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Article

A Review of the Research Methods Used to Determine the Health Effects of Respirable Atmospheric Particles

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ABSTRACT

The adverse health effects of air pollution are being increasingly recognized as major causes of disease. Atmospheric particles, as a major component of air pollution, have been extensively studied in terms of their sources, physicochemical characteristics, transport in the atmosphere, and changes in particulate composition during their time in the atmosphere. The relationships between particles and diseases are complex, so research on the health effects and damage mechanisms of particulate matter (PM) is of significant importance. This study reviews the health effects of PM and provides an overview of the hazards of atmospheric PM to various human organs. In addition, this review explores the mechanisms of damage, summarizes the research methods used to determine the health effects, and discusses the influential health factors caused by PM. In combination with current Chinese and global research, the modern technologies and research trends on the health effects of particles are elucidated.

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Research Highlights

- An understanding of the complex and heterogeneous nature of particulate air pollution.
- Elucidating the causes and mechanisms of disease related to particulate pollution.
- A review of analytical methods.
- An insight into likely future trends and technologies.

1. Introduction

Air pollution typically occurs in countries or cities where the daily average mass concentration of atmospheric particles exceeds recommended levels, and is a worldwide problem with important implications for human health. Atmospheric particles have a wide range of particle sizes and complex compositions, and affect human health through ingestion (gastrointestinal tract), inhalation (lung), and dermal (skin) contact, as well as through non-intestinal (extra-gastric) routes [1]. Atmospheric particles are solid or liquid particles suspended in an aerosol with various different definitions. Based on the size of the aerodynamic diameter of particles, particles have been classified as total suspended particles (TSP; total mass of all airborne solid and liquid particles suspended in the atmosphere; measured in micrograms per cubic meter ($\mu g/m^3$)), PM_{10} (particles with an aerodynamic diameter less than 10 μm), $PM_{2.5}$ (fine particles have diameters less than 2.5 μm) [1], PM_1 (aerodynamic diameter of particles less than 1 μm) [1–3], and ultra-fine particles (UFPs, particles with an aerodynamic diameter of less than 0.1 μm) [4, 5]. Atmospheric particles can be defined according to their emission sources, which are divided into two types, natural and anthropogenic. Natural sources include volcanic eruptions, forest fires, and crustal erosion, whereas anthropogenic emissions include factory, fossil fuel combustion, and transport-related emissions [6]. Atmospheric particles are further defined according to their components, as inorganic, organic and biogenic [1, 7]. The general nature of the classification of atmospheric particles is summarized in Table 1.

Atmospheric particles can function as carriers of pollutants such as hydrocarbons, sulphates, and nitrates [7–9]. Numerous studies have shown that the presence of heavy metals and polycyclic aromatic hydrocarbons (PAHs) in or adhering to particles are a crucial factor in health effects [10–14]. Due to the complex composition of atmospheric particles, the health effects can show complicated interactions, such as additive, synergistic, and antagonistic effects, potentiation, and independent actions. In general, the finer the particle size, the deeper it penetrates into the respiratory system [15, 16], and is then distributed throughout the body [17], resulting in a wide range of health effects. Exposure to atmospheric particles have been found to cause cardiovascular [18], respiratory [19, 20], neurological [21, 22], immune system [23], premature death [24–27] (Figure 1). In addition, microplastics, as an emerging pollutant, can also be present in significant quantities as atmospheric particles [28, 29] and have been demonstrated to cause lung dysfunction in *in vitro* toxicology studies [30].

The methods used to study the health effects of atmospheric particles include three main approaches: epidemiological surveys, health risk assessment and experimental methods. Epidemiological surveys are studies of the correlations between particular particle types and a specified disease, based on data collected on the disease and information on pollutants and meteorological factors. There are two categories of exposure: short-term and long-term exposure studies [27]. Numerous epidemiological investigations have shown that atmospheric particles can be hazardous to human health, especially for sensitive populations such as the young, old and people with compromised respiratory systems [27]. Health risk assessment is mainly based on the use of models to assess the likelihood of harmful substances affecting human health. Commonly used models include the carcinogenic and non-carcinogenic risk models published by the U.S. EPA [31]. Using this model, the carcinogenic and non-carcinogenic characteristics of organic and inorganic components from particles have been extensively studied [13, 14, 32, 33]. Health evaluations can cover determinations of the teratogenic (agent or factor which causes malformation of an embryo) and mutagenic (agent that causes genetic mutations) capacity of atmospheric particles. However, the results of epidemiological surveys and health risk assessments do not directly establish a causal relationship between atmospheric particles and adverse human health effects, therefore toxicological experiments can be used to confirm the link. Toxicological tests generally consist of two methods, *in vivo* and *in vitro*. The *in vivo* methods determine the risk of health effects caused by atmospheric particles by analyzing the acute and chronic responses caused by exposure to PM to organs and tissues of experimental animals. Commonly used laboratory animals include rabbits and rats. In contrast, *in vitro* methods mainly involves exposing target cells to different concentrations of PM suspensions for a certain period of time, determining the degree of damage to the subject sample by means of biomarkers, assessing the dose-effect

relationship between the particles and the subject sample, and thus deriving the degree of toxicity of PM [34]. Commonly used target cells are human lung cells (e.g., human bronchial epithelial [HBE]) and vascular endothelial cells (VEC). The comet assay, DTT (Dithiothreitol) assay, Ames test, micronucleus assay, apoptosis assay, SOS chromogenic test, hemolysis assay, chromosomal aberration test and plasmid scission assay can be used to assess the extent of damage caused by particles to tissues, cells, DNA, and chromosomes in *in vitro* cultures [35–38].

Table 1. Main characteristics of atmospheric particles [39–43].

Category	Particle Size	Composition	Source	Atmospheric Half-Life	Transmission Distance (km)
TSP	10–100 μm	Crustal material, dust, coal, fly ash, metal, sulphate	Coal burning, road dust, building dust, traffic emissions, plant emissions	Rapid settling	1–1000
Coarse PM	2.5–10 μm	Crustal material, dust, coal, fly ash, metal, sea salt, fungal spores, moulds	Road dust, resuspension of agricultural and construction dust, traffic emissions, sea waves, plant emissions, wind-blown pollen	Minutes to days	10–100
Fine PM	0.1–2.5 μm	Sulphate, nitrate, ammonium, water-soluble ions, organic matter (OC, EC, PAHs), metal (Pb, Cd, Cu, Zn), bacteria	Traffic emissions, crust/road dust, fossil fuel burning, biomass burning, waste burning, pollen	Days to weeks	100–1000
Ultra-fine PM	<0.1 μm	Organic matter, metal, sulphate, nitrate, ammonium, virus	Pollen, biomass burning, motor vehicle emissions, power plant emissions, smoking, industrial activities, waste burning	Minutes to hours	1–10

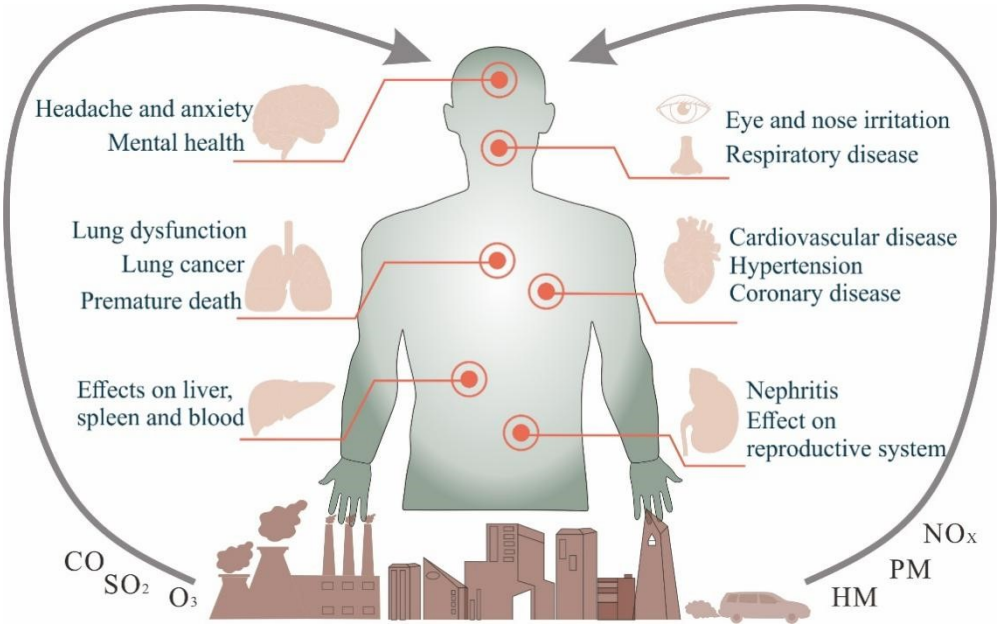

Figure 1. Schematic illustration showing health risks from exposure to various air pollutants.

In addition to toxicological experiments, the possible toxic properties of $PM_{2.5}$ have also been studied with the help of various individual particle analysis techniques. Individual particle analysis techniques such as Raman Microspectroscopy (RM), Atomic Force Microscopy (AFM), Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are used to analyse activity in individual cells and tissues to obtain cellular morphology, chemical components, biomechanical characteristics, and tissue changes. RM provides values for protein (phenylalanine), protein (C–C backbone stretch deformation), and DNA (cytosine, guanine) concentrations in cells. AFM captures individual cell morphology. Combined RM and AFM studies revealed that HBE cells exposed to $PM_{2.5}$ release a variety of pro-inflammatory cytokines, including IL-6 (Interleukin-6), IL-8 (Interleukin-8), GMCSF (Granulocyte-Macrophage Colony-Stimulating Factor), GROα (Growth-Regulated Oncogene Alpha) and TARC (Thymus and Activation-Regulated Chemokine) [44]. SEM observations of air-exposed brain tissue demonstrated that brain tissue exposed to filtered air exhibited few or almost no particles, while brain tissue exposed to polluted air had multiple particles scattered on the surface [45]. Brain tissue exposed to filtered air displayed no abnormalities, while brain tissue exposed to polluted air established neuroinflammation, enlarged perivascular spaces and ultrastructural signs of inflammatory cells adhering to the endothelium of cerebral blood vessels [45, 46]. SEM observations confirmed that skin exposure to PM is susceptible to toxic effects caused by metals in the PM [46].

Studies at the biological whole, organ, cellular and molecular level provide insights towards an understanding of the exposure site, nature and processes of toxic effects of chemicals, and are also important for early diagnostic indicators, and preventive and control measures. Although a significant number of toxicological experiments have been conducted, understanding of the biological mechanisms underlying the health effects of atmospheric particulate matter remains limited due to the complexity of these effects.

This review considers the results of previous studies on the toxicology of atmospheric particles and outlines the mechanisms of particle toxicity. In addition, the factors influencing the adverse health effects of atmospheric particles are discussed, and strategies and countermeasures to reduce the health effects of particles are proposed.

2. Influence of the Physico-Chemistry of Atmospheric Particles on Health Effects

Atmospheric PM has a complex composition and a wide range of particle sizes (aerodynamic diameters of 0.001–100 µm) (Figure 2). As a heterogeneous and complex mixture, the size, mass, surface area, shape and chemical composition of PM can vary depending on many factors. The various components of particles can also change over time and in different ambient atmospheric conditions. The physicochemical characteristics of particles are the main factors influencing the health effects of PM.

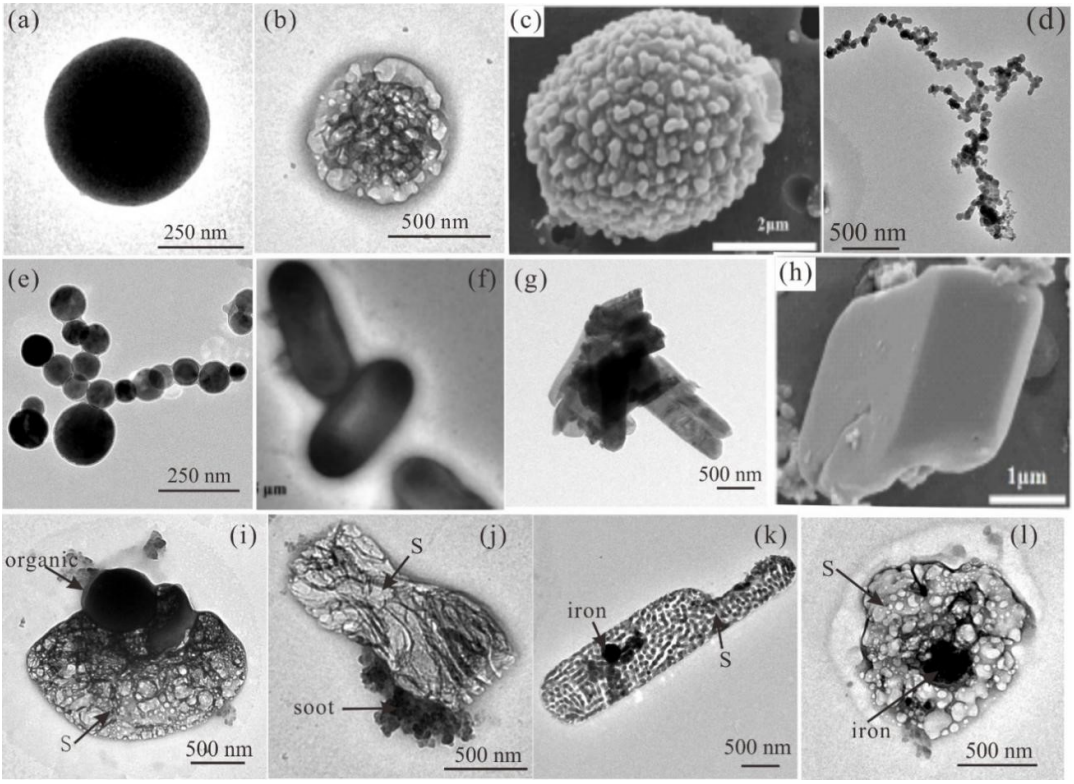

Figure 2. Electron microscopic images of different airborne individual particles. (**a**) organic; (**b**) sulfate; (**c**) spore; (**d**) soot; (**e**) iron; (**f**) bacteria; (**g**,**h**) minerals; (**i–l**) mixed particles (**c**, **f** and **h** are from Shao et al. [41]).

2.1. Chemical Components

The chemical composition of atmospheric particles is highly variable and depends on a number of factors such as original sources, atmospheric chemistry, climate, and seasonality. Non-homogeneous chemical reactions between PM and atmospheric ozone (O_3), free radicals and trace gases can also cause changes in the chemical composition of PM. Particles from oil combustion and traffic sources are highly correlated with short-term health effects, whereas the PM composition from coal combustion particles is more strongly correlated with long-term health effects [47]. The components of PM include organic compounds adsorbed on particles, which can be volatile or semi-volatile organic species (e.g., polyaromatic hydrocarbons [PAH], nitro-PAHs, quinones, and volatile organic compounds [VOC]), transition metals (iron, nickel, vanadium, copper), ions (sulphates, nitrates, ammonium salts), reactive gases (ozone, peroxides, aldehydes), carbonaceous components (mainly from combustion processes and vehicle exhaust particles), biological source fractions (endotoxins, bacteria, viruses, remains of plant and animal) and minerals (quartz, asbestos, soil dust). A health effects study conducted in Queensland, Australia, showed that exposure to low $PM_{2.5}$ levels was associated with total, cardiovascular and respiratory mortality [48], suggesting that these outcomes may be controlled by the chemical fraction in the particles. Since the WHO first defined $PM_{2.5}$ as carcinogenic in 2013, numerous studies have shown that the main carcinogens in atmospheric particles are PAHs and heavy metals. Some areas of high cancer incidence (e.g., Xuanwei, Yunnan) have received widespread attention, and studies have found that heavy metals such as water-soluble Zn, Pb and Cd [36, 38, 49], and PAHs [50] may be important contributors to the high bioreactivity and carcinogenicity of atmospheric particles in that cancer incidence area [51].

2.1.1. Inorganic Components

Metals in PM play a significant role in the health effects caused by PM exposure [52–54]. The International Agency for Research on Cancer (IARC) has designated As, Cd, Cr (VI), Pb- and Ni-containing compounds as public health carcinogens [36]. Although trace elements make up a small proportion of $PM_{2.5}$, many metals pose serious health risks due to their carcinogenic and non-carcinogenic risks. Transition metal elements cause oxidative damage to the cardiopulmonary system due to their bioavailability and redox properties, and Cu-containing nanoparticles (i.e., particles with dimensions between 1 and 100 nanometers; nm) have a significant oxidative stress effect on epithelial cells [55]. Studies have shown that metals in particles can cause damage to mice and their cells through the generation of reactive substances such as hydroxyl radicals (denoted as ·OH or HO·) [56]. Fe in PM causes nerve damage in mice and even increase the incidence of cancer in humans [57, 58]. An assessment of the health risk of heavy metals in road dust in different areas of Beijing, China, found that the bioaccessibility of heavy metals in commercial and transport areas was higher than in the three areas of education, residential zones, and parks [59]. A study of respiratory damage in mice exposed to $PM_{2.5}$ found that atmospheric sulphate, nitrate, and ammonium salts activate inflammatory cells in the lungs through the formation of ROS [55]. In general, the inorganic components of PM cause serious health effects either indirectly through the production of reactive oxides such as ROS or directly by their oxidizing properties.

2.1.2. Organic Components

The organic component is an essential part of atmospheric PM and consists of primary organic aerosols and secondary organic aerosols [60]. Dust storms can increase the mass concentration of organic components in aerosols [61]. Organic components in PM can trigger oxidative stress and genotoxicity that produces inflammatory effects [62]. PAHs and nitro-PAHs are released from incomplete combustion and vehicle exhausts, and PM with higher levels of PAHs lead to the expression and production of more pro-inflammatory mediators [55]. Short-term studies of organic carbon (OC) and elemental carbon (EC) in PM can cause mortality, with cardiovascular disease showing a positive correlation between organic components and mortality [27, 63]. Microplastic particles in the atmosphere are widespread in megacities and pose an ecological risk to humans [64]. The organic component of PM can also cause premature deaths, and it is estimated that 180,000 (117,000 to 389,000) premature deaths were prevented between 1990 and 2012 as a result of the reduction of anthropogenic organic aerosols [65].

2.1.3. Biological Components

Biological components are a key component of PM, accounting for 30–80% of PM [66], containing compounds of various biological origin such as bacteria, fungi, viruses, pollen, cellular debris, and biofilms [67]. The study shows that the number of bacteria and the diversity of the community are greater during dust storms than during non-dust periods [68], suggesting that the mass concentration of bio-aerosols increases with the occurrence of dust storms. Dust can also transport substantial amounts of archaea into the atmosphere and archaea levels increase when the air quality changes from unpolluted to lightly polluted [69]. Both haze pollution and dust storms increase the number of bacteria in the atmosphere [70, 71].

2.2. The Size and Surface Area of Airborne Particles

The atmospheric duration of particles suspended in the atmosphere depends on particle size and shape, and both coarse and fine particles can have an impact on human health. Coarse particle compositions tend to consist of mainly minerals, sea salt, and biogenic material. In a study of chronic obstructive pulmonary disease (COPD), asthma and respiratory admissions, the short-term effects of coarse particles were stronger or as strong as fine parti-

cles, suggesting that coarse particles may cause adverse pulmonary effects [72]. A study of the oxidation potential due to water-soluble fractions of PM of assorted sizes collected at an urban coastal site in Xiamen found that coarse particles (aerodynamic diameters greater than 2.5 μm) during non-exhaust emissions and dust contributed to the elevated oxidation potentials [73]. Coarse particles settle more quickly out of the atmosphere than fine particles, therefore fine particles are more likely to be transported to areas further away from the emission source. Coarse particles account for 90–95% of the total mass and fine particles account for only 1–8% [4]. Fine particles can remain suspended in the atmosphere for longer periods of time due to their small particle size and larger surface area [74], thus making it easier to adsorb and retain toxic substances. The smaller the particle size, the greater the toxicity of the particles [4, 5]. A study of the relationship between PM and cardiovascular disease found a higher correlation between long-term exposure to PM_1 and cardiovascular disease than $PM_{2.5}$ [75]. Ultra-fine particles can have a more severe inflammatory response and oxidative damage in humans than $PM_{2.5}$ due to their smaller particle size and larger surface area [76]. Epidemiological studies have shown that ultrafine particles are able to penetrate into the lungs [76], and are more strongly associated with cardiovascular and respiratory mortality [77]. PM less than 0.3 μm equivalent sphere diameter (ESD) is the main cause of the adverse effect of air pollution on COPD mortality [78]. Exposure to particles of different particle sizes can pose adverse health risks to the cardiovascular system, respiratory system, and fetal growth [79].

The location of particle deposition in the body depends mainly on their particle size, with fine and ultrafine particles more likely to be deposited in the lungs [16]. Particles larger than 5 μm tend to be deposited in the nose and upper respiratory tract [80, 81]. Particles of 2.5–5 μm enter the respiratory tract and are typically deposited in the trachea and bronchi of the lungs, particles of 1–2.5 μm are deposited in the fine bronchi and particles of less than 1 μm are deposited in the alveoli [4] (Figure 3).

2.3. The Mass Concentration of Atmospheric Particles

The mass concentration of atmospheric particles can also influence the level of health risk [82, 83]. $PM_{2.5}$ concentrations are strongly associated with respiratory disease [84]. Epidemiological studies have shown that elevated concentrations of fine particles in the atmosphere increase the morbidity and mortality of respiratory and cardiovascular diseases [85]. Based on a data set derived from 545 U.S. counties consisting of yearly county-specific average $PM_{2.5}$, yearly county-specific life expectancy, and several potentially confounding variables measuring socioeconomic status, a decrease of 10 μg/m^3 in the concentration of $PM_{2.5}$ was associated with an increase in mean life expectancy of 0.35 years. This association was stronger in more urban and densely populated counties [86]. Elevated $PM_{2.5}$ mass concentrations also contribute to increased hospitalisation rates for haemorrhagic strokes [87]. Reducing the annual average $PM_{2.5}$ concentrations from 35 μg/m^3 to 10 μg/m^3 could reduce premature deaths caused by air pollution by 15% in developing countries [88]. The guidelines issued by the World Health Organization in 2021 further reduce the annual concentration to 5 μg/m^3 to reduce the adverse health effects of PM exposure [88].

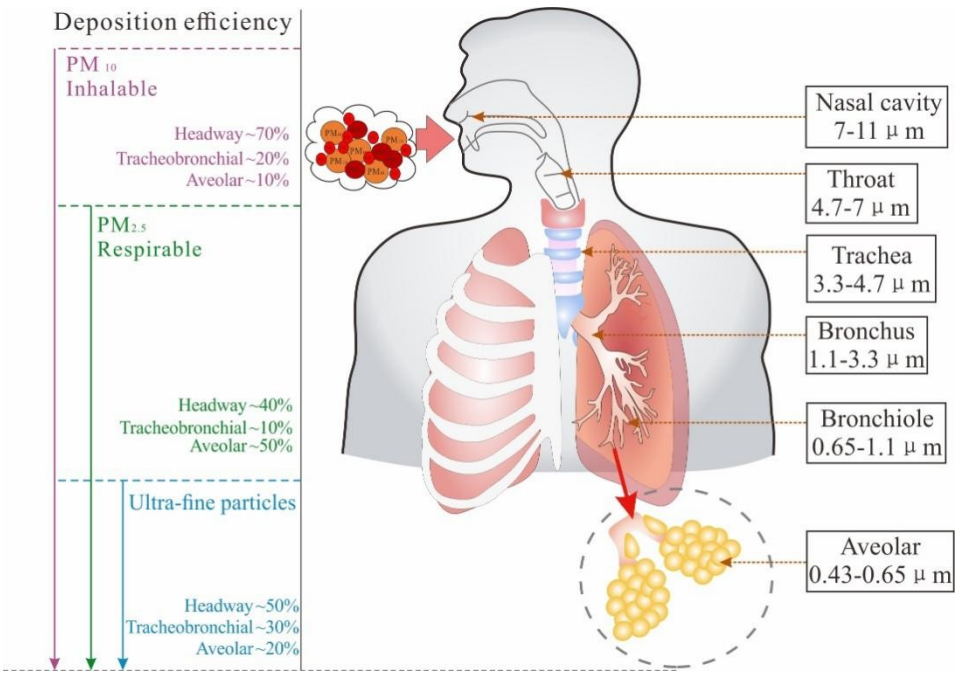

Figure 3. Deposition sites and deposition efficiency of size-segregated particles in the human body. Adapted from [5, 15].

3. Methods of Health Effects Analysis

There are many methods for studying the health effects of atmospheric particles, which can be divided into short-term and long-term exposure studies. Depending on whether experiments are conducted or not, they can be divided into statistical and experimental methods. In practice, researchers often used multiple methods in conjunction to assess the potential health effects of particles directly or indirectly. Under experimental conditions, toxicity is the dose or concentration of particles required to induce a certain toxic effect. The toxicity of particles can be expressed in terms of a dose-response/effect relationship, where the smaller the dose required to elicit a response in experimental animals, the more toxic the particles. Toxicological experimental methods are divided into two main categories: *in vivo* and *in vitro* tests. *In vivo* tests are those in which experimental animals are exposed to a specific dosage of particles and after a specified period of time are observed for possible reactions, or changes in their tissues or organs. *In vitro* tests refer to experiments in which organs, tissues, cells, proteins, and DNA, are exposed to particles. *In vitro* tests include studies at the organ and tissue level, the cellular level, and the molecular level.

3.1. Statistical Method

Where no tests are performed, statistical approaches may be applied through data modelling, observation or synthesis. These include epidemiological studies, health risk assessments, human clinical observations, and occupational exposure studies.

Epidemiological studies examine the correlation between short-term and long-term exposure to particles and disease or death, based on the collection of disease data (such as hospitalizations, deaths), pollutants ($PM_{2.5}$ and its chemical components such as OC, SO_4^{2-}, NO_3^-), meteorological factors (such as daily temperature, relative humidity, wind direction and speed), and questionnaires. Short-term exposure studies, usually consisting of time-series or case-crossover studies, explore the association between short-term changes in particle exposure and the number of daily deaths and morbidity. Long-term studies usually use a cohort design to compare mortality with long-term (monthly, annual, decades) exposure to particles in different populations, i.e., cumulative exposure effects. Studies of particles in relation to all-cause mortality and factor-specific mortality have found a significant association between particles and acute or chronic health effects [27, 89]. A study found that for every 10 μg/m^3 increase in PM_{10} concentration in China, the total non-accidental mortality rate, respiratory disease, and cardiovascular disease mortality increased by 0.36%, 0.36% and 0.42% respectively, while every 10 μg/m^3 increase in $PM_{2.5}$, those diseases increased by 0.40%, 0.63% and 0.75%, respectively [90]. Studies on the correlation between exposure to particles and mortality in the COVID-19 epidemic found that there is a correlation between viruses in aerosols and population mortality and it has a time lag effect [71, 91, 92].

Health risk assessment is the estimation of the potential impact of toxic and hazardous substances on human health by calculating health risk values based on health risk assessment models, which is based on the collection of basic data such as toxicological information, pollutant data, population dynamics, environmental and exposure factors. Contaminant data can be collected based on categories of toxic and hazardous chemicals classified by the IARC. Exposure-related toxicity influences are exposure dose, route of exposure, exposure duration and exposure frequency [93]. Health risks can be classified as carcinogenic risk (CR) and non-carcinogenic risk (expressed as a hazard quotient, HQ) depending on whether the pollutant is carcinogenic or not. There are also Monte Carlo models [94], Geo-accumulation Index (Igeo) [59, 95], Geographic information system (GIS) application models and other health risk assessment methods specifically for air, groundwater, soil and dustfall [96].

People can be exposed to airborne pollutants through three main routes: inhalation, ingestion, and dermal contact [97]. The health risk evaluation of toxic and hazardous substances such as heavy metals [59, 98], PAHs [99] found that toxic and hazardous substances in atmospheric particles have high carcinogenic and non-carcinogenic risks for both adults and children [100]. Studies have shown that the organic and inorganic components carried in particles can be hazardous to human health. Although the health risk assessment yields a probable value with many uncertainties, it can provide reference values for carcinogenic and non-carcinogenic risks to humans and provides scientific support for the development of pollution control measures and disease prevention.

3.2. Experimental Methods

Experimental methods are the most direct way to evaluate the health effects of particles, analyzing and evaluating the damage of PM on test samples, including oxidative damage, biological toxicity, genetic toxicity, and neurotoxicity. Experimental methods are divided into two main categories: *in vivo* tests and *in vitro* tests. Compared to the *in vivo* method, the *in vitro* test has the advantages of operational simplicity, lower cost, and high efficiency.

3.2.1. *In Vivo* Tests

In vivo methods involve PM acting on test samples by means of inhalation or tracheal perfusion, including animal testing and bronchoalveolar lavage. The animal testing methods consists of two approaches, one in which the experimental animal is directly exposed by inhalation to different doses of particles, and one in which the sample is perfused directly into the respiratory system of the experimental animal. Observation of pathological or morphological changes in target tissues or organs are undertaken to establish the dose-effect relationship with particles. Methods include doppler ultrasound, enzyme-linked immunosorbent assay (ELISA) or target organ or cell fluorescently stained and examined by microscopy (such as

laser confocal microscopy). Due to complicated experimental processes, ethical restraints, potentially long test periods, and high cost of *in vivo* tests, many researchers prefer to use *in vitro* methods for toxicology research.

3.2.2. Molecular Biology *In Vitro* Tests

In vitro methods at the molecular biology level are based on assays of DNA and chromosomes. The study subjects are incubated *in vitro* and mixed with controlled dose concentrations of particles for a specified period of time to observe the changes (Figure 4).

The Ames test, also known as the bacterial reverse mutation test, is an *in vitro* test for the mutagenicity of substances using the nature of the revertant mutation in a histidine mutant strain of *Salmonella typhimurium* (Figure 4). These bacteria are unable to synthesize histidine autonomously and cannot grow on histidine-free dishes, while bacteria that are stimulated externally are induced to revert by mutation and regain their ability to synthesize independently. The test works by identifying the strains to determine whether the bacteria have been stimulated by external mutagenic substances, and whether the contaminants are mutagenic [35]. The Ames test is fast, methodologically simple, and low cost, but is less sensitive for the detection of certain chemical species, for example heavy metals. A mutagenicity study of ambient atmospheric particles in Indian industrial areas revealed a high mutagenic potential and colony-forming properties of industrial $PM_{2.5}$ [101].

Single-cell gel electrophoresis (SCGE), also called the Comet assay, determines the extent of health effects caused by particles by detecting the level of DNA damage in lysed cells. If the cell is undamaged, the DNA is inside the cell after electrophoresis and there is no trailing. If the cells are damaged, the broken DNA fragments will spread into the gel and migrate towards the anode after electrophoresis, forming a trailing tail shaped like a comet. The relative amount of total DNA in the tail reflects the frequency of breaks (Figure 4). Analysis of the three indicators of DNA tail length, tail DNA percentage and Oliver tail torque uses infrared wavelength under fluorescence microscopy [102]. This method is sensitive, simple, and fast, and the sample amounts are small. Genotoxicity studies of PM_{10} in the air of Kandy, Sri Lanka and $PM_{2.5}$ in industrial areas of India found that PM can cause DNA damage to cells, with higher concentrations resulting in increased damage [101, 103].

The micronucleus assay assesses the level of chromosomal aberrations in cells by evaluating the rate of cell micronuclei (MN) exposed to PM, where micronuclei levels are a measure of chromosomal damage [104]. Assessment of DNA damage at the chromosomal level using human bronchial epithelial cells, 16HBE, revealed that the rate of micronuclei (MN) increased with increasing dose levels of $PM_{2.5}$ exposures [105].

The chromosomal aberration assay is a toxicity experiment that causes changes in chromosome number and structure either directly through DNA strand breaks and base damage or indirectly through the generation of ROS. It is widely used to assess the safety of compounds such as drugs, cosmetics, and food additives on mammalian cells (Figure 4). Exposure to winter $PM_{2.5}$ in Milan induced cell cycle alterations [106]. Commonly used methods for detecting chromosomal aberrations are microscopic observation, karyotyping and fluorescent in-situ hybridization. The micronucleus assay is similar to the *in vivo* aberration test in that both measure chromosomal alterations in treated mammals and both can be used for initial testing according to most regulatory guidelines.

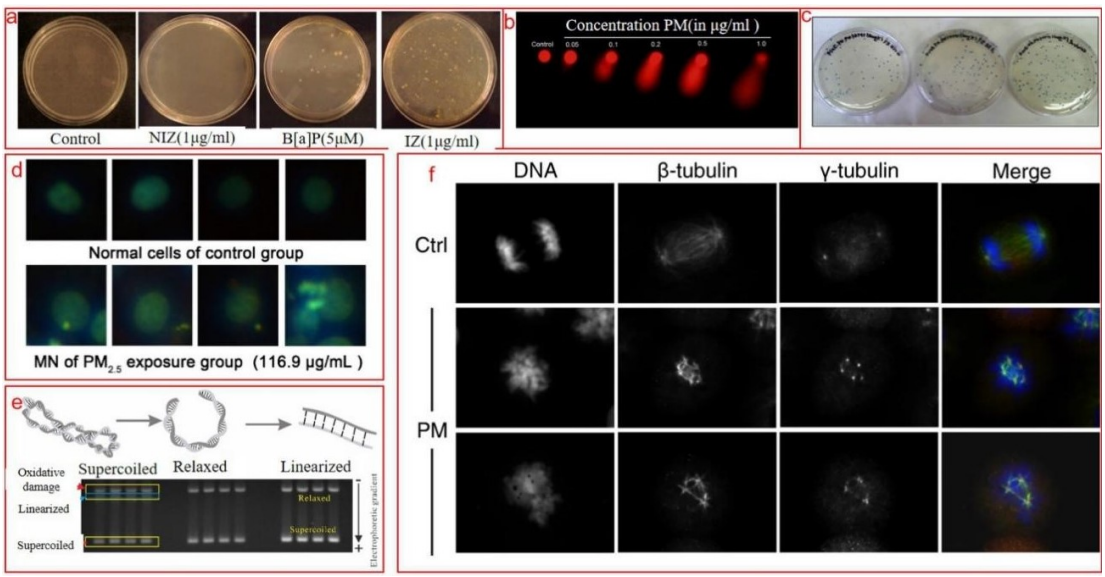

Figure 4. *In vitro* toxicology tests at molecular biology level. (**a**) Ames test [101]; (**b**) Comet assay [101]; (**c**) Determining DNA damage using gene expression [107]; (**d**) Micronucleus assay [105]; (**e**) Plasmid scission assay [52]; (**f**) Chromosomal aberration assay [106].

Plasmid Scission Assay (PSA) is an *in vitro* method to evaluate the ability of oxidative damage on supercoiled DNA caused by ROS carried or generated on the surface of particles (Figure 4). The results of evaluating the bioactivity of particles by counting different morphologies of DNA (superhelical, relaxed and linearized) show that particles from different cities such as Xuanwei [36], Beijing [52], Macau [108] and emitted from different sources such as coal combustion emissions [36, 109] and dust [110] produced different degrees of oxidative damage to DNA, suggesting that water-soluble Zn may be one of the important metals causing plasmid DNA damage. In addition, exposure to organic fractions in PM was found to inhibit gene expression by determining the number of coliform colonies [107].

3.2.3. *In Vitro* Method-Cell Level

After extracting target cells from human lung cells, HBE and VEC in culture, these cells are exposed to different concentrations of particle suspensions for a certain time.

The Apoptosis assay is a study of the toxicity of particles by counting the rate of apoptosis in a fluorescence test (Table 2). Apoptosis is an active process of cell death, the dynamic balance of which is strongly associated with many diseases and has specific morphological and biochemical characteristics. Apoptosis occurs through two distinct phases, one is the formation of apoptotic vesicles, the second is their phagocytosis and finally the degradation of the cell. A large number of approaches to determining apoptosis have been devised featuring combinations of microscopy (e.g., optical, fluorescence, phase contrast and electron) in conjunction with immune-histochemcial analyses (e.g., Annexin v/PI, Tunnel and apoptotic protease assays (i.e., gel electrophoresis, Western blotting and Enzyme-Linked Immunosorbent Assay)). Exposing cells to different doses of PM to study the effects of particles revealed that different dose concentrations of particles led to different levels of apoptosis [37].

A hemolysis assay is a test of the level of cleavage of the red blood cell membrane caused by particles (Table 2). The ability to cause oxidative damage can be obtained by counting the percentage of the red blood cell lysis caused by particles, which causes lipid superoxide reactions and consequently haemoglobin lysis from the red blood cell into the surrounding solution. The analysis of PM_{10} exposure characteristics in the Xuanwei lung cancer investigation to be a high incidence area for significant correlations between the rate of hemolysis and indoor PM_{10} dose concentration [38].

Table 2. Experimental methods of toxic effect assessment of atmospheric particles.

	Research Techniques	Purpose	Markers/ Assay Level	Advantages	Disadvantages	References
	Ames assay	Detection of genetic mutations	Strain	Economic; high positive detection rate; simple operation; no special equipment required; high sensitivity; wide detection range; suitable for a wide range of sample media	Multiple strains need to be measured simultaneously; strictly aseptic; samples containing histidine, glycine or lactose cannot be measured; strains are pathogenic, difficult to store and dangerous to handle; time-consuming and laborious	[35]
Molecular biology level	Micronucleus assay	Detection of chromosomal aberrations	Cells	Simple to operate; convenient to observe; suitable for all kinds of cells with the ability to divide	Prone to false positives; counts are subjective, and observations are subjective	[104]

Table 2. *(Continued).*

	Research Techniques	Purpose	Markers/ Assay Level	Advantages	Disadvantages	References
Cellular level studies	Chromosomal aberration assay					[106]
	Plasmid scission Assay	Detection of DNA damage	Plasmid DNA	Sensitive; simple; speedy, low consumption; no special equipment required; reproducible	Highly demanding laboratory environment; high cost	[52]
	Comet assay		Cells	Sensitive; simple; rapid, low consumption; reproducible; low cost; small number of cells required	Only for DNA damage in nucleated cells; prone to false positive or false negative results	[102]
	Apoptosis assay	Detecting cellular changes	Cells	Simple to operate; convenient to observe; reproducible; no special equipment required	High consumption; low sensitivity; Highly demanding laboratory environment	[37]
	Hemolysis assay	The level of particle-induced erythrocyte membrane cleavage	Cells	Relatively easy to operate, low cost, and can be quantitatively evaluated	Easy to be interfered with, requiring strict control of conditions, limited specificity, and unclear mechanism	[38]

The principle of the Colorimetric MTT (3-(4,5-dimethylthiazol-2yl)-diphenyl tetrazolium bromide) assay is that succinate dehydrogenase in the mitochondria of living cells reduces exogenous MTT to the insoluble blue-violet crystalline substance formazan, which is deposited in the cells, whereas dead cells do not have this function (Table 2). The MTT method is routinely chosen for cell proliferation toxicity assays. The MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay has been derived from the MTT assay. The MTS assay is reduced to produce a darker methan product, which is stable and water soluble and can be measured directly without the need for organic solvents to dissolve it. The MTT assay involves incubating a certain density of cells in a 96-well plate for 12 hours and then exposing them to particles. After 24 hours of incubation, MTT is added to each well and the absorbance of the sample is measured at 595 nm, which is proportional to cell viability. Results are expressed as cell viability as a percentage of alive cells relative to the control samples.

Cell staining is commonly used to detect cell mortality (Table 2). The neutral red dye uptake assay provides a quantitative estimate of the number of alive cells in culture and the neutral red dye penetrates the cell membrane of active cells and accumulates in the intracellular lysosomes. Altered cell surface or cell death with reduced uptake of neutral red dye. The principle of the propidium iodide (PI) uptake assay is to determine that the PI dye does

not penetrate the cell membrane of alive cells but can be inserted between DNA base pairs of dead cells. Determining the dead cells in a given cell suspension by measuring the fluorescence intensity in the cell suspension. The trypan blue exclusion assay measures cellular activity by using the principle that trypan blue enters cells with damaged membranes and binds to proteins within the cells, causing them to appear blue.

4. Mechanisms of Damage by Atmospheric Particles

The mechanism of toxic action is the study of the interaction of toxic substances or metabolically active products with target molecules in the target organ and the series of biochemical or biophysical processes triggered by this action that ultimately lead to toxic effects in the effector organ. In general, the action of a toxic substance or active metabolite on the body is divided into two phases. The first stage is the primary process, in which the toxicant or active metabolite interacts with the target molecule, causing structural and functional damage to the target molecule. The second stage is a secondary process, due to structural and functional changes in biomolecules, which trigger a series of biochemical or biophysical processes, culminating in the appearance of effects in the effector organs.

4.1. Oxidative Stress

Oxidative stress is a response to damage to organs, tissues, cells, and genetic material when there are too many free radicals in the body [111], and it is thought to be the main mechanism of health effect caused by respirable particles. The most crucial factors contributing to the oxidative stress response are ROS and reactive nitrogen species (RNS). ROS include superoxide anions (O_2^-), hydroxyl radicals (OH) and hydrogen peroxide (H_2O_2). RNSs include nitric oxide (NO), nitrogen dioxide (NO_2) and peroxynitrite ($ONOO^-$). ROS and RNS can be produced through a variety of metabolic pathways, such as chemical toxicant and drug metabolism, cellular respiration, radiation, and light exposure. In addition, metallic elements and organic components in particles can also induce the production of ROSs [112].

Elevated levels of ROS and RNS can damage or modify cellular biomolecules, such as proteins and nucleic acids, and thus trigger inflammation [111, 113] (Figure 5). Oxidative stress leads to fever, fibrosis, and bronchitis. [114]. In studies, the strength of the inflammatory response is commonly characterised by the amount of the biomarkers endothelial cells, serum amyloid A, tumour necrosis factor alpha, fibrinogen, and interleukins [115].

There are three stages of oxidative stress in the organism. The first stage is a period of relatively weak oxidative stress, when the body produces a range of antioxidant and detoxifying enzymes to ameliorate (scavenge or destroy) ROS and particles does not produce adverse biological outcomes. The second stage is the failure of the protective antioxidant response to cope with the increased production of ROS, leading to pro-inflammatory and various cytotoxic effects that cause inflammation in the body's tissues. The third stage is typified by the overwhelming antioxidant defense mechanism which could lead to cytotoxic effects and the release of pro-apoptotic factors from mitochondria to induce apoptosis, accompanied by the loss of tissue integrity, structure and function in different organs [116].

PM exacerbates the onset of many diseases such as lung and cardiovascular disease through oxidative stress [113]. ROS is considered to be the main mediator of pulmonary inflammation caused by PM [113]. In addition, persistent free radicals in dust particles can cause oxidative damage to human health [117].

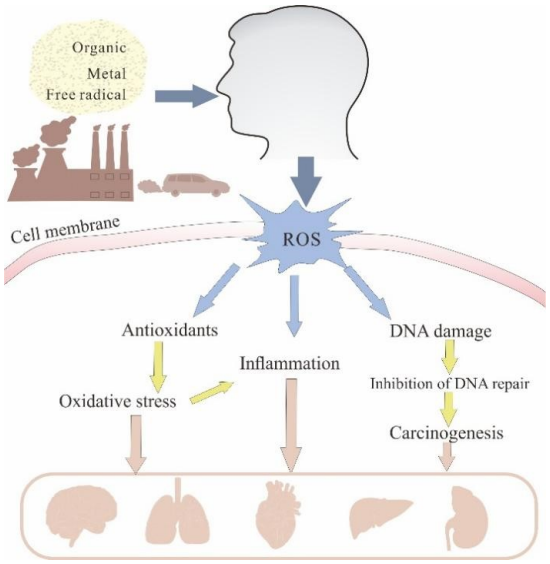

Figure 5. Mechanisms of health effects of atmospheric particles. Airborne particles derived from the anthropogenic sources may be inhaled or ingested into the human body, leading to oxidative stress related to a number of diseases such as those on nervous system, respiratory system, digestive system, and reproductive system.

4.2. Covalent Binding to Biomolecules

Active metabolites in the body covalently bind to protein molecules important for cell survival, causing them to undergo alkylation or arylation. This process leads to the loss of normal function of these proteins, which in turn causes cellular damage and death. Covalent binding in the organism is divided into three main categories: binding to protein molecules, binding to nucleic acids and binding to lipids.

Binding to protein molecules is covalent with amino, hydroxyl and sulfhydryl groups in the protein molecule. Biological consequences include: (i) changes in cell membrane structure and permeability, e.g., CCl_4 can cause a decrease in phospholipid and cholesterol content in rat liver cell membranes, and inhibition of microfilaments and microtubules composed of actin can affect cytoplasmic and mitotic cell division; (ii) cause structural and functional damage to various sub-cells, such as the detachment of ribosomes from the rough endoplasmic reticulum, leading to changes in the control of protein synthesis; affect the catalytic function of enzymes, leading to metabolic abnormalities and impaired energy supply, such as the reaction of lysosomal enzymes in macrophages with toxic particles, releasing hydrolytic enzymes and causing macrophage death [118]; (iii) Interferes with the normal ability of receptor-ligand interactions, e.g., methylmercury damages the central nervous system by inhibiting cholinergic receptors in the brain and cerebellum.

Binding to nucleic acids is done in two main ways of damage, one is direct covalent binding to nucleic acids, such as direct alkylating agents and sodium disulphite. Another common way is the covalent binding of active metabolites of exogenous chemicals to nucleic acid bases, causing hazards such as base substitution, base loss, strand breaks and cross-linking of nucleic acids.

Binding to lipids, mainly at the sites of serine, choline and ethanolamine, can cause changes in membrane structure and function [119].

4.3. Disturbed Cellular Calcium Homeostasis

As calcium ions are activators of the breakdown of biomolecules (proteins, phospholipids, nucleic acids), an imbalance in calcium ions can lead to the destruction of biomolecules and consequently to changes in cell structure and function. High intracellular levels of Ca^{2+} result in dysregulation of signaling systems, cytotoxicity, proliferation, apoptosis, developmental abnormalities, chronic irritation, and inflammation [120].

4.4. Interference with Cellular Energy Production and Supply

Energy for life comes from the biological oxidation of sugars and fats in the body, and the energy produced is stored in the form of Adenosine triphosphate (ATP), a process named oxidative phosphorylation. This process takes place in the mitochondria. Particles can prevent cells from producing ATP by interfering with sugar oxidation. Particles can also uncouple oxidative phosphorylation, resulting in the energy produced by sugar oxidation not being stored in ATP form. Studies have shown that $PM_{2.5}$ from biomass strongly inhibits oxidative phosphorylation coupling and ATP production in mitochondria of the rat brain and other organs [9], and that a reduction in ATP produces an inflammatory response leading to bronchial epithelial cell damage [121].

5. Health Effects of Exposure to Atmospheric Particles

The health effects of air pollution have been studied extensively over the last few decades. Although atmospheric pollutants and pollution status vary across locations, the basic characteristics of the acute or chronic effects caused by atmospheric pollutants are similar. WHO data show that almost all (99%) of the world's population on occasion or regularly breathes air that exceeds guideline limits, with the highest exposure in low- and middle-income countries [88]. According to the Global Air Status 2020 report, air pollution has become the world's 4th leading risk factor for premature death in 2019 [122]. Studies conducted in Asia, North America, and Europe on the association between lung cancer and $PM_{2.5}$ exposures have shown that $PM_{2.5}$ is associated with both lung cancer incidence and mortality [123]. There is a significant increase in new cancer cases and deaths in China in 2022 (4,820,000 and 3,210,000) compared to 2020 (4,568,754 and 3,002,899) [124, 125]. Health risks from long-term exposure to PM have a more persistent and cumulative effect than short-term exposure [126].

5.1. Short-Term Health Effects

Short-term health effects of PM exposure include irritation of the respiratory system and skin (Table 3). The main indicators for evaluating short-term health effects are mortality rates and hospitalization rates. Short-term exposure to $PM_{2.5}$ is positively associated with increased risk of cardiovascular disease (CVD), COPD hospitalization and related death incidents [126]. Mortality and hospitalization rates increase with increasing mass concentrations of PM. The study found that for every 10 $\mu g/m^3$ increase in PM_{10} and $PM_{2.5}$ levels, the hospitalization or mortality rate increased by 1.63% and 2.12% respectively [127]. Exposure to air pollution increases the incidence of heart failure, and studies have found that short-term exposure to PM increases heart rate variability (HRV) in rodents and affects cardiac autonomic function [126]. In addition, numerous studies conducted around the world have confirmed the harmful effects of dust storms on cardiovascular and respiratory diseases [128]. During the dust event, the number and duration of hospitalization for cardiorespiratory diseases increased, and the death rate also increased [128]. Histopathological examination of rat lungs revealed that short-term $PM_{2.5}$ exposure leads to lung fibrosis through oxidative stress [116].

Table 3. Health effects of atmospheric particles on humans.

Part	Diseases	Reference
Brain and nervous system	Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease), neuroinflammation	[129]
Respiratory system	Asthma, bronchitis, pneumonia, chronic obstructive pulmonary disease (COPD), COVID-19, decreased lung function, respiratory dysfunction, lung cancer	[130]
Cardiovascular system	Coronary heart disease, ischemic stroke, arrhythmia, hypertension, vascular dysfunction, myocardial infarction	[131]
Renal system	Decreased renal function, chronic kidney disease, interstitial nephritis, renal fibrosis	[126]
Liver system	Non-Alcoholic Fatty Liver Disease (NAFL), Non-Alcoholic Steatohepatitis (NASH), Progressive Fibrosis and Cirrhosis	[132]
Reproductive system	Premature birth, low baby weight, breast cancer	[80]
Immune system	Hypersensitive reactions, allergic diseases, infectious diseases (e.g., COVID-19), malignant tumours	[133]
Skin	Pigmentation, skin irritation, acne, worsening psoriasis, skin cancer, premature skin ageing	[119]

5.2. Long-Term Health Effects

The particles first contact the respiratory system after entering the human body, directly affecting the normal functions of the throat, bronchus, and lungs (Table 3). The long-term health effects of particles focus on reduced lung function, respiratory symptoms, chronic bronchitis, increased risk of lung cancer and increased mortality in the cardiopulmonary system [86, 131]. Studies have shown that fine particles contribute to increased mortality from heart and lung disease and that even long-term exposure to low levels of air pollution can increase health risks [134]. A 2-year study in China showed that for every 10 μg/m^3 increase in $PM_{2.5}$, the incidence of lung cancer increased in both men and women [135]. A time-series study of myocardial infarction during dust events found that reducing PM_{10} and $PM_{2.5}$ emissions reduced myocardial infarction rates in sensitive populations [136]. Particles can alter the number and activity of macrophages, reduce immune function, increase susceptibility to bacterial and viral infections, and reduce the body's resistance to infectious diseases [133]. Exposure to fine and ultrafine PM from vehicle emissions can cause cardiovascular dysfunction [137]. $PM_{2.5}$ emissions from traffic sources are significantly immunotoxic to human peripheral blood lymphocytes, disrupting immune homeostasis and thought to be associated with disturbances in intracellular calcium homeostasis [138]. In addition, long-term exposure to particles can cause damage to the reproductive and endocrine systems. Long-term exposure of pregnant women to particles pollution can affect fetal development and health [139] and even cause spontaneous abortions [140, 141].

6. Recommended Future Research

Based on the progress of research on the health effects of particles in China and worldwide, the future development direction of research on the health effects of atmospheric particles includes:

1. Reduce PM mass concentrations. Improve pollutant emission standards and upgrade air pollutant treatment technologies.
2. Combining multiple experimental methods to study mechanisms of toxic damage. Many researchers estimate the pathogenicity of particles only from the perspective of certain diseases by a single chemical component and lack multi-component combined damage studies. Methods such as the combination of toxicology experiments focus on the macroscopic analysis of the toxicity-effect mechanism and single-particle analysis focus on microscopic analysis of chemical components could be the important direction of future research.
3. Enlarge the scope of research. Air pollution is a global environmental problem due to the dispersion of air pollutants throughout the atmosphere followed by air mass transportation. Therefore, large-scale, multi-national research should play a key role in particle health effects research in the future.

4. Multi-disciplinary research. Research on particle health effects involves many different disciplines, such as chemistry, biology, pathology, physics, environmental science, and mineralogy. It requires multiple disciplines cooperation from different perspectives to conduct comprehensive studies and investigations.

5. Improving experimental precision. Most studies have also only been able to experiment with high dose concentrations of PM, representing only high pollution levels, and studies of low dose levels of PM (below national standard limits) are extremely limited, so future studies should also focus on the effects of long-term exposure to low concentrations of PM pollution on human health.

Author Contributions

L.S.: Conceptualization; Validation; Writing—original draft; Writing—review and editing. X.F.: Investigation; Writing—original draft; Visualization. S.F.: Investigation; Visualization. T.J.: Writing—review and editing, Validation. Y.C.: Investigation, Writing—original draft; W.L.: Investigation; Writing—original draft. M.Z.: Investigation. H.N.: Writing—review and editing. S.Y.: Writing—review and editing. K.B.: Writing—review and editing.

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Informed Consent Statement

Not applicable. This study did not involve human participants, human data, or identifiable personal information; therefore, informed consent was not required.

Data Availability Statement

Data is available upon request.

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Conflicts of Interest

The authors declare no conflicts of interest.

Use of AI and AI-assisted Technologies

The authors declare that AI and AI-assisted technologies were not used.

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