PM as an additional chemical analysis. The most commonly used technique for investigating PM cytotoxic effect is detecting ROS

production via the DCFH-DA assay. Due to its limitations, it is recommended to use either DHE and/or its derivative MitoSOX Red for a more accurate quantification of ROS levels.

For most airborne contaminants, the toxicity to human organisms is associated with contaminant solubility and bioavailability. However, bioaccessibility (an estimation of bioavailability) is generally not considered when estimating health risks following inhalation exposure. It is recommended to use bioaccessibility data instead of total elemental concentrations to conduct a more realistic human health risk assessment. The data obtained from the physicochemical characterization of PM using various techniques may be further utilized to enhance the human health risk assessment. More specifically, physicochemical characteristics including size, morphology, and solubility could be incorporated into the quantification of health risks.

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Abbreviations

AAS	Atomic absorption spectrophotometry
AES	Atomic emission spectrometry
AFM	Atomic force microscopy
AFS	Atomic fluorescence spectrometer
ALF	Artificial lysosomal fluid
BC	Black carbon
CC-SEM	Computer controlled scanning electron microscopy
CE	Capillary electrophoresis
CEN	European Committee for Standardization
CPF	Conditional probability function
DCFH-DA	Dichloro-dihydro-fluorescein diacetate assay
DL	Detection limit
DPPC	1, 2-dipalmitoyl-sn-glycero-3-phosphocholine
EDS	Energy dispersive X-ray spectroscopy
ED-XRF	Energy dispersive X-ray fluorescence
EELS	Electron energy-loss spectrometry
ESEM	Environmental scanning electron microscopy
FEG-SEM-EDS	Field emission gun scanning electron microscopy with an energy dispersive X-ray
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
Gpx	Glutathione peroxidase
GS	Gamble Solution
DHE	Dihydroethidium
HO-1	Heme oxygenase 1
HRTEM	High-resolution transmission electron microscope
IARC	The International Agency for Research on Cancer
IC	Ion chromatography
ICP-MS	Inductively coupled plasma
IL	Interleukin

INAA	Instrumental neutron activation analysis
JCPDS	Joint Committee of the Powder Diffraction Standard
LA-ICP-MS	Laser ablation inductively coupled plasma mass spectrometry
LC	Liquid chromatography
LMMS	Laser microprobe mass spectrometry
MCS	Monte Carlo simulation
NMR	Nuclear magnetic resonance spectroscopy
NIST	National Institute of Standards and Technology
NO	Nitric oxide
PC	Polycarbonate
OC	Organic carbon
PCA	Principal component analysis
PEEM	Photoemission electron microscopy
PESA	Particle elastic scattering analysis
PIGE	Particle-induced γ -ray emission
PIXE	Proton-induced X-ray emission
PM	Particulate matter
PMF	Positive matrix factorization
PAH	Polycyclic aromatic hydrocarbons
PTE	Potentially toxic elements
ROS	Reactive oxygen species
SEM-EDS	Scanning electron microscope with an energy dispersive X-ray
SIMS	Secondary ion mass spectrometry
SE	Secondary electron
SELF	Simulated epithelial lung fluid
SLF	Simulated lung fluid
SPEM	Scanning photoelectron microscopy
SPMS	Single-particle mass spectrometry
SRM	Standard reference material
SR-XRF	Synchrotron radiation X-ray fluorescence
STM/AFM	Scanning tunneling microscopy/atomic force microscopy
STEM	Scanning transmission electron microscopy
TEM	Transmission electron microscopy
TM-AFM	Tapping mode atomic force microscopy
TNF- α	Tumor necrosis factor- α
TOC	Thermal/optical carbon analysis
TOR	Thermal/optical reflectance
TSP	Total suspended particles
UBM	Unified BARGE Method
U.S. EPA	United States Environmental Protection Agency
VOCs	Volatile organic compounds
WD-XRF	Wavelength-dispersive X-ray fluorescence
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction
XRF	X-ray fluorescence

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