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Qi, Yu; Chen, Yucai; Xia, Tian; Lynch, Iseult; Liu, Sijin

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Extra-Pulmonary Translocation of Exogenous Ambient Nanoparticles in the Human Body

Yu Qi, Yucai Chen, Tian Xia,* Iseult Lynch,* and Sijin Liu*

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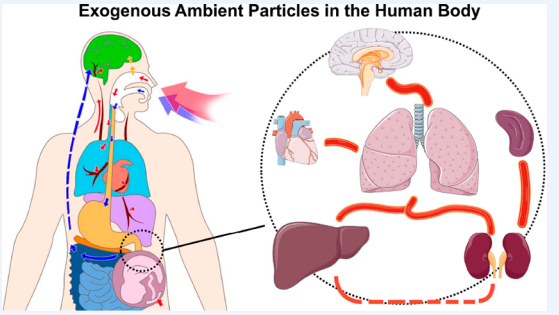
ABSTRACT: **As one of the major pollutants in the air, ambient fine particles are gaining considerable attention in terms of public health concerns. Significant progress has been achieved in recent years in understanding the biological effects and mechanisms of ambient fine particles. The airborne particles can enter the human body through various pathways and translocate to a range of different organs and further stay in these organs for extended periods. Current studies are making substantial achievements, while many challenges remain. On one hand, the whole picture of the concurrent exposure pathways and the translocation of particles in the human body should be explored, requiring technological advances and systematic biobanking of human samples for analysis. On the other hand, the correlation between the environmental exposure concentration of ambient particles and internal fate (i.e., dose, distribution patterns, and kinetics) of invasive particles needs to be investigated. Moreover, the biotransformation of particles in vivo should be considered, and more information is needed to differentiate exogenous particles from biological macromolecules and biogenically formed particles. We recapitulate the current knowledge gaps in understanding the fate of exogenous ambient fine particles in extra-pulmonary organs of the human body and the related biological effects and also propose future research directions to support both fundamental studies and policy making.**



KEYWORDS: *air pollution, particulate matter, biodistribution, health risks, retention and clearance kinetics*

Air pollution has been reported to be responsible for the greatest number of premature deaths, causing 6.7 million deaths in 2019.[1] Indeed, in a landmark legal case in the UK, air pollution was cited as having "made a material contribution" to the death in 2013 of a nine-year-old girl who lived near the South Circular Road in Lewisham, southeast London, and air pollution was listed as the cause of death on her death certificate, following an inquest ruling in 2021.[2] As one major component of air pollutants, ambient fine particles (commonly known as fine particulate matter, $PM_{2.5}$), in particular, are gaining considerable attention in various research fields, especially in public health.[3] Of note, the significant progress in the development and application of nanotechnology and the increasing utilization of plastics also increase the release of fine particles into the ambient environment.[4] In recent years, the global conditions of air pollution have improved with continued efforts to reduce emissions from industry and transportation (Figure 1).[5] In particular, the Chinese government has greatly increased investment in air pollution control, and as a consequence, the annual average concentration of $PM_{2.5}$ in China dropped to 33 $\mu g/m^3$ in 2020 (Figure 2).[6] Compared to 43 $\mu g/m^3$ in 2017, the great decrease made by China through strengthening the regulations on air pollution control shows exciting progress.[7] Correspondingly, other pollutants that are critical precursors of PM in the atmosphere, such as O_3, SO_2, and NO_2, have declined (Figure 2).[8] Despite these efforts, it still needs to engage in a protracted struggle with air pollution to reach the 2005 World Health Organization (WHO) Global Air Quality Guidelines (i.e., 10 $\mu g/m^3$) and especially to reach the revised 2021 WHO standard (reflecting the growing awareness that there are no safe exposure limits for air pollutants) of 5 $\mu g/m^3$ annual mean.[9] Although great reductions have been achieved, air pollution, especially ambient particle pollution, remains one of the most urgent issues to solve in many countries, both global north and south.

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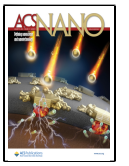

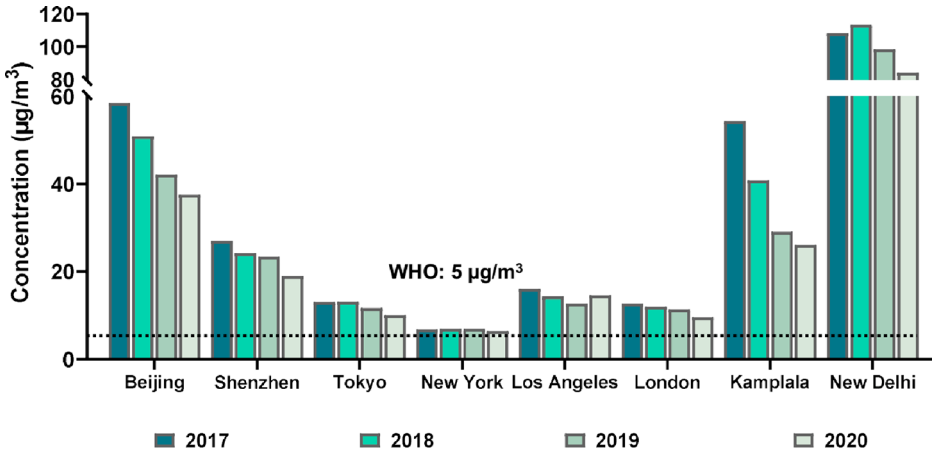

Figure 1. Annual mean concentration of $PM_{2.5}$ in different cities from 2017 to 2020. Although a significant decline is observed year on year, many countries still face severe PM pollution, compared with the WHO guidelines for annual exposure limits to PM. Note that the WHO guidelines were revised in 2021, and the updated guidelines state that annual average concentrations of $PM_{2.5}$ should not exceed 5 $\mu g/m^3$,[9] while 24 h average exposures should not exceed 15 $\mu g/m^3$ for more than 3−4 days per year. Note that the year 2020 included major periods of reduced industrial and transport activities globally due to the COVID-19 pandemic, explaining at least in part the reduced emissions in 2020.

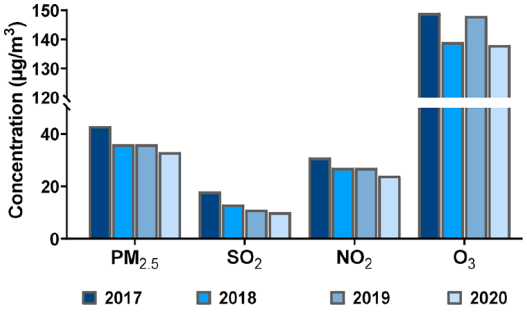

Figure 2. Annual average concentrations of $PM_{2.5}$, SO_2, O_2, and O_3 over the last 4 years in China (2017−2020), noting of course that the year of 2020 included major periods of reduced industrial and transport activities due to the COVID-19 pandemic.

Ambient fine particles (particles with aerodynamic diameter less than 2.5 μm), especially ultrafine particles (particles with aerodynamic diameter less than 0.1 μm), are thought to especially threaten human health as a result of their escape from the body's protective mechanisms in the inhalation system (e.g., mucociliary clearance) and their ability to further penetrate biological barriers (some of the most restrictive protections in the human body to prevent exotic invaders from reaching sensitive organs, such as the brain, the testes, and developing fetuses), leading to long-term health risks. Strikingly, mounting evidence shows a positive relationship between exposure to ambient fine particles and various inflammatory diseases, as well as growing evidence of the role of ambient particles as vectors for infectious diseases.[10,11] Generally, inhaled particle-induced diseases are thought to be caused by oxidative stress, including in the major target site (namely, the lung), and systemically via the release of cytokines.[4] The mounting findings of the physical presence of ambient fine particles in the human body (e.g., bloodstream,[12] knee joints,[13] and brain tissue[14,15]) provide an intriguing possibility that direct contact of tissues with the ambient particles and resulting physical damage could be an alternative mechanism of toxicity and is thus far poorly understood. For example, it has been proved both in vitro and in vivo that the exposure of carbon-based nanoparticles would induce synovial inflammation, articular degeneration, and osteoblast differentiation impairment. Importantly, whether the exogenous particles could reach the bone tissue and interact with the cartilage was addressed recently.[13] Besides, nanoparticles in vivo could cause indirect effects, namely, changing the systemic immune microenvironment.[16] Hence, the existence and state of nanoparticles in vivo picture a reasonable scenario for experimental research, especially animal and cell experiments. In addition, the relatively large surface-to-volume ratio of ambient fine particles means that their surface can become loaded with other pollutants (e.g., heavy metals and polycyclic aromatic hydrocarbons (PAHs))[3] and pathogens (e.g., viruses, even SARS-CoV-2),[17,18] such that the ambient fine particles also act as a "Trojan horse" carrying these threats into the human body (Figure 3). Notably, the high-risk components (i.e., various pollutants) attached to ambient particles exhibit significant temporal−spatial variation.[3] Both the particle generation sources and the environmental conditions, such as meteorological conditions and anthropogenic influences, shape the composition (namely, not only metallic, organic, and inorganic constituents but also the attached pollutants) of inhalable particles.[19,20] Due to the complex interplay of chemicals and the largely undefined surface properties of ambient fine particles, the bioaccessibility of such pollutants in vivo is difficult to evaluate (Figure 3). For instance, it has been proposed that ambient fine particles loaded with copollutants promote cellular uptake of these contaminant compounds. A recent study found that the attached copollutants could transform the surface of particles and change their intracellular bioaccessibility.[21] Meanwhile, the loading capacity of pathogens onto particles, the viability of pathogens on particles, and the transmission and invasive ability of pathogens through hitchhiking on ambient fine particles have been underestimated (Figure 3). For example, whether the interplay between particles and pathogens would increase (or decrease) the infection and replication of pathogens is elusive and is likely dependent on a multitude of factors including both the particle and pathogen properties. Moreover, methods and models are needed to differentiate the separate and combined detrimental effects after coexposure

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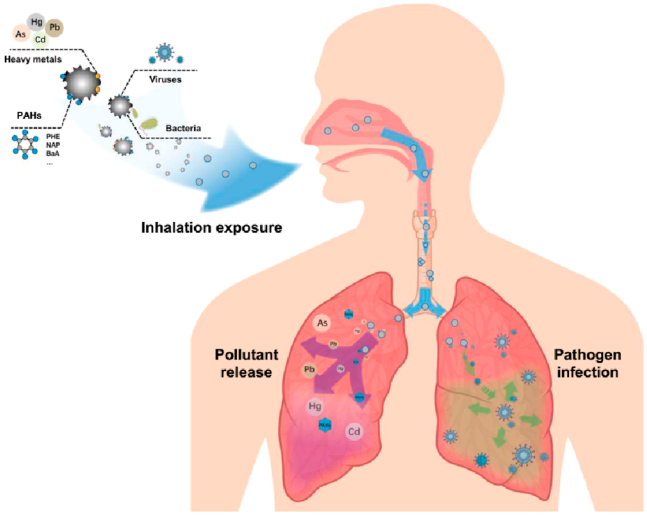

Figure 3. Schematic diagram delineating the health risks of ambient particles with their large and reactive surfaces as carriers of ambient copollutants and pathogens to the respiratory system. This vector mechanism has been termed as a "Trojan horse" exposure route and can lead to much higher localized concentrations of the copollutants or pathogens that would arise without the particles acting as carriers.

(i.e., acute and long-term exposure) to pathogen-laden particles, helping understand the mechanisms of mixture toxicity. It should be noted that the particles and the attached copollutants are all responsible for the toxicity but typically act via a range of different physical and biochemical mechanisms. Therefore, regarding the adverse health outcomes, increasing efforts have been directed toward teasing out the atlas of accumulation sites for exogenous ambient fine particles in the human body through diverse exposure routes. Here we will discuss the importance of extra-pulmonary translocation of exogenous ambient exogenous particles in the human body and the current knowledge gaps and challenges in the investigation of locations and biological effects of exogenous particles in vivo.

DISCUSSION

Ubiquitous fine particles can enter the human body through various pathways, including but not limited to the respiratory tract. Normally, the inhaled particles would deposit in the respiratory tract and then be cleared by mucociliary movements. However, particles with extremely small sizes (e.g., nanoscale particles or ultrafine particles) might escape from the body's protection system and reach deep into the alveolus regions of the lung and then penetrate the air–blood barrier. The particles that translocate to the blood circulation could distribute to other secondary organs, such as the heart, liver, spleen, and kidneys.[22] Other possible exposure pathways, e.g., oral exposure by swallowing, dermal exposure through hair follicles, and even ocular exposure, have also been proposed.[14,23,24] Some exposure pathways still need further scientific evidence to support them. For instance, based on recent evidence pointing to a correlation between air pollution and neurological disorders, the existence of exogenous particles in the central nervous system (CNS) has gained increasing attention (Figure 4).[25,26] The entrance of particles into the brain via the olfactory bulb from inhalation represents an important pathway into the brain.[27] Most recently, it has been proposed the particles could enter the CNS from the gastrointestinal tract after oral exposure through the vagus nerve.[14] This intriguing pathway is deduced by recognizing and identifying exogenous particles in the neuroenteric system. Moreover, the inhaled particles that enter the bloodstream may translocate from the lungs to the brain.[15] These exogenous particles from the blood circulation either can be transported across the blood–brain barrier (BBB) via transcytosis without damaging the BBB or may induce physical damage to the BBB structure and then enter the brainstem.[15,28] These pathways for exogenous particles entering the brain are uncertain, as the whole translocation process could not be visualized in vivo due to the limitations of both sampling and detecting techniques, and these can only be realized in animal models but not in human bodies. Although animal studies have provided plenty of information for the translocation of exogenous particles in vivo, the direct evidence taken from the human body means much more than animal studies.[29−31] Recent studies have only caught snapshots of the translocation, through the identification of the presence of exogenous particles in both the cerebrospinal fluid (CSF) and blood, hinting at a possible pathway of particles from the bloodstream to the brain.[15] Damage to the BBB may be the mechanism of the entrance of exogenous particles and has been supported mechanistically by both in vitro and in vivo studies by capturing the location of particles at the different locations along the pathway of travel, including in the blood vessels close to the brain tissue and the CNS in patient samples.[15] However, as these samples were at static time points, in samples collected from patients for other purposes, mapping the exact trail of particles in the human body in real-time to gather more direct proof is still warranted in the future.

Ultimately, the ambient particles that have entered the body via various exposure pathways could accumulate in different organs and tissues. The systemic distribution of inhaled particles was validated by both human and animal studies (Figure 4). Of note, the presence of exogenous particles in the human body was increasingly reported recently. The existence of exogenous magnetic particles in the human frontal cortex was reported in 2016.[27] Since then, researchers have found exogenous particles in different tissues of humans, including lung, vascular tissue,[32] heart,[33] liver,[34] spleen,[34] placenta,[35] in the blood,[12] in pleural effusion,[12] brain stem,[14] CSF,[15] and even in joint effusion.[13] Surprisingly, exogenous particles have been reported to have accumulated in tissues that are protected by compact barriers. For example, exogenous nanoparticles could translocate through the BBB, a protection shield of the brain, and enter the brain in the form of both particles and dissolved ions, causing cell membrane damage and blood vessel deformation.[15,28] Recently, exogenous fine particles (i.e., donpeacorite and hematite) have been observed in human joint effusions.[13] The joint cavity is protected by the synovium structure that filters nutrients from the bloodstream. The finding of particles in joint effusion points to the direct intrusion of exogenous particles, that might enter the body through inhalation exposure. In addition, the existence of exogenous particles in other distant tissues, e.g., sweat glands, lacrimal glands, breast milk, and hair, is completely unknown currently and needs to be investigated to further complete the atlas of particle accumulation. Although the presence of particles in the different parts of the human body has been reported, the most critical question is whether these particles are exogenous and how they reach the specific site (i.e., the

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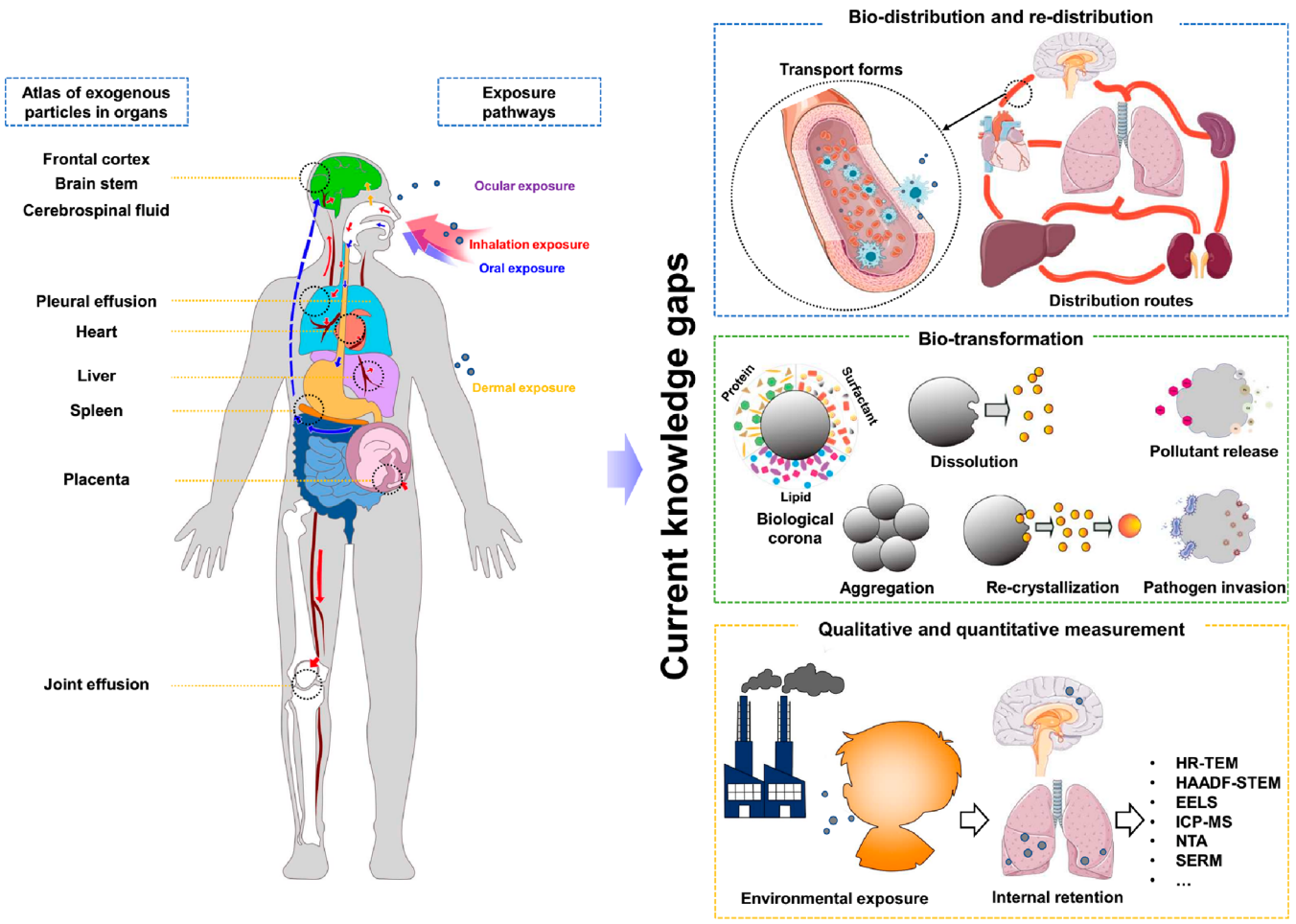

Figure 4. Schematic diagram illustrating the current understanding and knowledge gaps on exogenous particle exposure, accumulation, and retention in the human body. Left panel: Atlas of possible exposure routes of ambient exogenous particles into the human body and sites of particle accumulation based on current available studies. Right panel: Distribution and redistribution of particles among different organs and the transport forms (e.g., through blood circulation or via cells such as macrophages) should be explored. Meanwhile, the biotransformation (e.g., formation of a biological corona, agglomeration, dissolution, and recrystallization) of particles in the human body may give rise to complex coexisting states (forms of the particles) and distinct biological effects. Moreover, the qualitative and quantitative measurement technologies for detection, quantification, and compositional analysis of particles in situ in the body should be further developed to characterize the identity, internal dose, and clearance kinetics of exogenous particles in the human body.

exposure pathways). Moreover, the retention times (e.g., the clearance half-life of time taken to clear 50% of the particles) of exogenous particles in various organs in the human body is largely unknown, although recent findings with radioactive isotope labeled particles showed the overall retention time in animals.[13,15] Nonetheless, since most samples of exogenous particles in human tissues used tissue samples collected from patients with specific diseases, it is hard to understand the particle retention in the general population or specific disease populations, and systematic epidemiological studies based on large populations are warranted in the future.

The recent progress in this field largely relies on advances in analytic technology. Unlike mounting techniques for detecting the particles in the atmosphere environment, limited methods have been applied to observe the particles in vivo. High-resolution electron microscopy (HR-EM) coupled with energy-dispersive X-ray spectroscopy (EDXS) can be applied for particle characterization (i.e., identification techniques), while inductively coupled plasma-mass spectrometry (ICP-MS) and single particle inductively coupled plasma high-resolution mass spectrometry (spICP-HRMS) are often used for (destructive) high-throughput detection (i.e., quantification techniques). For instance, through the high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM), exogenous fine particles with different structural and chemical fingerprints could be identified from complex human body fluids.[13,15] However, the major limitation is that the images only offer a very limited view provided by the "zoom-in" from electron microscopy, rather than showing the whole picture. Thus, it is difficult to tell the amount or distribution of the particles in the organs or tissues from representative EM images. By contrast, the quantification techniques can provide the concentration of particles in the whole or part of the biological system, especially using stable isotopic fingerprints.[12] But some information on the physicochemical properties of the particles, such as the sizes, shapes, and compositions, is still missing. In addition, it should be noted that these analytic technologies are based on the samples extracted from the human body, involving invasive techniques that are usually not applied to healthy people. The analytical techniques are limited insofar as well-defined exogenous particles, which would not reflect what happens to all particles and would be of limited

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use. Therefore, the sampling methods and analytic technologies for combined information on various methodological fingerprints of particles, including structural, chemical, and even stable isotopic, will enable separations of exogenous particles from the complicated biological environment and retrieve the exposure sources.

The quantitative measurement of internal exposure (dose) is still one of the biggest bottlenecks, due to the trace number of particles in real exposure scenarios. The particles in human samples are often present at extremely low concentrations, even for occupational exposure (relatively high exposure dose and long-term exposure) (Figure 3). This could be deduced via animal studies that only a small portion of inhaled particles could translocate into the bloodstream and other organs.[29] This makes finding these small particles like finding a "needle in the haystack". Despite this, efforts have been made to calculate the concentrations of exogenous particles in different organs. For example, the concentration of magnetite-like particles was estimated at 0.34 (median) μg/g tissue (about 4.26×10^9 particles/g tissue) in cerebellum samples from young urbanites in Mexico City,[14] while 36 (median) ng of magnetite/g tissue (about 0.44×10^9 particles/g tissue) was estimated in brain samples in elderly people from Manchester (with and without Alzheimer's disease).[36] The content of magnetite particles was examined by saturation remanent magnetization, and the number concentration was also estimated according to the standard particles with a diameter of ~31 nm. This method could only be applied to the magnetite particles due to their ferromagnetic properties. Likewise, the total number of various exogenous particles in human CSF was estimated as more than ten thousand particles through HR-TEM observation.[15] For other metal-based particles, ICP-MS-related technologies could be applied to determine particle concentrations in tissue. For instance, the Ti content in the human liver and spleen was determined as an average of 0.04 (about 2 to 8×10^6 particles/g tissue) and 0.08 (about 4 to 13×10^6 particles/g tissue) mg/kg tissue in elderly people from The Netherlands, respectively.[34] These approaches only provide estimations of number concentration, since some exogenous particles may exhibit a much larger size than the standards used in the calculations. For comparison, NTA was used to detect the exogenous particle concentrations in human serum and pleural effusion, determined as 1.4×10^8 to 1.0×10^{10} per mL of serum and 4.2×10^8 to 4.0×10^{10} particles per mL of pleural effusion.[12] The limitation of this method is that the compositions and structures of particles could not be characterized. It should be noted that, due to the sampling and detection limits, the exact number of exogenous particles in the human body is unavailable as yet. The number concentration is obtained from small pieces of samples collected from different organs and then the total concentration in whole tissues is deduced or extrapolated. This estimation cannot reflect the real exposure dose since the particles may not distribute homogeneously, as massive particles may be taken up (endocytosed and phagocytosed) by the reticuloendothelial cells. Hence, there is a lack of universality in understanding the content of exogenous particles in a specific part of the body, warranting further advances in technology and more systematic sampling through for example epidemiological studies. Nevertheless, the presence of exogenous particles in the human body uncovered thus far suggests that exposure to exogenous particles is leading to bioaccumulation and that particle numbers might be much more than currently estimated. In a rough estimation, a healthy man with 70 kg body weight will breathe about 20 m^3 of air per day, equaling to exposure of 100 μg of fine particles in total (assuming air quality per 2021 WHO recommended limit of 5 $\mu g/m^3$). The much lower average dose in the whole body (0.0015 μg/g body weight) than the estimated concentration in some specific organs (i.e., brain and liver) thus indicates the accumulation of fine particles in these organs, but the distribution patterns and biodistribution and potential clearance kinetics are unknown. As discussed above, the existence of exogenous particles in the human body could be one of the direct toxicity mechanisms; however, it should be noted that "the dose makes the poison". The exposure dose is often unclear and difficult to quantify with confidence. The piece of the puzzle needs to be investigated to evaluate the concrete (cyto)toxicity mechanisms of exogenous particles and to understand their role in common adverse or disease outcomes.

Another challenge in the identification of exogenous particles in biological samples is the limited understanding of the biotransformation of particles, including endogenic bioparticles that might appear similar to exogenous fine particles (Figure 4). The exogenous particles may have already undergone biotransformation in vivo (such as dissolution, redox reactions, and even recrystallization), deciding the identities and sources of exogenous particles in the biological medium extremely difficult.[10,28,37] Additionally, particles entering the body would quickly interact with biological molecules (e.g., proteins, lipids, and surfactants) forming the "biological corona", which determines the fate and transport of particles in vivo.[38] It is unclear as yet how such transformation processes proceed in the body. For example, some metal oxides would undergo dissolution in vivo, and the signals of metal detected by ICP-MS need to be further confirmed by other methods to determine whether they appear in ionic or particle states, and the surface speciation. In addition, although imaging techniques could provide pictures with high resolution that can depict the appearances of particles (such as the precise size, morphology, exposed facet, and crystalline structure), more information is needed to differentiate the exogenous particles from the biological macromolecules and even from biogenic nanoparticles.[37,39] For example, the size of magnetic particles found in the human brain is much larger than biogenic Fe nanoparticles in ferritin, indicating the exotic identity of the particles. Some characteristics, such as more complex compositions (from natural minerals), special crystalline structures (from calcinated temperature), and stable isotopic fingerprints, may help us know whether the identified particles are exotic invaders. Additionally, since it is rare to have details on the environmental particles to which individual patients were exposed, it is difficult to understand if changes in the speciation have occurred, as the initial particle compositions were not known.

CONCLUSIONS

Despite the considerable progress, the knowledge gaps highlighted here should be filled in via future studies (Figure 4). Our recommendations thus include the following.

(i) Since the compositions of exogenous particles in the real environment are complicated and varied according to generations, environmental factors (e.g., weather and temperature) and even human activities, when tracking the existence of exogenous particles in vivo, epidemiological studies based

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on large populations should be combined with environmental sampling. This combination strategy could provide information and reference for further risk evaluation and prediction. In addition, based on synthesized particles with controlled physicochemical properties, basic research could provide a large amount of data, and then deduce the correlations between different physicochemical properties and biological effects. The database would help anticipate the effects of different types and proportions of particles, that is, what we call for more studies and attention. Therefore, the snapshots caught in the human body could be correlated with the real exposure environment, especially concerning the scale in space and time (namely, the time points and locations when exposed and sampled). The recent studies lack correlations and are limited by the sampling methods and detection techniques. Safer and less invasive sampling methods are needed, especially in healthy people. In addition, advanced analytical methodologies should be developed and used in combination, as proposed above, to characterize and confirm the identities of the exogenous particles, as well as the characterization of the ambient particles in situ.

(ii) The full set of exposure scenarios and the distribution atlas of sites of particle accumulation in the human body need to be mapped out, providing evidence for studying both direct and indirect toxicity to secondary organs. In addition, considering the clearance of particles in different organs, the retention times (e.g., particokinetics), and redistribution of particles, especially within organs protected by biological barriers, e.g., brain, eye, and testis, should be explored to evaluate the long-term effects and pollutant accessibility. The transport forms and routes also need to be investigated, for example, via blood circulation and coating with the protein corona, or endocytosis by reticuloendothelial cells and translocation by hitchhiking with macrophage cells.

(iii) The precise concentrations of exogenous particles, including elemental compositions and numbers, in various organs and tissues, should be determined. It should be noted that this is not a simple argument on the presence or absence of fine particles in the human body, as "dose matters". Quantitative concentration information is needed to determine the dose-dependent (cyto)toxicity of particles and the related toxicity mechanisms. In addition, the internal exposure dose in the human body has significant importance for the design of animal experiments and in vitro studies (namely, the applied experimental conditions for exposure) to assess the impacts of other materials in the future and to feed into the design of safer materials.

(iv) The identities of exogenous particles exhibit large variations due to different regions/cities (especially in terms of the attached copollutants) and emission sources that correlate to the subsequent harm or adverse effects. Thus, the mechanisms of particle-containing mixtures toxicity based on both in vitro and in vivo models and the detrimental effects of particle mixture on human health should be explored and included in the future framework for health protection. Notably, the interactions between particles and biomolecules (e.g., surfactants, enzymes, and lipids) via the formation of the biological corona would consequently alter the fate, translocation, and retention profiles of particles in the human body, as well as potentially displacing copollutants from the particle surfaces, leading to complex coexisting states and (cyto)-toxicity effects. There have been numerous studies on the corona formation of diverse particles in vitro, ex vivo, and in vivo. However, recent progresses have been made on the biological corona of well-designed particles, while the complex compositions of real ambient particles bring more challenges. Thus, studies on the health risks of air pollution should involve diverse disciplines, such as molecular biology, toxicology, environmental chemistry and epidemiology. Additionally, versatile in vivo, ex vivo, and animal models should be established to evaluate the exact exposure threshold and health risk of ambient particles, in combination with big-data analysis through epidemiological studies and high-throughput detection to correlate internal and tissue-level dose and effects.

AUTHOR INFORMATION

Corresponding Authors

Sijin Liu − *State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; University of Chinese Academy of Sciences, Beijing 100049, China; Science and Technology Innovation Center, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250000, China;* orcid.org/0000-0002-5643-0734; Email: sjliu@rcees.ac.cn

Tian Xia − *Division of NanoMedicine, Department of Medicine, University of California, Los Angeles, Los Angeles, California 90095, United States;* orcid.org/0000-0003-0123-1305; Email: txia@ucla.edu

Iseult Lynch − *School of Geography, Earth and Environmental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom;* orcid.org/0000-0003-4250-4584; Email: I.Lynch@bham.ac.uk

Authors

Yu Qi − *State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; University of Chinese Academy of Sciences, Beijing 100049, China;* orcid.org/0000-0002-4862-5347

Yucai Chen − *State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsnano.2c09299

Notes

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