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# Environmental and Human Health Risks of Aerosolized Silver Nanoparticles

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## ABSTRACT

Silver nanoparticles (AgNPs) are gaining attention from the academic and regulatory communities, not only because of their antimicrobial effects and subsequent product applications, but also because of their potential health and environmental risks. Whereas AgNPs in the aqueous phase are under intensive study, those in the atmosphere have been largely overlooked, although it is well established that inhalation of nanoparticles is associated with adverse health effects. This review summarizes the present state of knowledge concerning airborne AgNPs to shed light on the possible environmental exposure scenarios that may accompany the production and popularization of silver nanotechnology consumer products. The current understanding of the toxicity of AgNPs points toward a potential threat via the inhalation exposure route. Nanoparticle size, chemical composition, crystal structure, surface area, and the rate of silver ion release are expected to be important variables in determining toxicity. Possible routes of aerosolization of AgNPs from the production, use, and disposal of existing consumer products are presented. It is estimated that approximately 14% of silver nanotechnology products that have been inventoried could potentially release silver particles into the air during use, whether through spraying, dry powder dispersion, or other methods. In laboratory and industrial settings, six methods of aerosolization have been used to produce airborne AgNPs: spray atomization, liquid-flame spray, thermal evaporation-condensation, chemical vaporization, dry powder dispersion, and manual handling. Fundamental uncertainties remain about the fate of AgNPs in the environment, their short- and long-term health effects, and the specific physical and chemical properties of airborne particles that are responsible for health effects. Thus, to better understand the risks associated with silver nanotechnology, it is vital to understand the conditions under which AgNPs could become airborne.

## IMPLICATIONS

The increasing popularization of silver nanotechnology will surely lead to the release of AgNPs into the air. Humans and the environment will be exposed to the particles, and thus the public and policy-makers must be equipped with information to assess the potential risk associated with such exposures. This paper will help guide policy-makers toward defining airborne AgNP safety guidelines for industrial, residential, and outdoor environments and researchers toward identifying the most pressing questions for future study.

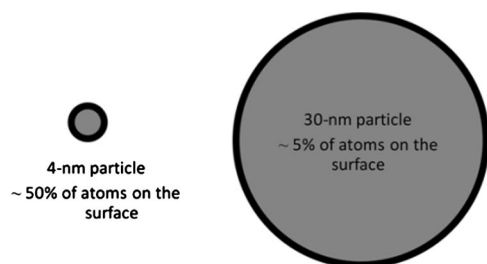
## INTRODUCTION

Airborne nanoscale particles pose a threat to human health because of their abilities to deposit in all regions of the respiratory tract, be taken up by cells, and translocate to sensitive organs via the blood or lymph.<sup>1</sup> Particles with at least one dimension smaller than 100 nm are typically described as “ultrafine” when occurring naturally or incidentally (e.g., secondary aerosol that condenses from gases or soot that forms during combustion) and as “nanoparticles” when purposefully engineered. Because of their antibacterial properties, silver nanoparticles (AgNPs) have become one of the most popular types of nanomaterials today. In terms of the number of consumer products and the volume of annual research investment, only carbonaceous nanomaterials exceed silver.<sup>2</sup> Like all nanomaterials, AgNPs may present an inhalation toxicity hazard should they become airborne,<sup>3,4</sup> a threat that has received inadequate attention and that is the focus of this review.

An important feature of nanoparticles is that, on a mass basis, more atoms are available at the particle’s surface to interact with its surroundings. At this scale, unique physicochemical characteristics appear, and reactivity is largely increased in comparison to the nanoparticles’ bulk counterparts.<sup>4–7</sup> With silver, antiseptic efficacy increases as particle size decreases because of the higher surface area per unit volume and subsequently enhanced surface reactivity.<sup>4,8–10</sup> As shown in Figure 1, a 4-nm particle has 50% of its atoms on the surface, whereas a 30-nm particle has only 5% of its atoms on the surface.<sup>11,12</sup> This order-of-magnitude difference exemplifies why surface forces are of critical importance in nanoparticles. These novel properties present opportunities for introducing and improving many products.

Bulk silver has historically been used in close contact to humans, in cutlery, jewelry, and currency. Ancient civilizations knew about silver’s antimicrobial potential,<sup>13</sup> and colloidal silver has been used for centuries to heal wounds and preserve materials with no obvious toxic effects to humans. Silver compounds were heavily used as antiseptics in World War I, before the development of modern-day antibiotics.<sup>14</sup> Soluble silver compounds (e.g., silver salts) have been used for treating mental illness, epilepsy, nicotine addiction, gastroenteritis, and infectious diseases.<sup>13,15</sup>

Despite the widespread and seemingly safe use of bulk silver, elemental silver is classified as a persistent and toxic pollutant to humans and the environment.<sup>4,16</sup> This



**Figure 1.** Smaller particles have a larger fraction of their atoms on the surface. The lines around the 4- and 30-nm particles represent atoms at the surface and have the same thickness.

dichotomy is the main source of controversy driving studies on the environmental implications of AgNPs. The toxicity of silver is much lower to human cells than to bacteria,<sup>17</sup> and the mechanism of action may be more closely associated with silver ions ( $\text{Ag}^+$ ), which can be released from bulk silver or more efficiently from AgNPs. However, the specific antiseptic mechanisms and toxicity of AgNPs to humans and the environment still have not been deduced.<sup>3,4,8,18,19</sup> Soto et al.<sup>20</sup> suggested that some nanomaterials (notably AgNPs) that are considered non-toxic, and even medicinal, for ingestion or in contact with the skin may pose a threat if inhaled.

According to the Project on Emerging Nanotechnologies' inventory of nanotechnology-related risk studies,<sup>2</sup> the lungs are the most researched area of the body, comprising approximately 70% of research projects. Recent reviews of AgNP applications and toxicity<sup>1,7,13,14,21–25</sup> address the specific effects associated with laboratory-generated inhalation exposures but not the potential for such exposures to occur in real-world situations. Despite the emphasis on the respiratory system in studies of AgNP toxicity, most research on the fate and transport of engineered nanoparticles has focused on aqueous, rather than gaseous (i.e., atmospheric) systems.<sup>4</sup>

There exists a gap in the body of knowledge between inhalation toxicology studies involving AgNPs and the mass consumption of silver nanotechnology; namely, in exposure characterization for airborne AgNPs. The purpose of this study is to shed light on the possible exposure scenarios for airborne AgNPs that may accompany the production and popularization of silver nanotechnology-related consumer products. Specifically, this paper reviews the literature with three objectives: (1) to describe

the possible routes of aerosolization of AgNPs from the production, use, and disposal of existing consumer products; (2) to catalog methods of AgNP aerosolization and characterization for the purpose of guiding future experiments; and (3) to gather published information on the potential toxicity of airborne AgNPs to people and the environment. At every turn, gaps in knowledge are identified where further study is needed.

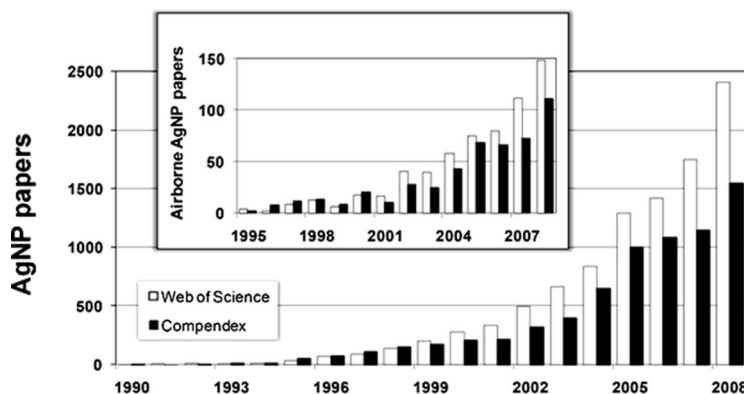
Silver nanotechnology-related papers have grown from less than a dozen per year in the early 1990s to more than 1500 in 2008 (Figure 2). Studies involving airborne AgNPs, rather than aqueous-phase ones, occupy a small niche within publications on silver nanomaterials; they comprise less than 10% of the total. The number of papers published per year on airborne AgNPs has increased from none in the early 1990s to more than 100 in 2008.

### PROPERTIES AND APPLICATIONS OF AgNPs

AgNPs and silver-based compounds are known for their high thermal stability, low solubility, and low volatility.<sup>8,23</sup> Elemental silver has the highest thermal and electrical conductivity of all metals.<sup>13</sup> There are several oxidation states for silver (i.e.,  $\text{Ag}^0$ ,  $\text{Ag}^+$ ,  $\text{Ag}^{2+}$ ,  $\text{Ag}^{3+}$ ), although the latter two are less common.<sup>15,26</sup>  $\text{Ag}^+$  is a very reactive cation and rapidly binds with available negatively charged ligands to reach a stable state.<sup>4,5</sup>

Because most naturally occurring colloids have negatively charged surfaces,<sup>27</sup> any silver aerosol originating from natural waters is likely to be charged or to be associated with anions, typically fluoride ( $\text{F}^-$ ), chloride ( $\text{Cl}^-$ ), sulfate ( $\text{SO}_4^{2-}$ ), hydroxide ( $\text{OH}^-$ ), or carbonate ( $\text{CO}_3^{2-}$ ). Organic matter may also act as a ligand. In fresh water, silver is more likely to be associated with sulfide,  $\text{SO}_4^{2-}$ , and bicarbonate. Silver may also form a sulfhydryl ( $\text{AgSH}$  or  $\text{HS-Ag-S-Ag-HS}$ ).<sup>26</sup> Wijnhoven et al.<sup>15</sup> questioned whether AgNPs can be clearly discerned from bulk silver because there are water-soluble silver compounds, such as silver salts (e.g., silver nitrate), that may release silver ions just as effectively as AgNPs and cause similar toxicological effects. There are also colloidal dispersions with broad size distributions, in which case all silver is not necessarily nanoscale.

An atmospheric chemist, Grassian,<sup>11</sup> has described nanoparticle properties in terms of seven variables: size,



**Figure 2.** Number of papers published on AgNPs in general and specifically airborne AgNPs (inset) in Compendex and Web of Science from 1990 to 2008.

shape, concentration, core composition, surface composition, aggregation, and nanostructure. In the atmosphere, the persistence of particles is mainly dependent on size.<sup>28,29</sup> Those larger than 10  $\mu\text{m}$  are removed by gravitational settling within minutes, whereas those smaller than 1  $\mu\text{m}$  (1000 nm) may remain suspended for days. Airborne silver is most likely to be in the elemental form, if nanoparticle powders are dispersed, or as  $\text{Ag}^+$  in an inorganic salt. Additionally, some AgNPs are coated with polymers and other compounds for stabilization of the particles in water and/or enhanced functionality. Once released, AgNPs should not be considered inert. McMahon et al.<sup>5</sup> demonstrated that AgNPs in contact with ambient air tarnish rapidly through chemisorption of sulfur to particles. The physical and chemical properties of airborne AgNPs are essentially unknown, and characterization is needed to assess the inhalation risk associated with use of nanosilver consumer products.

AgNPs are increasingly being used in emerging products. Silver nanotechnology appears in coatings and is impregnated in materials such as paints, soaps and laundry detergents, refrigerators, laundry machines, cooking utensils, medical instruments (dressings, catheters, pacemakers) and drug delivery devices, water purifiers, clothing, antibacterial sprays, personal care products (toothpaste, shampoo, cosmetics), electronics, air filters, and humidifiers.<sup>3,4,8,17,22,23,30–32</sup> Ji et al.<sup>10</sup> have developed an airborne AgNP generator for disinfection of indoor air. Considering these uses, high concentrations of airborne AgNPs could potentially be found indoors (in industrial and household environments) and outdoors (in the vicinity of smelters, nanotechnology industries, incinerators, wastewater treatment plants, etc.).<sup>4,8,33</sup>

## AgNP AEROSOLIZATION

### Production, Use, and Disposal of Consumer Products

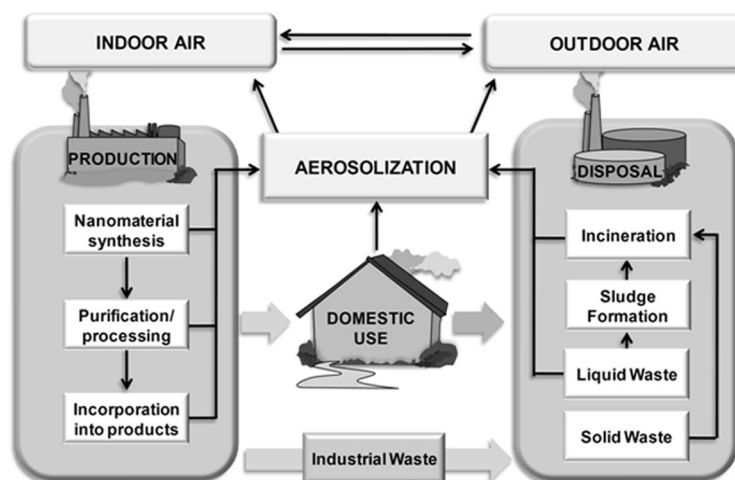
As consumer products utilizing silver nanotechnology become increasingly popular,<sup>2</sup> environmental releases of AgNPs are expected to escalate. There are multiple potential aerosolization scenarios for AgNPs that can be divided into the same phases that comprise the life cycle of any consumer product: production, use, and disposal (Figure 3).

Studies are needed to characterize AgNP emissions across the entire life cycle of nanosilver products; results will facilitate exposure assessments to airborne AgNPs.

**Nanoparticle Production.** To understand how AgNPs could be aerosolized as a result of manufacturing processes, it is imperative to know how these materials are handled through the industrial line. Specific techniques used to produce AgNPs or to incorporate them into consumer products, as well as the applied air pollution control equipment, are difficult to ascertain because industrial methods are usually considered privileged information. Most AgNPs are produced using bottom-up methods, in which nanoparticles are synthesized from smaller units, mainly by promoting nucleation from liquid, vapor, or solid precursors.<sup>6</sup>

Aerosolization of nanoscale particles has been detected during production of carbonaceous nanoparticles,<sup>34–36</sup> so the potential for aerosolization may also exist for AgNPs. Some methods used for AgNP synthesis, especially through bottom-up approaches, are carried out in aqueous media,<sup>26</sup> but even then there may be an opportunity for aerosolization if the particles are dried to form a powder. In addition, some of the aerosolization methods discussed in the following section of this paper (i.e., spark discharge) could be scaled up to produce large amounts of high-purity AgNPs in powdered form.<sup>37</sup> Fugitive and accidental releases are a potential source of AgNP emissions to the atmosphere. Production waste could also lead to airborne particles, through direct emission of aerosol streams, incineration of solid waste, or aerosolization of liquid suspensions. AgNPs may also become airborne as byproducts of other industrial methods. Even industries that are not related to nanotechnology (e.g., photography before the digital age) might be responsible for emitting AgNPs.<sup>15</sup>

Production of AgNPs can result in two different exposure scenarios: occupational exposure of workers to the particles generated inside of the industrial environment and ambient exposure of the public to AgNPs emitted to the atmosphere by industries. In occupational exposure,



**Figure 3.** Possible aerosolization routes for AgNPs during the life cycle of consumer products. For simplification, the diagram shows only routes that can lead to aerosolization.

the main issue is designing capture, ventilation, and personal protective equipment that is effective for nanoparticles. In environmental exposures, the main concern is the use of particulate control equipment with high collection efficiencies for nanoparticles and minimization of the volume of AgNPs aerosolized in the first place.

**Nanoproduct Use.** The domestic use of consumer products that contain AgNPs is a potential source of silver-containing aerosols in the household. Research is needed to determine whether the extended use of these products would pose a long-term threat to consumers, but these products must first be identified and characterized.

The Project on Emerging Nanotechnologies (PEN) has compiled an inventory of nanotechnology-based consumer products that were on the market as of 2009, and more than 800 different items are listed, from mouth sprays to computer keyboards.<sup>38</sup> The same organization has also published a database of more than 200 silver nanotechnology products that were commercially available in 2007<sup>39</sup>; many more are likely to be available now. Of the 240 silver nanotechnology products listed from 65 manufacturers at the time of writing, 214 are in fact commercial products and the remaining 26 are precursor products (e.g., master batches, colloids, and powders). AgNPs or other nanostructures have been used in these products to promote antimicrobial protection.

These products, among others identified in the marketplace through the Internet and, in some instances, e-mail contact with sellers and manufacturers to obtain clarification on how nanoparticles are used in the products, are listed in Table 1. Half of the products fall into the categories of fabric applications (29%) and cosmetics or medical dressings (21%). In addition to listing the form of AgNPs in the products, each product category has been rated on its potential to produce airborne silver-containing particles. It is estimated that approximately 14% of the products could potentially release silver particles into air during use, whether through spraying (e.g., liquid cleaning products or personal care sprays), dry powder dispersion (e.g., vacuum cleaners and hair dryers), or other unknown methods. Other products containing embedded or coated AgNPs may also act as sources through erosion and suspension of the material, but these are

expected to be much less important for inhalation exposures compared with products that intentionally release particles.

A major challenge in this work is understanding and classifying exactly how nanoparticles might be released or emitted from these consumer products because most manufacturers are reluctant to describe explicitly how nanoparticles, coatings, or other nanostructures are incorporated into products. Some marketing material simply includes the word “nano,” or the expression “silver nano,” alongside the product’s name or description, without a more detailed explanation other than a claim that silver nanotechnology lends antibacterial or anti-odor properties.

**Nanomaterial Disposal.** A review by Bystrzejewska-Piotrowska et al.<sup>21</sup> urged that policy-makers define waste management practices for nanotechnology-related consumer products before disposal of the first nanoproducts begins. As shown in Figure 3, the disposal step applies to industrial and consumer waste. The two major opportunities for aerosolization of AgNPs during disposal are incineration and treatment of liquid waste. At this point in the life cycle, AgNPs have been mixed with other components of the industrial or municipal waste stream. In liquid waste, some silver may remain in a pure form, but some will be present as dissolved ions and complexed with ligands. Hence, aerosolized particles may consist of pure AgNPs or inorganic silver salts, (e.g., silver chloride and silver iodide) mixed with other components of the waste.

Consumer products and industrial waste that contain AgNPs may become a source of airborne AgNPs through municipal or industrial waste incineration. Incineration may lead to the vaporization of metals, which subsequently condense and form airborne nanoparticles upon cooling. One study reproduced incineration processes for simulated ash containing metals and detected a high concentration of nanoparticles under 10 nm.<sup>40</sup> Particulate emissions from incinerators are typically estimated using data from the U.S. Environmental Protection Agency (EPA)’s AP-42 compilation of emission factors, but the document does not yet address nanoparticles, let alone AgNPs.

**Table 1.** Summary of consumer products claiming to use silver nanotechnology.<sup>21,38,39</sup>

| Product                                                                | Form of AgNP             | Potential for Aerosolization |
|------------------------------------------------------------------------|--------------------------|------------------------------|
| Disinfectant sprays, deodorants, oral sprays                           | Liquid                   | High                         |
| Hair dryers                                                            | Solid coating            | High                         |
| Air filters                                                            | Embedded in solid        | Medium                       |
| Vacuum cleaners                                                        | Solid coating            | Medium                       |
| Humidifier                                                             | Colloid                  | High                         |
| Fabrics (shirts, pants, hats, socks)                                   | Incorporated into fibers | Medium                       |
| Medical instruments, milk bottles, teether, toothbrush                 | Embedded in solid        | None                         |
| Hair straightening or curling irons                                    | Solid coating            | None                         |
| Cosmetics/dressings                                                    | Powder or cream          | Low                          |
| Hardware (computer, mobile phone, handles, etc)                        | Embedded in solid        | None                         |
| Mineral supplements                                                    | Liquid                   | None                         |
| Food containers, cooking utensils                                      | Embedded in solid        | None                         |
| Refrigerators, washing machines, pet products, algacide, laundry soaps | Solid coating            | Low                          |



AgNPs could become dispersed into the atmosphere in the vicinity of wastewater treatment plants when aeration takes place, promoting droplet suspension. Numerous papers describe the dispersion of bioaerosols around aeration tanks.<sup>41–44</sup> If these microorganisms are subject to aerosolization and transport in the atmosphere, it is likely that nanoparticles could be as well.

### Laboratory-Scale Aerosolization

AgNPs have been aerosolized in the laboratory using various methods, typically as part of inhalation toxicology studies. Understanding the differences between techniques is important for those wishing to produce the most environmentally relevant types of particles. Of course, characteristics of AgNPs aerosolized during the product life cycle have yet to be determined, so these two efforts— aerosolization for laboratory studies and environmental characterization—are intimately linked. Most of the reviewed studies aimed to provide a nanoparticle-rich aerosol flow for *in vivo* or *in vitro* toxicity studies or to produce high-purity AgNPs in the gas phase at industrial scales.<sup>45</sup> A smaller portion of studies used a known silver aerosol for other research purposes, such as testing a new filtration technique<sup>46</sup> or measuring diffusional losses to tubing.<sup>47</sup>

Table 2 catalogs the six aerosolization methods that appear in the literature. Atomization, also referred to as nebulization or spray, has been used for inhalation toxicity and therapeutic studies.<sup>47–52</sup> This method relies on the forces of an air jet or high voltage (electrospray) to produce a spray from a liquid solution or suspension. The aerosol can subsequently be directed through a diffusion dryer containing desiccant to remove excess humidity and reduce the liquid content of the particles. In these studies, spherical AgNPs of aerodynamic diameters as low as 5 nm were synthesized and characterized. Most size distributions were narrow, with geometric standard deviations ranging between 1.2 and 1.88. There are three different types of nebulizers: jet, ultrasonic, and piezoelectric crystal. The degree of aggregation in the particles produced depends on the nebulization method and particle hydrophobicity.<sup>48</sup> Ultrasonic nebulizers with hydrophilic particles produced less aggregated aerosols than did jet nebulizers with hydrophobic particles.

The size distribution of AgNPs produced by atomization can be further narrowed by subjecting the aerosol to intense heating and cooling in an inert atmosphere (generally nitrogen [N<sub>2</sub>]) to vaporize and recondense silver. This method, known as liquid-flame spray,<sup>53</sup> and another similar method described as flash pyrolysis involve the

exposure of a liquid spray to a high-temperature hydrocarbon (H<sub>2</sub>)/oxygen (O<sub>2</sub>) flame. The liquid solvent evaporates, and the product species can decompose or volatilize and recondense to form aerosols with narrow size distributions and small size (10–50 nm).<sup>54–56</sup> Ku et al.<sup>57</sup> affirmed that the shape and crystal structure of the final product depends on the probability of droplet collision and sintering (heating at temperatures lower than the melting point of metals).

Metal evaporation and condensation in ceramic heaters is a widely used method for producing small (in some cases <10 nm)<sup>10</sup> and relatively monodisperse nanoparticles.<sup>57</sup> A small (dimensions <0.5 cm) block of silver is placed into a furnace at 1100 °C. An inert gas runs through the furnace and carries the metal vapors until the aerosol is cooled, and nanoparticles are formed.<sup>3,10,31,32,57–63</sup> Another method for generating airborne AgNPs is chemical vaporization of solid precursors using arc plasma discharge or spark discharge generators.<sup>37,45,64,65</sup> Only a few studies have produced aerosols from the physical handling of powders, whether manually or mechanically (e.g., using a brush dust generator); these methods often produce aerosols with large agglomerates and broad size distributions.<sup>32,50,66</sup>

In summary, most studies used a relatively pure silver aerosol, carried by a chemically inert gas, such as argon or N<sub>2</sub>. This approach ensures well-controlled experiments and minimizes variation. Nevertheless, AgNP properties such as size, degree of aggregation, shape, and crystal structure can vary depending on the synthesis method, so it is imperative that researchers report all details about the aerosolization method to enable proper interpretation of and comparison between results. Although other papers describe AgNPs that may be engineered in many different shapes (spheres, cubes, rods, etc.),<sup>15</sup> all of the AgNP aerosols that were produced for the studies cited in this work reported spherical morphology.

A fundamental question arises regarding the representativeness of these aerosols to real-life human exposure scenarios. For instance, the work of McMahon et al.<sup>5</sup> showed that AgNPs tend to tarnish quickly because of sulfur chemisorption to the particles' surfaces. A similar process could affect AgNPs that are released into the atmosphere, where sulfur is present in many forms. Because nanoparticle toxicity may be influenced by characteristics such as aggregation, morphology, crystal structure, composition, and coating,<sup>22,67,68</sup> it is critical to understand the characteristics that airborne AgNPs would exhibit under environmentally relevant, and not just laboratory, conditions.

**Table 2.** Aerosolization methods used to synthesize AgNPs.

| Aerosolization Method                                                                                              | References                             |
|--------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Spray atomization of AgNP suspension, colloid, or silver salt solutions                                            | 47, 49–52, 117                         |
| Liquid-flame spray, flash pyrolysis, or corona discharge of super- or ultrasonically atomized silver colloid spray | 53–56                                  |
| Evaporation-condensation (ceramic or other furnace heaters, or using heated silver wires)                          | 3, 10, 31, 32, 46, 57–63, 78, 118, 119 |
| Chemical vaporization using arc plasma, or spark discharge generators                                              | 37, 45, 64, 65, 120                    |
| Dry powder dispersion (e.g., brush dust generator)                                                                 | 50                                     |
| Manual pouring or handling of particles                                                                            | 66                                     |

## SAMPLING AND CHARACTERIZATION OF AIRBORNE NANOPARTICLES

Historically, the most common metric of airborne particles has been the mass concentration ( $\mu\text{g m}^{-3}$ ).<sup>29</sup> Because of the very small mass of individual nanoparticles, their concentrations in the environment are better described in terms of particle surface area ( $\text{m}^2$  of surface area  $\text{m}^{-3}$  of air) or particle counts (number of particles  $\text{cm}^{-3}$ ).<sup>1,9,34,67,69</sup> More recent aerosol studies describe the use of state-of-the-art single-particle analysis techniques for characterizing carbonaceous, metallic, oxide, or organic aerosols.<sup>70</sup>

Existing standard methods for analysis of airborne silver particles will not necessarily be effective for AgNPs. The Occupational Safety and Health Administration (OSHA) recommends a filter-based sampling method for silver using a mixed cellulose ester filter (MCEF) with a pore size of 0.8  $\mu\text{m}$ . Although the pore size is larger than nanoparticles, they deposit to the filter anyway mainly by Brownian diffusion, which can carry them out of streamlines to the filter surface. The recommended analytical methods are atomic absorption spectroscopy (AAS) or inductively coupled argon plasma mass spectroscopy (ICP-MS).<sup>71</sup> Samples are desorbed from filters using water extractions or mineral acid digestions, often involving hydrochloric and nitric acids.<sup>72,73</sup> Drake et al.<sup>74</sup> also suggest filtration using polytetrafluoroethylene (PTFE) filters with a pore size of 2  $\mu\text{m}$  for differentiating metallic silver and soluble silver compounds. Unless airborne concentrations are very high, it will be challenging to collect a sufficient mass of AgNPs in ambient samples to enable use of the recommended analytical techniques.

A second problem with standard filtration methods is that certain artifacts are magnified with nanoscale particles. The main factor that affects deposition of the smallest nanoparticles (<10 nm) is thermal rebound, which occurs when the particles have a thermal velocity higher

than their critical “sticking” velocity.<sup>75</sup> It is a function of aerosol temperature and causes collection efficiency to decrease.<sup>46</sup> However, Heim et al.<sup>76</sup> attempted to differentiate electrostatic and other effects from true thermal rebound effects and did not observe thermal effects on particles as small as 2.5 nm.

Many advanced techniques for the characterization of aerosolized nanoparticles are now available. Table 3 summarizes the analytical methods used in published experimental research on nanoparticles, including AgNPs. Most of the studies used the techniques described in the preceding section to generate synthetic test aerosols consisting of AgNPs<sup>3,5,10,31,32,37,45,49–63,77,78</sup> or other types of nanoparticles.<sup>34,47,48,64,79</sup> Electron microscopy has been used to characterize the size and morphology of nanoparticles. Various spectroscopic and diffraction techniques have been used to describe the crystal structure and chemical composition of nanoparticles. Of the techniques that have been applied to AgNPs, only a subset of those measuring the size distribution (scanning mobility particle sizer [SMPS], aerodynamic particle sizer [APS], optical particle counter [OPC], environmental dust monitor [EDM]) is applied to the aerosol in real time. AgNP surface area has been characterized using the Brunauer, Emmet, and Teller (BET) method<sup>80</sup> and estimated through calculations based on transmission electron microscopy imaging.<sup>57,81</sup> To the authors’ knowledge, characterization techniques for surface charge (e.g., the application of an aerosol electrometer<sup>82</sup>) have been used for other types of aerosol particles but not AgNPs.

Some studies have used these techniques to characterize ambient (indoor or outdoor) nanoparticles,<sup>34,66,82–84</sup> but none of them have attempted to detect AgNPs. Measurements of airborne silver have focused on the total silver concentration in the air samples, usually by collecting

**Table 3.** Analytical methods used for characterizing AgNPs.

| Characteristic                        | Technique                                                                      | Used for AgNP? | References                                                                          |
|---------------------------------------|--------------------------------------------------------------------------------|----------------|-------------------------------------------------------------------------------------|
| Morphology                            | Transmission electron microscopy (TEM)                                         | Yes            | 3, 31, 37, 50, 53–55, 57, 59–61, 64–66, 77, 79, 84, 98, 105, 108, 117, 119, 121,122 |
|                                       | Scanning electron microscopy (SEM)                                             | Yes            | 46, 48, 50, 54,55, 59, 66, 79, 108                                                  |
| Crystal structure                     | X-ray diffraction (XRD)                                                        | Yes            | 53, 59,60, 77, 84, 117, 122                                                         |
|                                       | Selected-area diffraction (SAED) <sup>a</sup>                                  | Yes            | 77, 83, 84, 105                                                                     |
| Composition                           | Aerosol photoemission spectrometry (APE)                                       | Yes            | 45                                                                                  |
|                                       | Energy dispersive X-ray spectroscopy (EDS)                                     | Yes            | 37, 60, 64, 66, 84, 108                                                             |
|                                       | Scanning auger spectroscopy (SAS)                                              | Yes            | 5                                                                                   |
|                                       | ICP-MS                                                                         | Yes            | 51                                                                                  |
| Surface composition and functionality | Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy | No             | 117, 122                                                                            |
|                                       | X-ray photoelectron spectroscopy (XPS)                                         | No             | 117, 122                                                                            |
|                                       | SMPS or similar setups <sup>b</sup>                                            | Yes            | 3, 31,32, 34, 46,47, 49, 51–53, 56–59, 62,63, 66, 78,79, 119                        |
| Aerosol size distribution             | TEM imaging                                                                    | Yes            | 60, 79                                                                              |
|                                       | APS                                                                            | Yes            | 49, 52                                                                              |
|                                       | OPCs                                                                           | No             | 49,50                                                                               |
|                                       | Differential mobility analyzer + EDM                                           | Yes            | 37                                                                                  |
|                                       | BET algorithm (BET N <sub>2</sub> adsorption)                                  | No             | 50, 80, 117, 122                                                                    |
| Surface area                          | Aerosol electrometer (AE)                                                      | No             | 82                                                                                  |

Notes: <sup>a</sup>SAED is commonly incorporated into transmission electron microscopes; <sup>b</sup>Fast mobility particle sizers (FMPS) or setups with DMAs + ultrafine particle counters (UFPs).

particulate matter on filters, extracting them, and analyzing for chemical composition and total silver concentration. Methods used include ICP-atomic emissions spectroscopy (ICP-AES), ICP-MS, and neutron activation analysis.<sup>30,74</sup>

Card et al.<sup>22</sup> warned that several published studies on the inhalation toxicity of nanoparticles do not sufficiently describe particles they used. The authors attribute this deficiency to the lack of a well-defined standard set of nanoparticle characteristics to be described when performing airborne nanoparticle studies. Numerous authors have emphasized the need for a standard set of nanoparticle properties for environmental and human toxicity studies.<sup>22,85–87</sup> On the basis of these papers and for the specific scenario of airborne nanoparticles, the authors recommend that the following nanoparticle characteristics be described in studies involving the aerosolization of AgNPs: size distribution (of aerosol), chemical composition (of core and surface), shape, crystallinity, surface area, surface charge (whether aerosol is neutralized or charged before deposition), and purity of sample.

#### FATE AND TRANSPORT OF AgNPs IN THE ENVIRONMENT

Historically, airborne particulate silver has been found mainly near smelters that process silver-rich ores.<sup>15,30,88</sup> Silver is a frequent byproduct of nickel, lead-zinc, copper, platinum, and gold ore processing in North America and South Africa.<sup>26</sup> Chow et al.<sup>89</sup> identified silver concentrations up to  $0.03 \mu\text{g m}^{-3}$  in fine particulate matter ( $\text{PM}_{2.5}$ ) in Mexico City. Lee et al.<sup>90</sup> detected silver in atmospheric aerosols in Atlanta. Although the exact size of the atmospheric silver was not identified in these studies, if it originated during a combustion process, it was likely to initially fall in the nanoscale size range. Atmospheric processing could then lead to growth of the particles into the accumulation mode, 100–2000 nm. Other studies, some dating as far back as 1965,<sup>91</sup> have detected silver in rainwater resulting from cloud seeding for which silver iodide was used. With such use, there is the possibility for incorporation of silver into atmospheric particulate matter.

Fate of nanoparticles is determined by the physical and chemical properties of the particles and environmental factors. Once nanoparticles are released into the environment, they may follow any one of countless paths through soil, water, and/or air. In the atmosphere, AgNPs may (1) remain suspended as individual particles; (2) agglomerate, aggregate, or coagulate (agreement upon terminology is lacking) among themselves or with other particles; (3) become coated by inorganic or organic compounds that condense on pre-existing particles; (4) dissolve in slightly acidic conditions<sup>4</sup> (into cloud or fog droplets), releasing silver ions; or (5) chemically react with other compounds (e.g., organic matter or atmospheric oxidants).<sup>4,24,50,68,92–95</sup> Finally, they will be removed from the atmosphere back to terrestrial ecosystems by dry or wet deposition. A combination of these phenomena is the most likely scenario, and the order in or extent to which they occur is of great importance in determining the health and environmental risks that AgNPs may pose.

#### TOXICITY OF AIRBORNE AgNPs Ecotoxicity

Although it is possible that airborne AgNPs could exhibit ecotoxic effects, the main route for their ecotoxicity is expected to be the aqueous phase. Because the focus of this paper is on airborne AgNPs, the reader is directed to other reviews on the ecotoxicity of AgNPs and related materials (aggregates and ions) in water systems.<sup>4,15,25,96</sup> AgNPs have been shown to be toxic to bacteria (e.g., *Escherichia coli* and *Staphylococcus aureus*), fungi (e.g., *Aspergillus sp.* and *Penicillium sp.*), and green algae (e.g., *Chlamydomonas reinhardtii*).<sup>93,96,97</sup> Here, mechanisms of ecotoxicity are described that might also be applicable to the inhalation exposure route.

Specific AgNP characteristics have been discovered to cause microbial toxicity. Navarro et al.<sup>97</sup> demonstrated that the environmental toxicity of AgNPs may be related to their shape and size, but more importantly may depend on the Trojan-horse mechanism (described in the following subsection), which facilitates release of silver ions inside cells. A study by Khaydarov et al.<sup>96</sup> showed that smaller AgNPs have a greater antibacterial/antifungal efficacy than do larger ones. Choi and Hu<sup>98</sup> demonstrated that AgNPs were more toxic to nitrifying bacteria than were silver ions or silver chloride colloids. Additionally, neither the ions nor colloids disrupted cell integrity at the tested concentrations. Fabrega et al.<sup>93</sup> and Lok et al.<sup>95</sup> also reported that antibacterial activities could not be explained solely by the presence of ions or the mass concentration of silver. These results support the Trojan-horse hypothesis, although the authors hypothesized that AgNPs can attach to the outside of cell membranes and induce oxidative stress without compromising the membrane.<sup>98</sup>

Silver ion release seems to be an important toxicological mechanism for AgNPs in the environment because toxicity has been observed mainly in the aqueous phase and is proportional to the concentration of free silver ions.<sup>99</sup> When dispersed in aquatic systems, ionic silver is extremely toxic to certain organisms, especially bacteria, phytoplankton, and fish.<sup>4,97</sup> The ion's toxicity is thought to be due to its attraction to thiols ( $\text{HS}^-$ ), which are present in proteins and enzymes.<sup>4,23</sup> Correspondingly, studies show that when sulfide and thiosulfate are present in the water to complex with silver ions, their toxicity to microorganisms declines remarkably<sup>4</sup> because silver is no longer bioavailable. These results suggest that atmospheric processing of airborne AgNPs could alter their toxicity.

#### Human Toxicity

*Existing Guidelines for Airborne Silver.* There are several occupational guidelines and exposure limits in the United States for airborne silver. All are defined on a mass basis.<sup>13,74</sup> OSHA<sup>71</sup> has adopted the threshold limit value on a time-weighted average (TLV-TWA) for a 40-hr/week exposure from the American Conference of Governmental Industrial Hygienists (ACGIH) of  $0.1 \text{ mg m}^{-3}$  for metallic silver and  $0.01 \text{ mg m}^{-3}$  for soluble silver compounds. The National Institute for Occupational Safety and Health (NIOSH) has set a limit for immediately dangerous to life or health (IDLH) concentration of  $10 \text{ mg m}^{-3}$ .<sup>100</sup> Presently, there are no air quality standards for nanoparticles.



The closest is the National Ambient Air Quality Standard for  $PM_{2.5}$  of diameter of  $2.5\ \mu m$  or less. The 24-hr and annual standards of 35 and  $15\ \mu g\ m^{-3}$  are the same order of magnitude as the TLV-TWA for soluble silver. NIOSH<sup>101</sup> and EPA<sup>102</sup> are performing research to advance understanding of critical topics in nanotechnology to fill knowledge gaps and guide regulations in the future, but it is likely to be years before sufficient information is available to establish new standards.

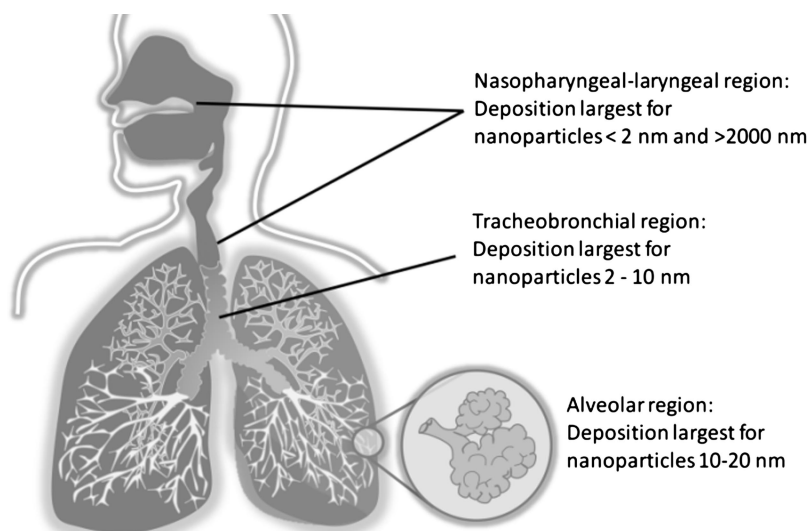
**General Particle Inhalation Toxicity.** Inhaled particles can lead to inflammation in the respiratory and cardiovascular systems, and known health effects include asthma complications, chronic bronchitis, and respiratory tract irritation and infections.<sup>20,92,103</sup> Particle size and surface area are important determinants of inhalation toxicity.<sup>8,22,24</sup> Numerous studies have demonstrated that airborne nanoparticles, regardless of chemical composition, pose a potential hazard to the lungs.<sup>8,9,66,92,104</sup> Nanoscale particles are capable of penetrating further into the respiratory system than are larger, micrometer-scale particles, and they can also permeate through cell membranes of organisms and interact with subcellular structures.<sup>8,22,24</sup>

Nanoparticles' shape, crystal structure, and composition may present additional risk.<sup>1,9,20–22,64,85</sup> For instance, Bang et al.<sup>83</sup> asserted that crystalline particles seem to be more damaging to lung epithelial cells than are amorphous structures. In the studies performed by Duffin et al.,<sup>9</sup> in vitro and in vivo inflammation was not a function of nanoparticle mass, but of surface area. Also, nanoparticles may serve as carriers of pollutants that would otherwise not become airborne and enter human lungs.<sup>4,61,92</sup> Nevertheless, uncertainty and disagreement still exist on whether the main cause for toxicity is related mainly to physical properties (namely size and shape), chemical composition, or a combination of both.<sup>103</sup>

Once inhaled, particles may deposit along the airways, from nasal and oral cavities to alveoli of the lungs, by impaction, sedimentation, interception, Brownian motion, or electrostatics. The efficiency of each mechanism depends strongly on size<sup>29</sup> and on the local geometry and flow conditions within the respiratory system. A

common misperception is that larger particles are deposited exclusively in the upper respiratory system and that all nanoparticles penetrate to the alveolar region. In fact, although Brownian motion is the dominant deposition mechanism for all nanoscale particles, there are subtleties that lead to deposition in different compartments of the respiratory system (Figure 4) depending on the particle's exact size. For instance, particles with aerodynamic diameter of 1 nm deposit with more than 80% efficiency in the nasopharyngeal-laryngeal region and more than 10% efficiency in the tracheobronchial region, leaving very few to reach the alveolar region. The deposition efficiency of larger 10- to 20-nm particles in the nasopharyngeal-laryngeal and tracheobronchial regions is less than 20% (per region); these particles have the highest deposition efficiency (50%) of any size in the alveolar region. The deposition efficiency of particles of 20–100 nm is less than 40% in the alveolar region. Particles in this size range tend not to deposit in significant amounts in the other respiratory regions.<sup>1,15,22,24,29,92</sup> Predicting where airborne AgNPs will deposit in the respiratory system will require accurate sizing of the particles.

**AgNP in Vitro Studies.** In vitro studies have demonstrated that the toxicity of AgNPs can be higher than that of other nanomaterials.<sup>105–107</sup> Soto et al.<sup>105</sup> showed that AgNPs were more cytotoxic than all other nanomaterials tested, including titanium dioxide ( $TiO_2$ ), iron oxide ( $Fe_2O_3$ ), aluminum oxide ( $Al_2O_3$ ), zirconium oxide ( $ZrO_2$ ), silicon nitride ( $Si_3N_4$ ), and carbon nanotubes. Some studies suggested that the mechanism of toxicity of inhaled nanoparticles is increased oxidative stress.<sup>17,20,106,108</sup> It is caused by the formation of intra- or extracellular reactive oxygen species (ROS), such as oxygen ions or radicals, and peroxides at the surface of or within cells. ROS may induce inflammatory processes in the human nose, lung, and cardiovascular system.<sup>9,20,67</sup> Numerous in vitro studies<sup>1,8,20,23,67,69,92,104</sup> on the effects of particles in the respiratory system concentrate on their potential to induce oxidative stress and cell lipid peroxidation (oxidative degradation of the lipids present in cell membranes),



**Figure 4.** Regions of the respiratory system and size (aerodynamic diameter) of particles with the greatest deposition efficiency in each region.

which leads to cell damage and rupture. Nanoparticles may also interfere with metabolic activities inside of the cell.<sup>8,9,69,85,104,109</sup> In vitro studies with AgNPs reported that they could enter cells and damage DNA.<sup>4,17,20,22,103</sup> Wijnhoven et al.<sup>15</sup> hypothesized that “toxic effects of silver substances are proportional to the rate of release of free silver ions from them.”

**AgNP in Vivo Studies.** The results of multiple inhalation studies with AgNPs in animals justify concern about this route of exposure.<sup>3,31,78,110</sup> Tang et al.<sup>111</sup> showed that AgNPs were capable of translocating through rats’ main organs in the form of particles, whereas silver microparticles could not. Rosenman et al.<sup>112</sup> found an association between decreased night vision and exposure to airborne silver nitrate and oxide. Oral administration of AgNPs to rats was related to a decrease in liver function.<sup>113</sup> Rats exposed to a AgNP aerosol showed an increase in neutral mucin (substance found in mucous secretions) production in lung tissues and the presence of foamy macrophages in alveolar tissues.<sup>78</sup> Macrophages are large immune system cells that phagocytize foreign materials and degenerated cells, and their presence suggests that AgNPs deposited in the rat’s alveoli. Wijnhoven et al.<sup>15</sup> suggested that contact of AgNPs with the olfactory nerve during respiration may constitute an exposure route to the brain. Still, there is a lack of conclusive information on the relative toxicity of AgNPs versus nanoparticles of other compositions because there are no standardized methods for in vitro studies that would allow for direct comparison between results.<sup>4,20,103</sup>

Silver has been found to be a potent enzyme inhibitor.<sup>4</sup> In rats, AgNP exposure caused decreased liver function because of oxidative stress, and silver was the most toxic of six different metallic nanoparticles.<sup>107</sup> Studies involving the kidneys and cardiovascular system were inconclusive. Park et al.<sup>104</sup> reported that AgNPs showed a lower cytotoxicity than did zinc or nickel nanoparticles to human alveolar epithelial cells, but the samples consisted of 150-nm AgNPs, which may have been too large for optimum ion release. Two studies found that AgNPs and/or their released ions directly or indirectly resulted in oxidative stress and may have interfered with metabolism inside of the cell.<sup>17,104</sup> The relative impacts of AgNPs versus silver ions remain unclear, and the state in which silver travels through the bloodstream, whether as nanoparticles or complexed silver ions, is also unknown.

### Discussion of AgNP Toxicity

The Trojan-horse effect (Figure 5) has been proposed as the mechanism for inhalation toxicity of AgNPs. Some

semiconductor and oxide nanoparticles are known to affect lung epithelial cells via this mechanism.<sup>8</sup> According to this theory, if a AgNP is able to cross the cell membrane, it may continuously release silver ions once inside. Its toxic effects would be stronger than those of silver ions by themselves because the ions would be largely consumed before breaching the cellular membrane. Inside of the cell, the ions can form ROS and cause lipid peroxidation.

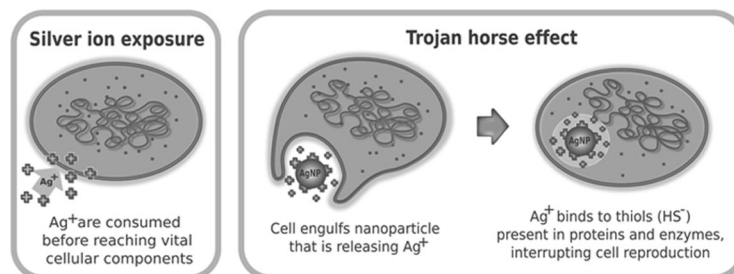
Various authors have affirmed the potential for inhalation exposure to various nanoparticles.<sup>22,61,104</sup> An array of properties (e.g., size, density, crystal structure, surface charge, and composition) may influence their toxicity,<sup>22,64,81,104</sup> and these properties have not yet been characterized thoroughly for airborne nanoparticles. Many fundamental uncertainties remain about the specific physical and chemical properties of airborne particles that cause known health risks.<sup>31,67</sup>

### CONCLUSIONS

AgNPs are gaining attention from the academic community, not only because of their antimicrobial effects and product applications, but also because of adverse health effects and environmental exposure scenarios. The fate of AgNPs in the environment and their short- and long-term health effects cannot yet be described in detail.<sup>31,114</sup> There are currently no official government registries or regulations for products containing nanomaterials as exist for the same materials in bulk form.<sup>4,7,115</sup> Thus, understanding the fate of these materials in the environment by studying their physical properties and chemical stability is important for predicting environmental exposure to AgNPs.

The current state of knowledge on the toxicity of AgNPs points toward a potential threat via the inhalation exposure route. Nanoparticle size, chemical composition, crystal structure, and surface area are expected to be important variables in determining toxicity, and the rate of silver ion release is also expected to be a major factor. Still, there are fundamental uncertainties about the specific physical and chemical properties of airborne particles that are responsible for health effects. Thus, to better understand the risks associated with airborne AgNPs, it is vital to carefully describe the conditions under which they could become airborne and available for inhalation.

The life cycle of silver nanoproducts contains multiple opportunities for AgNP aerosolization throughout production, use, and disposal of these products. The domestic use of consumer products that contain AgNPs is a potential source of silver-containing airborne particles in



**Figure 5.** Silver ion exposure vs. Trojan-horse effect.

the household. Nanoproducts such as sprays, hair dryers, and misting humidifiers are especially worrisome. Toxicity studies using laboratory-generated particles are important for identifying possible hazards, but exposure characterization including thorough physical and chemical descriptions of the particles is needed to help determine whether or not AgNPs pose a real risk.

Regulatory agencies will need to move rapidly toward new metrics to keep pace with the changing paradigms introduced by nanotechnology. The authors agree with Bystrzejska-Piotrowska et al.,<sup>21</sup> who stated that Amara's law may apply to the effects of nanotechnology. The law is, "We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run."<sup>116</sup> The short-term benefits of AgNPs and their antimicrobial properties might be overestimated, but their long-term effects might be underestimated, including those initiated by airborne exposure to AgNPs.

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