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Airborne Nanoparticles and Human Health: Toxicological Insights with a Focus on Inhalation Exposure and Mechanisms of Toxicity During Pregnancy

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Abstract: Air pollution, particularly from airborne particulate matter (PM), is a major global health challenge and a leading cause of premature death. In this perspective, we provide an overview of human exposure routes to airborne PM and engineered nanoparticles, their subsequent translocation across biological barriers, and their biological effects within barrier tissues and beyond with a focus on the pulmonary and placental barrier. Emphasis is placed on direct versus indirect toxicity mechanisms in the absence of barrier crossing as well as on the 'Trojan Horse effect' that can enhance toxicity. Based on the current state of research, we outline critical knowledge gaps and highlight selected research efforts with Swiss participation that seeks to address these challenges. Collectively, these efforts will contribute to advancing risk assessment frameworks, informing regulatory policy, and ultimately reducing the global health burden of particle exposure.

Keywords: Biological barriers · Engineered nanoparticles · Nanoparticle toxicology · Particulate matter · Trojan Horse effect

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Dr. Tina Buerki-Thurnherr received a PhD from ETH Zurich (2006) and continued her scientific career at Empa where she is currently heading the Particles@Barriers group and serves as Deputy Head of the Nanomaterials in Health Lab. She is leading cutting-edge research in the field of nanosafety and particle interactions with biological barriers. A special focus of the group is systematic studies of particle-tissue effects in dependence of material properties and identification of toxicity mechanisms, which forms important groundwork towards the safe design of nanomaterials, the development of innovative particle-based therapeutics and the protection of vulnerable populations.

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1. Introduction

Humans are inevitably exposed to tiny nano- and micrometer-sized particles in their daily lives (Fig. 1A). A notable fraction is ambient **particulate matter** (**PM**), a complex mixture of solid particles and liquid droplets suspended in the air, categorized according to their aerodynamic diameter as PM_{10} (< 10 µm), $PM_{2.5}$ (< 2.5 µm) and $PM_{0.1}$ (< 0.1 µm).[1] The smallest fraction, $PM_{0.1}$, falls within the EU definition of nanomaterials (although this definition is often not used in the context of particulate matter). Nanomaterials are natural, incidental, or manufactured materials containing particles where 50% or more have at least one external dimension between 1 and 100 nm.[2] PM is chemically heterogeneous and typically consists of complex mixtures of metals, nitrates, sulfates, and organic compounds such as polycyclic aromatic hydrocarbons (PAHs) (more details in Heeb *et al.* in this issue). PM concentrations are regulated in the Swiss Clean Air Act (Luftreinhalteverordnung), which takes into account the guidelines from the World Health Organization (WHO).[3] These exposures arise mainly from incidental sources, such as combustion-derived particles from biomass, burning of fossil fuels, or traffic-related PM.[4] The increasingly discussed micro- and nanoplastics (MNPs), which can form through various processes, including degradation and abrasion such as those from vehicle tires, are also considered a part of particulate matter.

On the other hand, **engineered nanoparticles** (**ENPs**) (see definition above) are another emerging fraction of airborne particulate exposure, given their increasing use in industrial and consumer applications.[5] ENPs are deliberately synthesized with defined physicochemical properties and compositions for specific applications, focusing on exploiting unique functionalities such as mechanical strength, catalytic activity, antimicrobial effects, optical and magnetic properties.[6] Nevertheless, ENPs used in industrial and occupational contexts may be unintentionally released into the surrounding environment, leading to potential health hazards. Although Switzerland has implemented regulations on the use of ENPs in consumer products,[7] the incidental release of ENPs in the environment cannot be avoided.

Considerable emphasis has been placed on monitoring air quality, particularly $PM_{2.5}$ and PM_{10} levels, but given that larger particles can degrade into ultrafine/nanosized fractions in the environment, the absence of $PM_{0.1}$ regulation highlights a critical blind spot.[8] There is growing evidence that smaller particles possess the greatest potential to interact with biological systems due to their high surface area-to-volume ratio, making them more reactive.[9] Therefore, in studies on nanoparticle (NP) toxicity, particle metrics based on particle number or surface area are more appropriate than mass-based metrics alone, as they better account for the high particle count and large reactive surface area characteristics of NPs.[10] Overall, there is an urgent need to clarify exposure routes, levels, and biological consequences of airborne PM and ENPs exposure, in order to accurately evaluate their health hazards and develop effective strategies to protect human health.

Although PM, MNPs and ENPs are very different with regards to their sources, compositions, sizes distributions and heterogeneity, knowledge gained in one field can help to better understand the others, and vice versa.[11] Therefore, in this article, we use data of PM as well as MNPs and ENPs to explain pathways and mechanisms.

2. Pathways of Exposure and Biological Barrier Crossing

2.1 *Inhalation as Primary Entry Route for Airborne Particles*

The airways branch into three levels, namely the trachea, bronchi, and bronchioles and ultimately lead into the alveoli.[12] Across the respiratory tree, the composition of the airway wall changes. The ciliated epithelial layer, thick in the trachea and the larger bronchi, gradually becomes thinner throughout the bronchioles, and is thinnest in the non-ciliated respiratory bronchioles with scattered alveoli consisting of a squamous epithelium where the gas exchange happens by diffusion.[12] 99% of the alveolar epithelium consists of squamous type I alveolar cells facilitating rapid gas exchange, and type II alveolar cells synthesizing and secreting surfactant. This surfactant reduces the surface tension and prevents the alveoli from collapsing.[13] The epithelial tissue serves as a barrier against inhaled environmental stressors (such as particles). These may be removed by macrophages or other immune cells in the alveolar region and airways, as well as by mucociliary clearance driven by ciliated epithelial cells covered with mucus produced by goblet cells in the conducting airways.[14] Additionally, epithelial cells can attract, activate and modulate immune cells and responses through the secretion of chemokines, cytokines and lipid mediators.[15]

PM_{10} is the PM fraction that can enter the lungs upon inhalation, with smaller particles penetrating deeper into the airways. While larger particles of PM_{10} are primarily deposited in the upper airways[16] and removed *via* mucociliary clearance, the smaller $PM_{2.5}$ can even reach the alveoli. Once the particles reach the alveolar region, they become wetted by the surfactant and are displaced by surface forces exerted on them by interaction with the surfactant.[17] Upon interacting with the epithelial cell surface membrane, the smallest fraction ($PM_{0.1}$) may cross the air-blood tissue barrier and reach the bloodstream,[18] either *via* transcellular or intercellular pathways, or facilitated by immune cells. Particles can enter the cells through different mechanisms, including phagocytosis, micropinocytosis, or different types of endocytosis. The deposition of PM in the alveoli recruits phagocytic cells due to an upregulation of proinflammatory cytokines, leading to phagocytosis of the particles.[19] Once the particles have crossed the air-blood tissue barrier, they can reach other organs *via* the bloodstream.[20] This translocation process is highly dependent on the dose, size and other characteristics of the particles.

In a study by the Swiss group of Gunasingam *et al*., the translocation of diesel exhaust particles (DEPs) across alveolar tissue was investigated by exposing cells to multiple concentrations of DEPs. Approximately 60% of the DEPs were taken up by the cells when the DEP concentration was low, whereas only 20% were taken up at high DEP concentrations. Translocation of the particles was independent of the exposure time and concentrations.[18]

Ingestion serves as a secondary exposure route when airway particles are cleared by mucociliary clearance and swallowed into the digestive system.[21] The intestine forms a multilayered barrier comprised of mucus and intestinal epithelium, where larger particles are trapped in the mucus, while smaller ones may reach the epithelial surface.[22] Both *in vitro* and *in vivo* studies provide evidence that numerous ENPs, including titanium dioxide (TiO_2), silica (SiO_2), and industrial MNPs can translocate across the gastrointestinal tract.[23,24]

Dermal exposure is another potential route of contact, as the skin can be indirectly exposed to airborne particles. However, intact skin has been shown to provide an effective physical barrier, making this route of exposure of minor importance for human exposure.[25]

2.2 *Crossing Internal Biological Barriers: Lessons from the Placenta*

Growing evidence indicates that a fraction of inhaled PM and ENPs can cross pulmonary and intestinal barriers, enter systemic circulation, and spread to secondary organs (Fig. 1B). This is of particular concern during pregnancy, as the unborn child is highly sensitive to adverse exposures. To reach the developing fetus, NPs must cross the placenta, a protective biological barrier forming the

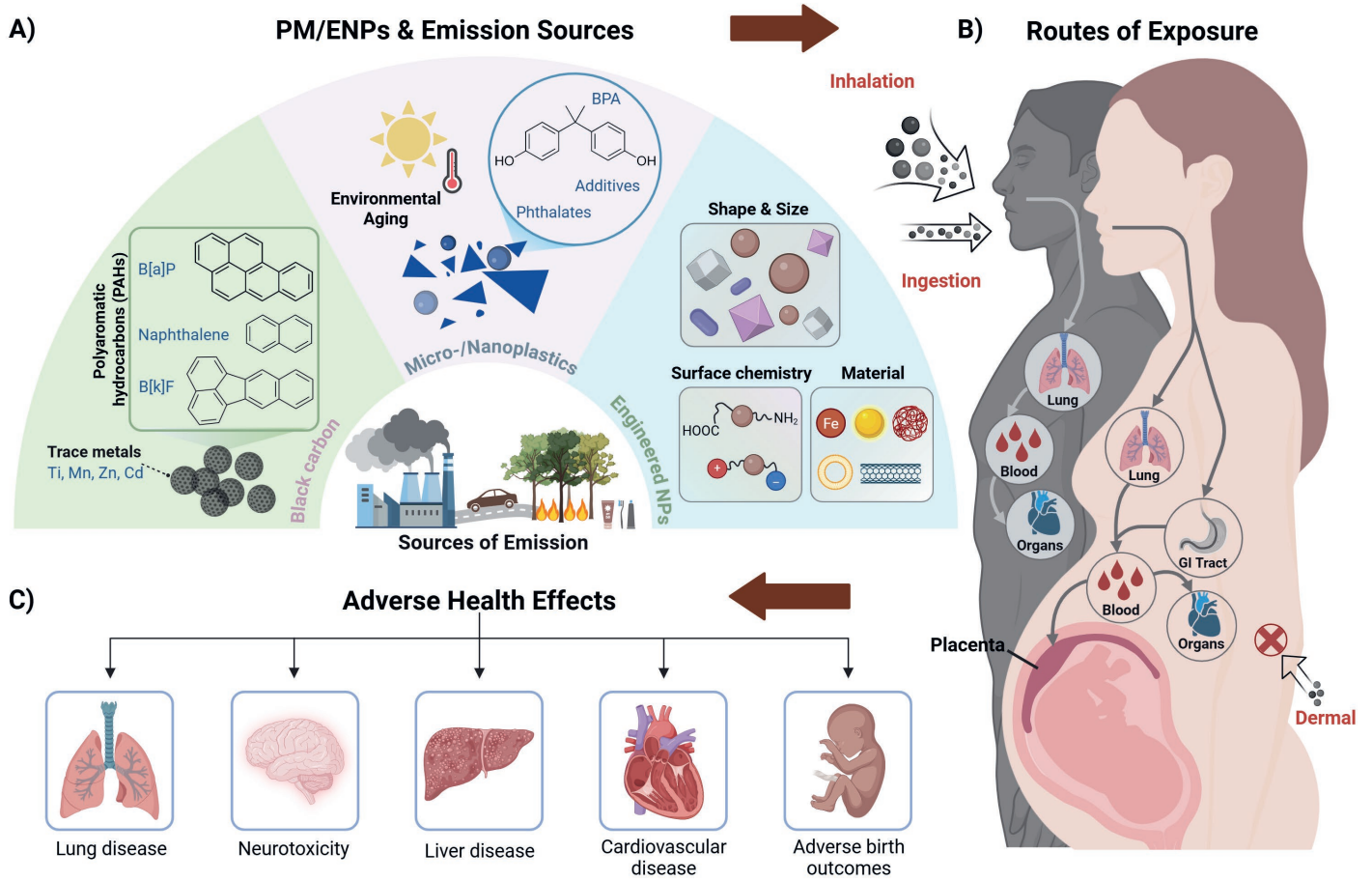

Fig. 1. Schematic illustration of (A) PM and ENPs and their sources (A), human exposure routes (inhalation, ingestion or dermal) (B), and organs affected by associated adverse health effects (C). This figure was created with BioRender.com

interface between the mother and the developing child. Moreover, the placenta regulates the transport of nutrients, oxygen and waste and performs a multitude of metabolic, immunological and endocrine functions indispensable for embryo-fetal development. The separation between the maternal and fetal blood circulation is formed by three cellular layers, the syncytiotrophoblast, cytotrophoblast and fetal endothelium.[26] As pregnancy progresses, the outer syncytial layer starts to thin out, the cytotrophoblast layer fragments, and the fetal capillaries move closer towards the maternal blood space, enhancing nutrient transfer to support fetal growth.[26] In recent years, airborne particles such as black carbon (BC) and microplastics were detected in the placenta.[27,28] Targeted exposure studies in pregnant animal models likewise confirmed placental translocation of DEPs,[29] MNPs[30] and ENPs.[31] Mechanistic *in vitro* and *ex vivo* placental transfer studies demonstrated that placental translocation of NPs is strongly governed by their physicochemical characteristics, including size, surface properties, charge and chemical composition.[32–34]

While transport mechanisms for small compounds are well studied and involve simple-, facilitated- and transporter-mediated diffusion processes,[35] the transport pathways for PM and ENPs often relies on endocytic pathways (reviewed by Almeida *et al.*[36]). For instance, an early placenta perfusion study with polystyrene NPs observed significantly higher fetal-to-maternal than maternal-to-fetal transport, suggesting an active, energy-dependent transport pathway rather than passive diffusion.[34]

Ex vivo perfusion of human term placenta revealed further insights into the kinetics of maternal-fetal transfer and subcellular localization of particles in the placental tissue. In one study, DEPs showed minimal translocation after 6 h of perfusion, with most particles accumulating in the syncytiotrophoblast and smaller amounts detected in placental macrophages. A few particles could also be detected in the fetal endothelium and circulation despite the washout during perfusion, indicating limited and gradual fetal transfer of DEPs.[29] Further observational studies reported the presence of BC[37] and MNPs[38] in fetal appendages and organs such as fetal membranes, amniotic fluid, umbilical vein blood or fetal brain, liver and lung tissues, confirming placental barrier crossing in humans under real-life exposure.

3. Biological Responses in Barrier Tissues and Beyond

3.1 *Links Between Airborne Particles and Human Diseases in the General Population and In Pregnant Individuals*

According to the Lancet Commission on pollution and health, diseases caused by pollution are responsible for approximately nine million premature deaths worldwide, nearly half of which are attributed to outdoor air pollution.[39] For instance, acute and chronic exposure to air pollution has been linked to pulmonary and cardiovascular effects,[40,41] intestinal inflammation,[42] increased risk of liver cancer,[43] neurodegenerative diseases and declining cognitive function (Fig. 1C).[44] Further details on epidemiological findings are reported in Eftens *et al.* in this issue.

In the specific context of pregnancy, PM exposure is connected to adverse pregnancy outcomes such as preterm birth and preeclampsia.[26] Air pollution exposure during pregnancy can additionally impair fetal organ development, with first trimester exposure disrupting neurodevelopment and placentation, second trimester exposure increasing asthma risks, and third trimester exposure linked to allergic rhinitis and low birth weight.[45] Moreover, prenatal exposure to $PM_{0.1}$ was associated with altered placental gene expression and allergy development in children.[46]

3.2 *Toxicity Pathways Triggered by Direct NP Exposure*

NPs that reach various organs can directly interact with cells through different mechanisms including impairment of barrier integrity, induction of oxidative stress, pro-inflammatory responses, DNA damage, all of which compromise normal cellular functions and may ultimately lead to cell death.

An impairment of the **barrier integrity**, typically evidenced by reduced transepithelial electrical resistance (TEER) and increased permeability to diffusion markers, has been demonstrated following exposure to PMs, MNPs, and ENPs.[47,48] The resulting increase in paracellular permeability can interfere with processes such as nutrient absorption, efflux transporter activity, and mucus secretion.

Oxidative stress occurs when the antioxidant defense cannot counterbalance the reactive oxygen species (ROS) produced. ROS are chemically reactive oxygen-derived molecules, formed endogenously as by-products during mitochondria electron transport and usually eliminated by antioxidants produced by cells. However, PM and ENPs with ROS-generating potential can disrupt this balance and dissolution of metal ions such as Zn^{2+} ions can further contribute to ROS generation.[49] The quantification of glutathione (GSH), an anti-oxidative stress agent, demonstrated detrimental effects of DEPs in respiratory cell models.[50]

Excess ROS can interact with lipids, proteins and DNA,[51] leading to downstream effects in cells exposed to PM and ENPs. These include **DNA damage**, mitochondrial dysfunction, impaired nutrient transport, and mitophagy.[52] Hydroxyl radicals ($^{\bullet}OH$) can attack DNA bases and the sugar-phosphate backbone, forming oxidative adducts such as 8-oxoG and result in double strand breaks.[53] These lesions activate the DNA damage response, as observed in placental trophoblast cells following exposure to oleic acid-coated iron oxide (Fe_3O_4) and TiO_2 NPs as well as $PM_{2.5}$.[54,55]

Furthermore, scooter exhaust particles have been shown to have a **pro-inflammatory effect**, as tumor necrosis factor α and interleukin 8 concentrations were increased after exposure to the scooter exhaust PM.[56] Another toxicity mechanism is **autophagic dysfunction**, impairing the lysosomal degradation of damaged components or foreign materials, thereby compromising homeostasis and stress adaptation. It has been demonstrated that cerium dioxide (CeO_2) NPs impair placental development by disrupting autophagy in mice and inhibiting migration and invasion of trophoblast cells.[57] In endocrine organs such as the placenta, PM and ENPs can elicit **endocrine disrupting** activities. Exposure to CeO_2 NPs impaired trophoblast differentiation, thereby reducing placental hormone production.[58]

3.3 *Indirect Mechanisms of NP Toxicity in Distant, Non-Exposed Tissues*

Recently, attention has turned to indirect mechanisms of toxicity, in which NPs elicit adverse effects (such as described in Section 3.2) in distant organs and tissues without physically crossing biological barriers. Instead, these secondary effects are mediated by soluble factors and signaling molecules released from the initially exposed cells or tissues (Fig. 2A). Such mediators may include ROS, inflammatory cytokines, stress-related signaling molecules, and vascular or endocrine factors that propagate systemic responses. Through these pathways, local NP exposure can provoke systemic inflammation, oxidative stress, or metabolic alterations, thereby linking localized particle interactions to whole-body effects.

In a mouse study, it was investigated whether cardiovascular effects of inhaled carbon NPs (CNPs) were attributed to particle translocation into circulation (direct effect) or from pulmonary particle-cell interactions (indirect effects). Inhalation of CNPs revealed early pulmonary responses as the main driver of extra-pulmonary effects, rather than particle translocation into circulation, highlighting the key role of lung-derived soluble mediators in mediating systemic outcomes. Lung inflammation was absent when CNPs were infused into the arteries, bypassing the lungs.[59] In placental models, NPs have been reported to induce DNA damage in cells beneath multilayered cellular barriers, even without direct particle translocation. Apical exposure of a bilayered placental trophoblast barrier to cobalt chromium NPs resulted in DNA damage in human fibroblasts cultured on the basolateral side. This was attributed to intercellular communication (*e.g.* purine nucleotides such as ATP) *via* pannexin and connexin channels.[60] In another study using a microfluidic placenta-embryoid body chip, a reduction of cell viability (ATP content) of the embryoid bodies was observed although particles did not cross the placental barrier. The authors hypothesized that the reduction may be driven by placental release of metabolic products, inflammatory factors or oxidative stress-derived factors.[61] Impaired maternal-fetal signaling can have adverse implications for the offspring, influencing processes such as neurodevelopment, angiogenesis, and vascularization. In mice, prenatal exposure to TiO_2 NPs caused behavioral alterations in offspring reminiscent of autism spectrum disorder, without evidence of NP translocation.[62] Dugershaw-Kurzer *et al*. revealed that TiO_2, SiO_2 NPs and DEPs dysregulated the placental secretome in human placental explants, and that conditioned media inhibited angiogenesis and vascular branching processes.[63] This emphasizes the important role of placental signaling as a mediator of developmental toxicity even when direct fetal exposure does not occur.

3.4 *'Trojan Horse Effect': Particle-Mediated Transport of Contaminants*

In nanotoxicology, the 'Trojan horse effect' refers to the phenomenon where NPs act as a carrier to facilitate the cellular entry and bioavailability of adsorbed toxic substances such as metals or organic pollutants. Environmentally relevant particles can remain airborne for extended periods, during which organic compounds such as PAHs and trace metals (both termed as toxicants in Fig. 2B) adsorb onto their surfaces, altering their physicochemical properties and reactivity. Once internalized, these contaminant-loaded particles can release their cargo in the acidic or enzymatic intracellular environment, leading to enhanced oxidative stress, inflammation, or genotoxicity compared to the pristine material (Fig. 2B). While it has been argued that direct binding of additives to particles reduces their surface area and consequently their toxicity,[64] numerous studies have shown that these surface-bound additives can be more toxic than the particle core itself. For instance, acetylene combustion-derived PAH mixtures and P90-benzo[a]pyrene (BaP) induced cytochrome P450 (Cyp1A1 and Cyp1B1) mRNA expression in Calu-3 and tracheal epithelial cells, leading to metabolic activation of reactive electrophilic metabolites, which further enhances ROS production.[65] These lipophilic PAHs can rapidly desorb following deposition in the alveoli, enter pulmonary cells and reach systemic circulation within minutes,[66] and cardiovascular effects have been increasingly attributed to this organic fraction. This is exemplified by the organic extract of DEPs inducing depolarization of airway sensory nerves in humans and guinea pigs *via* activation of the aryl hydrocarbon receptor, leading to subsequent mitochondrial ROS production.[67] In another study, surface coating of soot NPs with secondary organic matter amplified proinflammatory effects in human bronchial epithelial cells, highlighting the role of adsorbed compounds in mediating toxicity.[68] Once in the circulation, these contaminated particles could eventually cross into the placental tissue or fetal circulation, releasing their toxic payload, a mechanism that warrants further investigation. More details and examples on the 'Trojan Horse effect' can be read in Heeb *et al*. in this issue.

In addition to adsorbed molecules, MNPs and PMs often contain harmful chemical additives and contaminants, either intro-

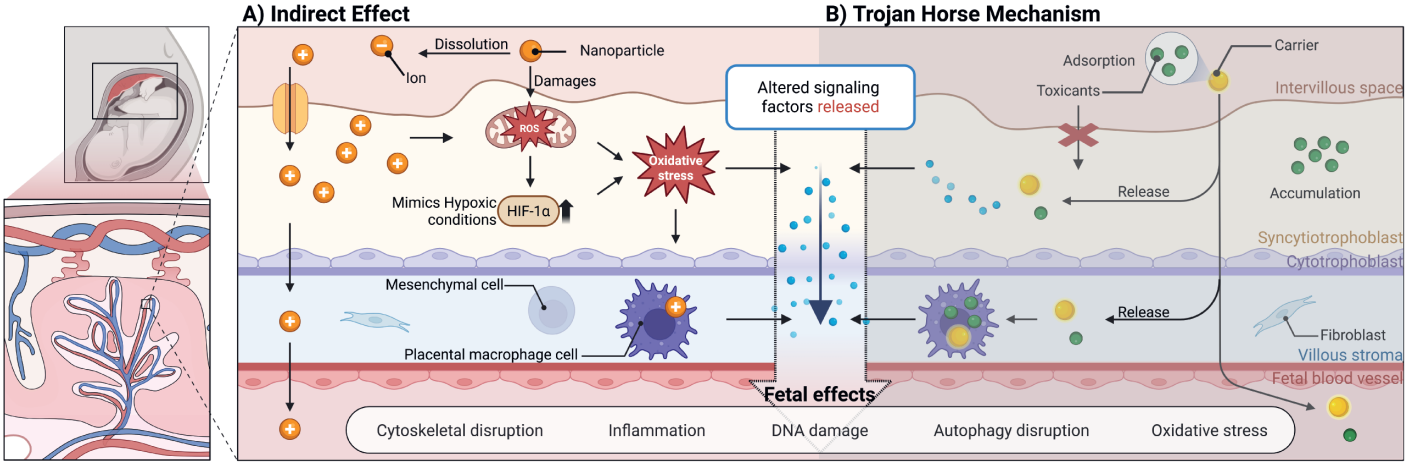

Fig. 2. Schematic illustration of the placenta barrier showing indirect effect (A) and Trojan Horse mechanisms (B), and their consequent fetal impacts. The figure was created with BioRender.com.

duced during manufacturing or formed unintentionally through anthropogenic processes (*e.g.* combustion). Endocrine disruptors such as bisphenol A, nonylphenol, and octylphenol can impair endocrine function and cause adverse health effects.[69]

Overall, the binding of molecules to particles creates a new particle type whose biological activity results from both altered physicochemical properties and the toxicity of the bound substances. This raises concerns about unknown synergistic interactions, including amplified biological effects or increased bioavailability of toxicants that would not otherwise cross biological barriers.

4. Conclusions and Future Directions

4.1 *Remaining Knowledge Gaps*

In this article, we reviewed the human exposure routes of PM and ENPs, their ability to traverse biological barriers and their potential to elicit direct, indirect or 'Trojan horse' mediated toxicity. The physicochemical properties of particles are recognized as key determinants of biological uptake, translocation, and effects; however, major knowledge gaps remain regarding which specific properties govern their biodistribution and toxicity as well as the molecular pathways driving adverse health outcomes of PM and ENPs. To uncover novel toxicity mechanisms, omics technologies offer powerful tools by providing a comprehensive view of altered molecular responses, including changes in gene expression and proteins.

Another key challenge is the heterogeneity of particle types, chemistry, and size fractions as well as their tendency to bind airborne pollutants, making a comprehensive particle characterization essential to understanding their biological effects.

To better understand the long-term health effects of air pollutant particles, the use of advanced *in vitro* models suitable for prolonged exposures could provide systematic and human-relevant insights. Current knowledge largely stems from animal and epidemiological studies, which presents limitations due to species differences and a lack of mechanistic insights.

Mixture exposures also represent an important but underexplored aspect, as air pollution contains diverse particulate pollutants such as PM, MNPs, and ENPs, that may provide synergistic or antagonistic effects. Moreover, emerging concepts such as the 'Trojan Horse effect' underscore the need to better understand how cargo loading and release, altered biodistribution and subcellular localization differ from those of free cargo.[70]

PM and ENP exposure can also impact the outcome of microbial infections at biological barriers. Different studies have shown that the impairment of the airway epithelial integrity and the induction of oxidative stress and/or (pro-) inflammatory responses can facilitate viral entry and replication.[71,72] However, the underlying mechanisms are not yet fully understood and warrant further investigation.

Lastly, mechanistic *in vitro* studies can only yield meaningful insights when realistic concentrations and mixtures are tested. Yet, major knowledge gaps persist in exposure assessment, highlighting the need for more sensitive detection methods (*e.g.* for nanoplastics in complex matrices) and expanded biomonitoring efforts.

4.2 *New Research Efforts with Swiss Participation*

Multidisciplinary global consortia that integrate expertise in environmental exposure assessment, clinical cohort, and experimental models, as well as *in silico* studies, hold great promise for advancing our understanding of the health impacts of pollution particles. For instance, the recently launched EU project UPRISE brings together environmental scientists, clinicians, and public health experts to unveil how air pollutants such as $PM_{0.1}$ and MNPs influence fetal health.[73] By combining epidemiological data with preclinical studies conducted by scientists from the Swiss Federal Laboratories for Materials Science and Technology (Empa) using advanced human placental models, UPRISE aims to establish causal links between maternal exposure and adverse birth outcomes, thereby providing robust evidence to inform interventions and health policies.

Another initiative aims to better understand PM exposure from non-combustion particles such as tire wear particles. The joint project between the University of Bern and the Applied University of Bern is interested in identifying factors that cause toxicity of tire wear particles in human respiratory cell models. This project also aims to develop recommendations to reduce emissions of toxic tire wear particles, providing guidance for urban planning and road construction to reduce tire wear particle release from passenger cars.[74]

A third example is the EU-funded ULTRHAS project, which investigates the health threats posed by NPs from different transport sources and aims to inform policies on air quality and health.[75] Scientists from the University of Fribourg are responsible for investigating the effects in advanced tissue models of human secondary organs.

Taken together with existing knowledge and the many ongoing projects worldwide, these efforts are key to creating the evidence base and tools required to strengthen risk assessment, redefine air quality policies, and better protect human health.

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