Review Article

The Transport and Deposition of Nanoparticles in Respiratory System by Inhalation

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The inhaled nanoparticles have attracted more and more attention, since they are more easily to enter the deep part of respiratory system. Some nanoparticles were reported to cause pulmonary inflammation. The toxicity of nanoparticles depends not only on its chemical component but also on the quantity and position of the deposition. The deposition of nanoparticles is not uniform and is influenced by airflow transport. The high deposition mainly occurs at the carinal ridges and the inside walls around the carinal ridges. Many factors could affect the transport and deposition of nanoparticles, such as particle size, flow rate, structure of airway, pulmonary function, and age. In this review, we discussed the methods and technique involved in particle transport and deposition studies. The features of particles deposition could be observed in clinic experiments and animal experiments. The mechanism of transport could be studied by numerical simulation. Numerical model and experiment study supplement each other. Some techniques such as medical imaging may support the study of nanoparticles transport and deposition. The knowledge of particles transport and deposition may be helpful both to defend the toxicity of inhaled particles and to direct inhaled drug delivery.

1. Introduction

More and more attention has been paid to air pollution. The high concentration of fine particle matter (PM 2.5) during the 2013 severe haze of north China has caused public worries [1, 2]. The most worries are due to the adverse effect of air pollution on health [3]. It is believed that the most airborne particles were derived from fossil, biomass, and solid fuels combustion [4–6]. The traffic exhausts have been verified as the source of particle matter [7, 8]. The particles emitted by engines have a high proportion of nanoparticles, though most of them are in accumulation mode [9]. Epidemiological studies have confirmed that air pollution makes adverse health effect, especially the pollutant in nanoscale [10, 11]. Thus, nowadays most attention paid to airborne pollutants lies in nanoparticles and ultrafine particles.

Though some studies did not differentiate ultrafine particles from nanoparticles [12], the different definitions have also been reported. The particles in nanoscales (<100 nm) in one dimension could be generally called nanoparticles, while ultrafine particles are limited to 100 nm in all dimensions [13]. For the purposes of this review, we do not differentiate nanoparticles from ultrafine particles: they are both particles in nanoscales.

People have great expectation for nanotechnology and have been trying to apply nanomaterial in many fields [14, 15]. Thus airborne nanoparticles are unavoidable. For the reason of small size, nanoparticles may enter the deep part of human respiratory system with breathing. Pulmonary inflammation has been reported after inhalation exposure to nanoparticles [16, 17], so the toxicity of nanoparticles in air should be considered [18].

Respiratory system is an important pathway for substance to enter human body besides alimentary canal. Air enters the trachea through nasal and oral cavities, passing by the tracheobronchial tree, and arrives at the alveoli, so does some airborne nanoparticles. The transport and deposition of particles have great relations with the complicated airway.

The structures of respiratory system have been described by Weibel as a bifurcating tubes' model with 23-generation bifurcations, and the airways are named as G0–G23 [19, 20]. The airways from G0 to G16 belong to conducting zone, and the airways from G17 to G23 have the function of gas exchange. The upper airway, which begins from the nose and mouth to the trachea (G0), functions not only as the passageway but also as a filter to protect the lower airway; however some small-scale pollutants could still enter the respiratory system and may cause disease [21–23].

Although many researches have confirmed that the toxicity of airborne particles changes along with their compositions [24], the quantity of transport and the position of deposition also have great relations with the toxicity of nanoparticles. This review aims at the toxicity of nanoparticles by inhalation with great emphasis on the transport and deposition of nanoparticles in respiratory system. The research methods for toxicity of airborne nanoparticles were compared. The potential application of a medical imaging technique was also mentioned.

2. The Toxicity of Nanoparticles by Inhalation

Airborne particles especially nanoparticles have been recognized as a potential risk for health. Since airborne nanoparticles enter human body by inhalation, respiratory system has higher risk exposed to nanoparticles [25]. In the view of epidemiology, the increased morbidity and mortality may have relations with particles in air [23, 26]; for example, fine particulate pollution is confirmed to be associated with all-cause, lung cancer and cardiopulmonary mortality [27]. For their small scale, nanoparticles can enter lower airway, reach alveoli, and can even pass the alveolar epithelium to intrapleural space [28]. Pulmonary inflammation could be caused when exposed to some nanoparticles [17].

Nanoparticles harm respiratory system mainly by the injury of epithelium [29], and the most important mechanism is the oxidative stress induced by nanoparticles [30, 31]. The adverse effects happen not only in respiratory system but also in extrapulmonary organs. Once nanoparticles reach pulmonary alveoli, some of them may pass through the alveolar epithelium and capillary endothelial cell and then enter the cardiovascular system and other internal organs [32]. In the long term exposure experiment using sensitive mouse model, inhaled nickel hydroxide could increase mitochondrial DNA damage in the aorta and exacerbate the progression of atherosclerosis as well as the inflammation in lung [30]. The pathological changes in liver have also been reported when inhalation exposed to ferric oxide and zinc oxide nanoparticles [33].

The toxicity of airborne nanoparticles depends on the chemical component of the nanomaterial. To confirm the toxicity of individual nanoparticles, the effect on health of nanoparticles has been studied, respectively. Some nanoparticles may cause pulmonary inflammation, while some nanoparticles may not. A great deal of metallic oxide and hydroxide may cause pulmonary inflammation. Nanoparticles of zinc oxide [34, 35], aluminum oxide [36], copper oxide [37, 38], cobalt oxide [37], iron oxide [39], cadmium oxide [40], and nickel hydroxide [30, 41] have been reported to induce pulmonary inflammation and adverse effects, while no significant inflammation nor adverse effects have been observed when exposed to some nanomaterials, such as carbon nanoparticles [41], graphite nano platelets [42], carbon black [42], and silica [43].

The toxicity of nanoparticles depends not only on the chemical component, but also on dose, size, and other factors [13, 17]. For the nanoparticles of the same component, size and concentration are also crucial [44–46]. More obvious infection signs have been found in animal experiment after instillation of smaller size polystyrene particles [45]. The toxicity of some nanoparticles may also depend on concentration. Inflammatory processes appeared when the exposure concentration reached 0.5 mg/m^3 for multiwall carbon nanotubes and 10 mg/m^3 for graphene [42]. Significant inflammation could be observed when titanium dioxide was inhaled in high dose, compared with no significant pulmonary inflammation when it was inhaled in low and medium dose [47].

The toxicity of particles also depends on the position where the particles arrive and deposit [48]. Respiratory system has complicated bifurcate tree-structure airways which can be divided into conduction zone and respiratory zone. In conduction airway the particle matters may stick to the mucus and be removed with the help of cilia, as well as the phagocytosis of macrophage [49]. In alveoli, the important region for gas exchange, there is only macrophage protecting the body from infection [50]. When particles accumulate in alveoli, the pulmonary inflammation will be induced [17]. Thus the understanding of how nanoparticles transport and deposit is as important as the cytotoxic study.

3. The Means to Study Transport and Deposition of Nanoparticles

As the toxicity of nanoparticles has attracted great attention, the study of nanoparticles deposition is developing step by step. Many different methods have been used in particles deposition study, as shown in Figure 1. The study of particles transport and deposition could be classified as clinical or animal experiment studies and computer simulation studies. Each kind of study method is irreplaceable. They supplement each other. At first the relations between inhaled particle pollution and health were detected by epidemiological studies. At the same time clinical or animal experiment studies were conducted to understand the particles' deposition in respiratory system. Then mathematical models, including CFD model, were established to find more details of particles' transport and deposition.

The experiment studies include in vivo experiments and in vitro experiments. The respiratory tract deposition of particles could be determined from in vivo experiments during spontaneous breathing of volunteers, patients, and experimental animals [51–53]. For the reason of ethics, there are many limitations of in vivo experiments in volunteers and patients. For volunteers and patients, the total deposition fractions were derived by comparing the difference between
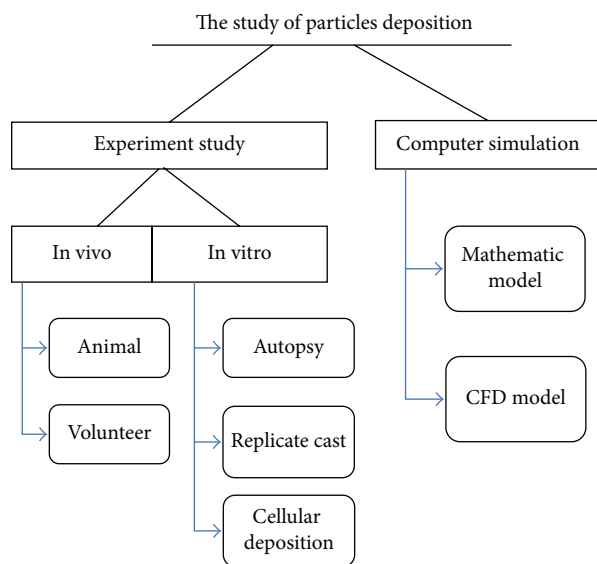
FIGURE 1: The classification of the method to study particles deposition.

inhaled and exhaled particle concentrations. In animal experiments, the accumulated particles were recovered and assessed from the excised tissue after sacrifice [54]. The lung tissue could be excised to proceed with pathological examination [55]. The response of the physiological system, such as the inflammation caused by inhaled particles [56], could be also observed during in vivo experiments. For patients and volunteers, induced sputum after inhalation could be obtained to analyze inflammation and immune function [52]. The in vivo experiment is good to observe the actual physiological response, but it is not enough to investigate the mechanism of transport, deposition, and toxicity of nanoparticles.

In the study of autopsy, the retained particles in human lung parenchyma could be examined [57], while, to understand how these particles were retained, some designed in vitro experiments proceeded. In the end of last century, many particle deposition experiments had been conducted with replicate human airway cast [15, 58, 59]. Gurman et al. and Cohen et al. used a replicate cast of human upper tracheobronchial tree to examine the deposition of particles [60, 61]. Some small airways were hard to build cast, so most of the casts were trimmed to airways with diameter >3 mm. In the study of Cohen et al., the replicate airway cast included 10-generation airway and retained 141 airways [58]. Most of the casts were made of silicone rubber [62] and just used to simulate the transport phenomenon of particles in tube; the deposition in cell was studied by cell exposure experiment [63]. The cell exposure experiment could be used to study the mechanism the toxicity of nanoparticles without cross-species correlation and ethical concerns, while the results of in vitro cell exposure experiment were different from those of in vivo experiment [64] because the cell culture system could not represent the multicellular organism.

To describe the transport and deposition of nanoparticles quantitatively, some mathematical models have been established based on the results of experiments [65]. Martin and Finlay used a simple algebraic formulation to predict the total respiratory tract deposition fraction with an empirical fit to experiment data [66]. A two-compartment model has been established to describe the deposition and clearance of particles in surfactant layer of the alveolar surface and in the cell plasma of alveolar macrophages [67]. A semiempirical model has been used to study the particle deposition difference between a single breath and multiple breathing cycles [68]. This kind of mathematic model explained the result of experiment with lumped parameters, instead of providing detailed transport and deposition of local region.

It is difficult to observe and to accurately measure the local deposition of ultrafine particles in real-time experiment. Computational fluid dynamics (CFD) simulation could provide the detailed flow mechanics in airway and predict the deposition of nanoparticles [69]. In CFD studies, the structure of human airway is the basis for analyzing particle transport and deposition. The geometric model of airway was divided into tiny meshes; thus the deposition feature could be compared in very small local regions. The number of meshes and the time of simulation increase with the complexity of airway. Thus most of the CFD simulation just focused on some part of the airway. For example, Zhang and Kleinstreuer studied ultrafine particles deposition and heat transport with an oral airway model and G0–G3 airway model [70], and they studied inertial and gravitational deposition of microparticles in medium-size bronchial generations G6–G9 [71]. They also attempted to study the deposition in the entire tracheobronchial airway. Five levels of triple-bifurcation unit constituted a 16-generation model [72]. The simulation study was conducted for each triple-bifurcation unit. The respiratory zone of airway was not considered in existing CFD deposition studies because of the complexity of structure. Although the CFD technique has been utilized to study in many fields including the transport of particles in airway, the reliability of the simulation should be validated by data from experimental studies.

4. Factors Influence the Transport and Deposition of Particles in Respiratory System

The transport of particles with air flow in curved tubes of respiratory system can be described by fluid mechanics. In the study of gas-solid-two-phase flow, Stokes number is used to describe the behavior of particles in the flow, and Reynolds number is used to distinguish flow patterns. For low inspiratory flow rate, the transport of particles in airways can be described as laminar flow with secondary flow, while turbulence appears with the increase of flow rate [73]. Low Reynolds number K-ω model for turbulence can be used to study the transport and deposition of nanoparticles [74, 75]. Though the flow rate is oscillatory in spontaneous breathing, the flow fields seemed similar to those in steady state inhalation in case of the equivalent Reynolds number [76]. In most cases, the deposition fraction increases with the increase of Stokes number [77]. The deposition could also be influenced

by many factors, such as size of the particles, inhalation waveform, and also the structure of respiratory airway [12, 73, 78].

For the complicated airway structure, the deposition of particles is not uniform in the total respiratory system. Some parameters were introduced to describe the total and regional deposition. The deposition fraction (DF) is the mostly used not only for deposition in total respiratory system, but also for that in regional part, which is defined as the ratio of number of particles depositing to the number of particles entering the system. The deposition efficiency (DE) is derived as the ratio of particles depositing within a region to the particles entering that region. The deposition enhancement factor (DEF) is defined as the ratio of the number of particles depositing per unit area in local region to the average number of particles depositing per unit area in the whole bifurcation [79], which could indicate the deposition "hot spots" [12]. In the studies of Gurman et al., the replicate casts of human upper tracheobronchial model were used to examine the deposition of microparticles in 0–5 airway generations [60]. The DE of microparticles in each airway generation was different, especially between trachea and bronchi. The position-dependent deposition fraction feature also appears for nanoparticles. In the human tracheobronchial cast deposition experiments, Cohen showed the different DE of nanoparticles from airway generation 0 to generation 7 [58]. The DE in trachea (generation 0) was greater than that in main bronchi (generation 1), while the DF increased from the second generation airway to the sixth generation airway. In numerical study, the difference of deposition was also observed in great detail. The deposition fraction of different parts has been studied such as nasal cavity, nasopharynx, larynx, and trachea [80]. The deposition fraction in head airway is much higher than that in larynx and trachea. The local region with high DEF, meaning the hot spot of deposition, mainly occurs at the carinal ridges and the inside walls around the carinal ridges [12].

Size of particles plays an important role in particles transport and deposition in respiratory system. The transport of microparticles mainly depends on inertial impaction and sedimentation [71], while that of nanoparticles mostly relies on diffusion [74]. The particles in small scale are easier to enter the lung. From the analyses of particle content of autopsy lungs, it was found that the sizes of the particles and aggregates in autopsy lung were obviously smaller than the average sizes in air, which were mostly in nanoscale [25]. The places where particles deposit have great relation with particle size. For microparticles, the deposition in head airway is much greater than that in tracheobronchial and alveolar region. Only when the diameter of particle is less than 10 μm, the deposition in alveoli became obvious, and the ratio of the deposition in alveoli to that in total respiratory system increases remarkably for particles with diameter from 10 μm to 0.5 μm [81]. For nanoparticles, the total deposition and head airway deposition will increase with the decrease of nanoparticles diameter (from 100 nm to 1 nm) [82, 83]. In alveolar region and tracheobronchial region, the deposition fractions of nanoparticles increase firstly and then decrease along with the decrease of nanoparticle's diameter, while the deposition variations in these two regions are not synchronous [84].

The influence of flow rate on particles deposition has been studied by experiments and numerical simulation. In deposition experiments for microparticles and nanoparticles, it was found that the DE in high flow rate was less than that in low flow rate [58, 60]. The same results have been received from computer simulation that the flow rate may influence the deposition of particles [85]. While in some other measurement experiments, the influence of flow rate is not obvious [83], which may be because of the differences in the applied methodologies and the difference of airway model [84]. Besides the flow rate, the influence of inhale waveform has also been studied. The flow rate, cyclicity, and velocity inlet profile influence particle deposition to a certain extent [77, 78], while these influences seemed minor compared with the influence of particle size [12]. Some reports about flow influences were not coincident, which may be because of the difference of the airway models. It has been reported for microparticles, in bronchi, that the DE is greater under cyclic flow than under constant flow, but the DE in the entire tracheobronchial tree showed no observed difference under these two different means of flow [60].

The transport and deposition of nanoparticles in respiratory system also vary with age, lung function [51, 86, 87]. In volunteer respiratory tract deposition experiments, it was found that the deposition probability of nanoparticles had relations with the lung function and severity of the disease [51, 88]. In simulation study, there was a higher particle deposition rate for child than that for adults [75, 86]. The deposition variation is due to the difference of airway geometry and breath parameters. The deposition during exercise is obviously higher than that in rest, because of the different breath pattern [89]. The geometry model is also an important factor to study particles deposition. When considering the laryngeal model, the DF of microparticles in tracheobronchial airway increased, while that of nanoparticles in tracheobronchial decreased [90].

5. Other Techniques Involved in Particle Transport and Deposition Study

Some other techniques were also involved in the study of particles transport and deposition, such as medical imaging. Medical images can not only provide detailed anatomy structure of airway but also be used to observe the deposition in vivo. In some early studies, the airway casts were made from a cadaver [91]. With the development of medical imaging, the geometrical morphology of airway can be picked up from medical images. CT, MRI, and some other imaging techniques have been used in particles' transport and deposition study. Grgic et al. built a realistic extrathoracic model with simple geometric shape based on CT scan and MRI scan [92]. Then many realistic airway geometric models were constructed by CT scan and MRI scan [75, 80, 93], which make it possible to realize individual airway deposition CFD analysis. Together with the development of 3D printing technique [94], detailed individual airway solid model for in vitro experiment will be achievable.

Some molecular imaging techniques, which have been used to detect nanomedicine distribution, can also be used

in the deposition study of nanoparticles in respiratory system [95]. Fluorescent imaging has been used to detect the distribution of aerosols in each lung lobe [96]. The γ-camera has been used to scan bronchial airway after radiolabeled particles were inhaled [52]. SPECT and PET have been used to measure the deposition and postdeposition kinetics of some aerosol in the lung [97, 98]. Although the developed imaging technique such as PET can provide three-dimension kinetics of the tracers' distribution, up to now the poor spatial resolution is still the limitation to observing the transport process in detail.

Besides the knowledge on defense against the toxicity of nanoparticles, the transport and deposition of nanoparticles also have another potential application. Medicine in nanoscale could be inhaled through the tracheobronchial airways down into the alveolar region [32, 99]. The transport and deposition study of nanoparticles may also provide useful information for aerosol drug delivering system. With the assistance of medical imaging, the personalized risk assessment and individual drug delivery scheme could be achieved in future.

6. Conclusions

More and more nanoproducts appear together with the concern about the toxicity of nanoparticles by inhalation. Not only in occupational conditions but also in resident conditions, airborne nanoparticles have been detected, which bring the risk of toxicity by inhalation. Though strict exposure limits have been established to protect human body from the toxicity of airborne nanoparticles [100], knowledge on the transport and deposition of nanoparticles is also significant.

In this review, the methods for the particles deposition studies have been classified and listed. The advantages and disadvantages of each method have been mentioned. The nonuniform deposition feature of nanoparticles has been described, and the effect of factors of their transport and deposition has been discussed. The flow rate, respiratory pattern, and even individual airway structure may influence the particles deposition. The combination of medical imaging and other techniques may promote the study of the particle deposition.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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