Exposure to nanoparticles and occupational allergy

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Purpose of review
To provide an update on the possible role of nanoparticles as sensitizing occupational agents and on the influence of nanoparticles-exposure on the appearance/exacerbation of occupational allergy.

Recent findings
Recent case reports, epidemiological studies, and experimental investigations in cellular and animal models demonstrated the potential for nanomaterials to favor/interfere with occupational allergy. First data are emerging on the sensitizing potential of nanoparticles that can act as haptens linking to proteins, with a formation of a 'corona'. Nanoparticles with carrier protein become a complete antigen and induce specific immune response. Moreover, they act as adjuvant favoring sensitization to bound molecules. The disruption of the respiratory and skin barrier, the modulation of immune response toward Th1 or Th2 immune reaction and the interaction with immune effector cells (mast cells and eosinophil in particular) can explain the potential for nanoparticles to exacerbate pre-existing allergic conditions.

Summary
The exposure to nanoparticles represents a possible risk for occupational allergy both in the respiratory tract and in the skin. A deeper knowledge on the role of nanomaterials in the etiology/development of the allergic disease will allow to implement risk assessment and preventive measures for nanosafety in the contest of technological expansion.

Keywords
nanomaterials, nanosafety, occupational allergic contact dermatitis, occupational allergy

INTRODUCTION

Exposure to nanomaterials is increasing in the occupational setting, as they are utilized in a wide range of industries, many people who work outdoors are exposed to ultrafine particles (UFPs) present in pollution, and even the most common work tools, such as laser printers, emit nanoparticles. Nanomaterial exposure is associated with appearance or worsening of allergies, the most common occupational illnesses [1▪,2]: 9–25% of adult-onset asthma cases are of occupational origin [3] and allergic contact dermatitis (ACD) represents 20% of all work-related cutaneous disorders [4]. However, occupational health risks in general (and allergic in particular) associated with nanomaterials are not well established and little information is available on their safe exposure levels, biological interaction and toxicity [5,6▪▪]. Assessing the level of nanoparticles environmental contamination and the internal dose in exposed workers is not easy due to the lack of appropriate measure devices and bioassays and even more difficult for the co-presence of other particles of different type than those of interest [6▪▪]. Furthermore, airborne chemicals can be adsorbed onto nanoparticles that gain new bioactive function [7,8]. Despite the continuous increase in number of workers exposed to nanoparticles there are few reports in literature on nanoparticle specific sensitization in humans [9]. More data are available on nanoparticles worsening pre-existing allergic/immunologic diseases [9]. Moreover, clear demonstration has been shown *in vitro* and in animals on the role of nanoparticles in modulating the immune

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KEY POINTS

- Nanoparticles can act as haptens inducing activation of the adaptive immune system with specific responses.
- Nanoparticles enter immune cells and the nucleus inducing toxic effects or modulating their immune function.
- Nanoparticles have an adjuvant effect that facilitates sensitization to environmental allergens.
- Nanoparticles can damage and cross the epithelial barriers of the airways and skin causing the aggravation of preexisting diseases.
- There are few human studies on the immune potential of nanoparticles, the knowledge gained on the mechanisms derives mainly from *in vitro* and animal studies.

response favoring sensitization to occupational and nonoccupational allergens [9–11].

The aim of this review is to discuss the scientific evidence supporting the role of nanoparticles in the development and/or exacerbation of allergies and to explore mechanisms through which a pathological outcome might derive from professional exposure, analyzing them in the perspective of occupational biosafety of nanowork.

NANOPARTICLE BIOLOGICAL INTERACTIONS

Nanoparticles can enter the human body through inhalation, ingestion and skin absorption, reach tissues and enter cells (Fig. 1) [12]. In cells, nanoparticles can be included within exosomes, that allow them to spread from the capturing cells (macrophage and epithelial or endothelial cells) to the blood stream and other cell types and tissues [13▪]. Metal-based nanoparticles release ions in biological environment (cells, tissues, culture medium, circulation) [14–19]. Physics (dimension, specific surface area, shape, crystal structure), chemistry (elemental components, ion release) and aggregation tendency are responsible for the biological effects of nanoparticles [20,21▪▪]: for instance, BALB/c 3T3 fibroblasts undergo a higher

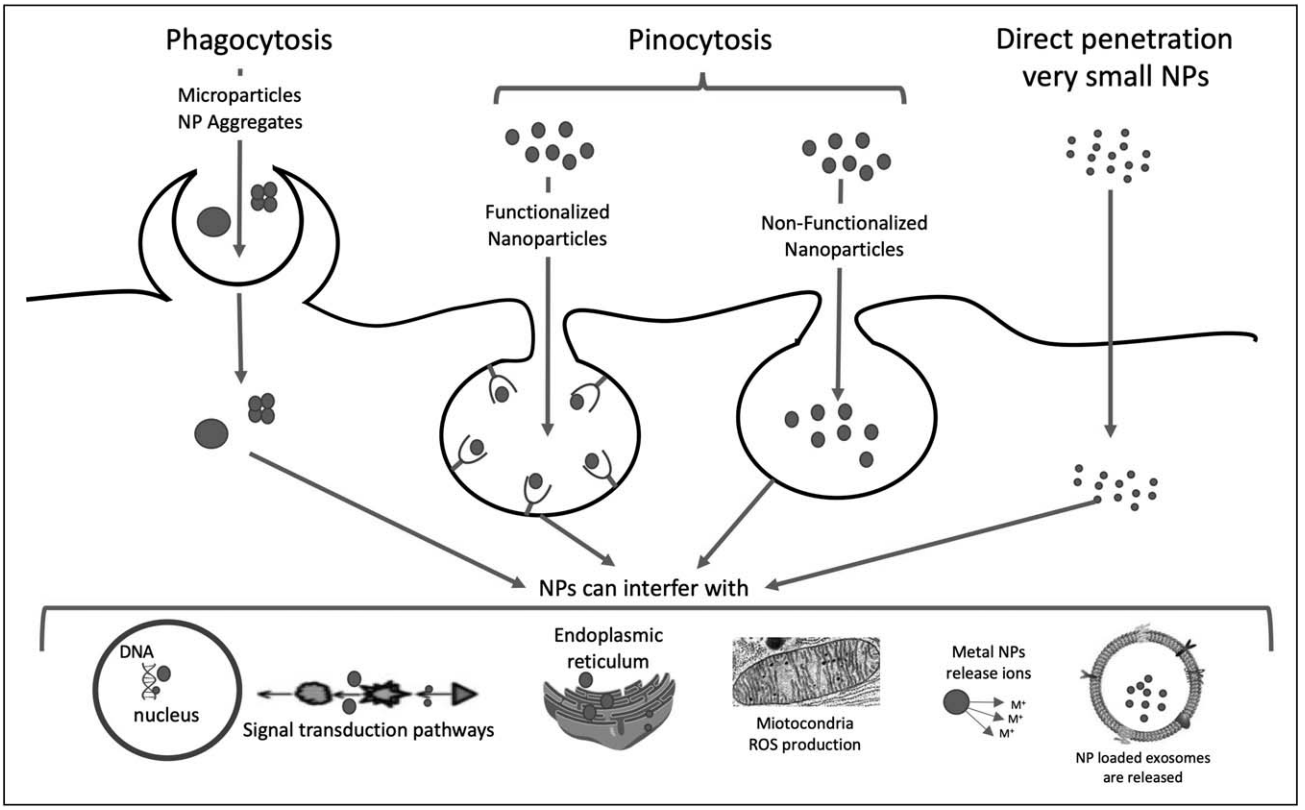

FIGURE 1. Mechanisms of nanoparticle penetration in cells. Microparticles and nanoparticle aggregates enter cells by phagocytosis, smaller nanoparticles by pinocytosis and the very small of diameter <10 nm penetrates directly. Inside the cells, nanoparticles reach the nucleus and can react with DNA, interfere with protein synthesis in the endoplasmic reticulum, interact with mitochondria with ROS production, can be incorporated in exosome that are released and spread all over the body and metal-nanoparticles release ions (responsible for their toxicity).

degree of cell death when exposed to Cobalt(Co)-nanoparticles rather than Co-microparticles and ions, whereas only micro- and nanoparticles have morphological transforming potential [22]. Furthermore, Co-nanoparticles influence innate immunity and apoptosis, whereas microparticles and ions affect different functional pathways [23]. There are definite observations that nanoparticles influence primarily immune cells and that their interaction can modify the immune response [9,10,24,25] and there are data showing the influence of nanoparticles in eliciting, favoring, and treating allergic diseases [1▪,9,11, 26,27▪▪].

NANOPARTICLE-INDUCED OCCUPATIONAL ALLERGY

Most nanoparticles are considered poorly immunogenic in terms of inducing an adaptive immune response [27▪▪]. However, nanoparticles may act as haptens when bound to proteins, with conformational changes which might trigger immune responses [9]. Antigen presenting cells (APCs) can detect and bind nanoparticles by toll-like receptors, through which they deliver signals to the immune system [28,29]. In fact, there is evidence that specific antibodies can be produced against nanoparticle liposomes, synthetic polymers, and fullerenes conjugated with proteins [27▪▪,30] and repeated exposures to gold(Au)-nanoparticles induce a nanoparticle-mediated isotype class switching to immunoglobulin E (IgE) [31].

At present, data on the immune effects of occupational exposure to nanoparticles are essentially based on limited case reports.

A chemist, working in the synthesis of dendrimers, suffered from throat congestion, flushing of the face, rhinitis and erythema multiforme-like. Biopsy of the lesions showed inflammatory infiltration at perivascular and subepidermal areas and confluent epidermal necrosis consistent with the diagnosis of erythema multiforme-like ACD. Symptoms disappeared after 3 weeks out of work and steroid treatment and recurred after re-exposure [32].

Nickel (Ni) allergy with throat congestion, postnasal drip, flushing of the face and skin reactions to earrings, never presented before, was diagnosed in a young healthy nonsmoking female occupationally exposed to dry Ni-nanoparticles powder [33], suggesting that sensitization via inhalation may favor elicitation reactions to other tissues.

A questionnaire-based study showed that workers handling various types of nanoparticles reported sneezing (as direct effect) and ACD (as worsened symptom) [34]. However, there was no clear evidence of a metal specific immune response, or other aspecific (e.g., irritant) mechanisms. In 416 Taiwanese workers, titanium oxide(TiO)-nanoparticles exposure was significantly associated with increased fractional exhaled nitric oxide (FENO) concentrations, in turn significantly associated to asthma, allergic rhinitis, peak expiratory flow rate, and NF-κB in exhaled breath condensate [35]. A study conducted in workers handling carbon nanotubes (CNTs) and nanofibers (CNT/F) demonstrated a significant positive association between respiratory allergy appearance and the amount ($P = 0.040$) and time of exposure ($P = 0.008$), with 18% of workers evidencing CNT/F in sputum [36].

Throat irritation and cough appeared 24 h after the inhalation challenges with zinc(Zn)-nanoparticles in healthy nonsmoking subjects with nanoparticles in concentrations comparable with those of an emission study of galvanized materials (sham, 0.5, 1.0 and 2.0 mg/m3) [37]. Symptoms were associated with increase in neutrophils, interleukin (IL)-8, IL- 6, matrix metalloproteinase and tissue inhibitors of metalloproteinases in induced sputum starting at the lowest Zn-nanoparticle concentration.

Significant increase in tumor necrosis factor-α, IL-6, and IL-8 were found in workers exposed to wood and metal nanoparticles (zinc, manganese, and chromium) respect to office workers [38].

In a prospective panel study, significant higher levels of sCD62P, sCD40 and sTNFR2 were found over a working day in nanoparticle-handling respect non-nanoparticle-handling control workers, without changes in lung function and FENO [39].

However, dermal and respiratory exposure to nanoparticles nearly always occurs contemporary to exposure to other substances to which allergic sensitization easily occurs. Studies are mostly *in vitro* or in animals and the only evidence in humans derives from the study of the influence of UFPs, present in air pollution, on allergic sensitization to environmental allergens. In this case, however, the effects of nanoparticles are in conjunction with those of other chemicals and distinguish the role of various substances is not always easy.

The enhancement of the immunogenicity of the allergens, the increase in the permeability of the airway and skin epithelial barriers, and the enhancement of the Th2 immunological response in the airways and Th1 in the skin are the nanoparticle-induced mechanisms favoring sensitization to co-exposed allergens (Fig. 2).

Some nanoparticle characteristics can impact the biological properties of the nanoparticle-bound allergen. As example, mesoporous Silicon dioxide(-SiO2)- nanoparticles have a higher binding capacity for allergens than nonporous ones with influence on the three-dimensional fold of the protein. The

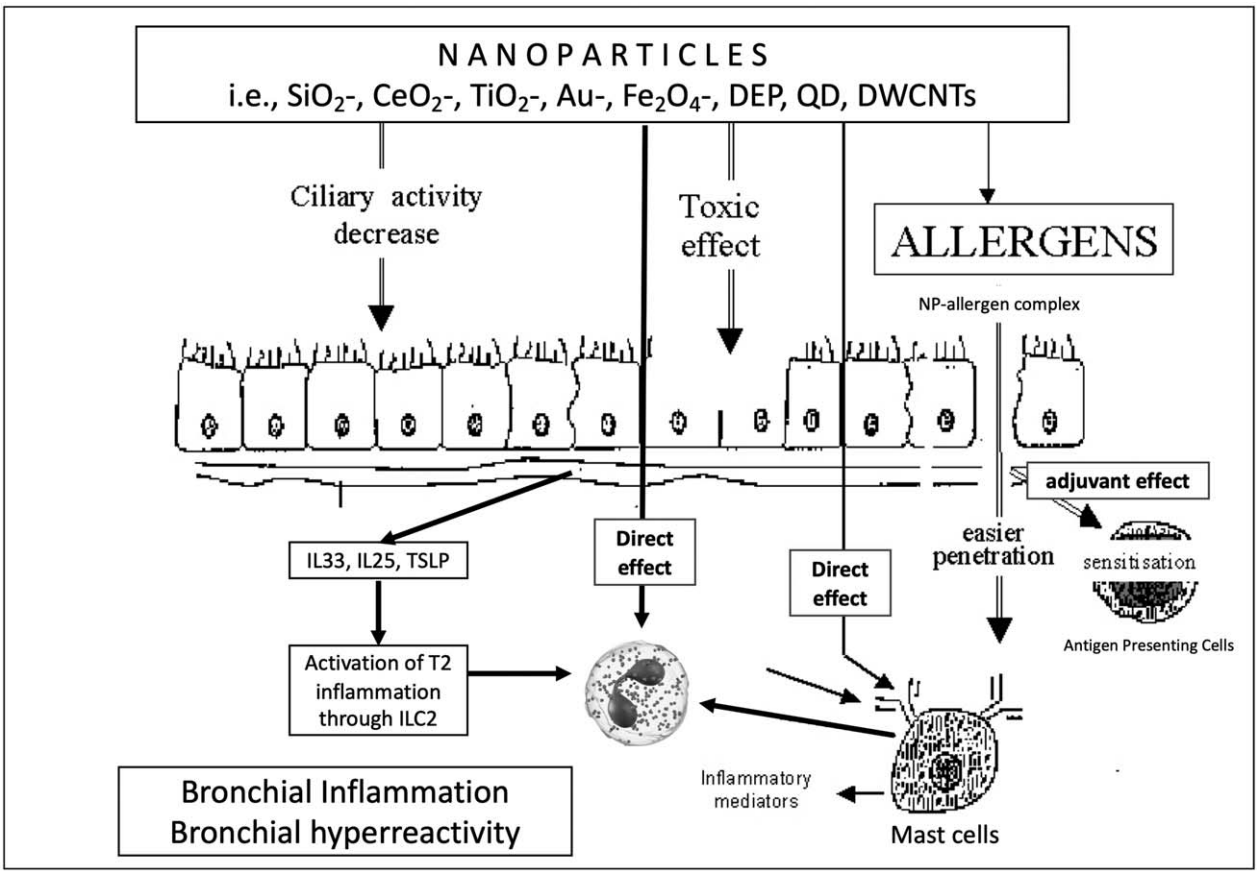

FIGURE 2. Mechanisms of nanoparticle-induced bronchial inflammation and hyperreactivity. Several nanoparticles have a direct toxic effect on ciliary activity and bronchial epithelium allowing easier penetration of allergens alone or conjugated with nanoparticle. The adjuvant properties of nanoparticles facilitate allergic sensitization by inducing antigen presenting cellmaturation and stimulating a Th2 reaction. In sensitized individuals, the allergen reacts with mast cells inducing severe asthma attacks. Nanoparticlescan have a direct effect on mast cells and eosinophils which release chemical mediators, chemokines and cytokines thus inducing inflammation. Damaged epithelial cells produce alarmins (IL33, IL25, TSLP) which promote type 2 inflammation through the activation of type 2 innate lymphoid cells. The resulting inflammation is a direct cause of bronchial hyperreactivity.

allergenic response to the resulting partial unfolded allergens was enhanced, as observed by mediator release assays [40▪▪].

Diesel exhaust particles (DEPs) and UFPs present in air pollution, favor sensitization to associated allergen by its direct effects on the elemental composition of pollens causing numerous cracks in its surface and facilitating pollen content liberation [7,41,42].

Nanoparticles alter the bronchial epithelial barrier, allowing an easy penetration of allergens in the mucosa where they react with immune cells promoting allergen sensitization and inducing a heavy mast cell degranulation with severe reactions. Graphene-nanoparticles (substance composed by a monatomic layer of carbon atoms used in the semiconductor systems and in car batteries) damage the bronchial epithelial barrier altering the phosphorylation level of proteins in the adherens junction and tight junction pathways [43]. TiO2-nanoparticles and SiO2-nanoparticles interact with lipid bilayers, cause dysfunctions of various lipid-rich environments, such as pulmonary surfactants, enhance IL-1a synthesis and induce unbalanced overexpression of immature neurotrophins, leading to apoptotic death of lung epithelial cells [44].

Nanoparticles can bypass the mechanisms that prevent APC/antigen interactions in the respiratory tract [45]. Small hydrophilic nanoparticles with neutral charge evade the mucus layer [46], and nanoparticles, such as TiO2-nanoparticle, ZnO-nanoparticle and Aluminum(Al)- nanoparticle, can escape phagocytic clearance thus increasing the potential interaction with APCs [47].

The simultaneous administration of allergen with SiO2-nanoparticles, Cerium(Ce)O2-nanoparticles, quantum dots, and TiO2-nanoparticles during

sensitization induce in experimental animals a severe asthmatic response, characterized by high allergen-specific antibody levels, inflammatory cell infiltration, and high levels of Th2 cytokine [48–50]. Metallic nanomaterials, in particular iron(Fe)- nanoparticles, TiO2-nanoparticles, and Si-nanoparticles, induce cytotoxicity to lung epithelial cells that release IL-33, TSLP, GM-CSF, and IL-25 with activation of dendritic cells (DCs), disruption of the Th1/Th2 balance in the lung, and amplification of oxidative stress, all factors evidencing an adjuvant effect on sensitization [44,51].

The formation of a 'corona' is a crucial feature of nanoparticles. It is due to the high free energy of nanoparticles that facilitate the interaction with different biomolecules. The complex 'corona-nanoparticles' can change the extrinsic properties of the nanoparticles, but also structure and function of the bound biomolecules. Experiments made with nanoparticles with allergens as 'corona' demonstrated the potential for the complex to induce and modulate the allergic response [52,53▪].

A similar condition can be described in the skin. In fact, immune effects following dermal exposure to an agent are dependent on the degree to which the skin protects from its entry into the body. Nanoparticles skin penetration depends on many factors: intrinsic to nanoparticles (size, hydrophobicity, surface charge, ion releasability and morphology), epidermis status (epidermal thickness, integrity, degree of hydration, and skin pH,) and environmental stimuli (UV exposure) [54–63]. Detailed description of cutaneous disfunction in allergic diseases by exogenous and occupational factors, including nanoparticles, are extensively described [64,65, 66▪]. Epithelial barrier dysfunction is a key factor in the pathogenesis of skin allergy favoring allergen sensitization through transcutaneous route. When in the derma, nanoparticles interact with the immune system triggering a cascade of cytokines characteristic of delayed allergic reactions. It is the case of palladium(Pd)- nanoparticles that favor the release of interferon (IFN)-γ, while inhibiting the tolerogenic IL-10 [67–69] and multiwalled CNTs (MWCNTs) inducing IFN-γ production by mitogen-stimulated T-cells from healthy subjects [70].

Nanoparticles can pass the intact skin barrier via three main pathways: intracellular, intercellular and follicular [71] (Fig. 3). Amphiphilic nanoparticles pass the skin by intracellular route [71]; size, mechanical properties, interference with tight junctions are essential for the intercellular route [72,73]; whereas the follicular route is the main way for metal nanoparticles [74]. Nanoparticles enter cells by endocytotic and nonendocytotic pathway gaining access to the cytoplasm [75] and reaching the nucleus [15]. Metal nanoparticles can release ion into the cells [14,15,18,27▪▪,75–77] so facilitating allergic sensitization and toxicity [15,18,20,21▪▪,22, 76]. Single-walled carbon nanotubes, TiO2-nanoparticles, and C60-nanoparticles are classified as skin sensitizer being able, when internalized into keratinocytes, to interact with skin proteins, to increase CD86 expression and to modulate inflammatory cytokine production [78].

NANOPARTICLES WORSENING ESTABLISHED ALLERGY

Whatever form and chemical species they acquire inside the body, nanomaterials can cause oxidative stress, important factor for the increase of the immunogenicity of allergens [79] for the induction of allergic reactions [80–83] and responsible for lung [84] and skin inflammation [54,85]. The increase in reactive oxygen species (ROS) can worsen already present allergic conditions [45].

Clear demonstration of nanoparticles worsening established allergy has been evidenced for UFPs. In fact, UFPs can favor airway remodeling [86] and lung function decrease especially when associated to reactive chemicals as polycyclic aromatic 6 hydrocarbons (PAHs) from diesel exhaust and other sources [87].

Inflammation is a critical step for the nanoparticle-exacerbated respiratory symptoms in patients with chronic airway diseases [88▪,89]. UFPs, from DEP in particular, trigger airway hyperresponsiveness (AHR) and inflammation via neuro-mediator release with a dose-dependent increase of bradykinin, ATP, and CGRP levels in nanoparticle-exposed normal human bronchial epithelial cells [90].

The increase of AHR and worsening of preexisting asthma after exposure to nanoparticles (as example generated by laser printers) and to CNTs are also evident humans, but the mechanism remains poorly understood [91–94]. Most studies focused on combustion-derived particles, demonstrating the capacity of environmental UFPs to favor the progression of respiratory allergy [95–100]. A negative association between the level of UFP exposure and percentage predicted forced expiratory volume/forced vital capacity ratio has been evidenced. The effects were greater in asthmatics compared to non-asthmatics, indicating an interaction between asthma status and the likelihood of experiencing respiratory symptoms when exposed to UFPs [101].

Silver(Ag)-nanoparticles have the potential to prime mast cells to allergic responses, which could be of particular concern to atopic populations as the large use of Ag-nanoparticles in industrial applications [27▪▪,102,103].

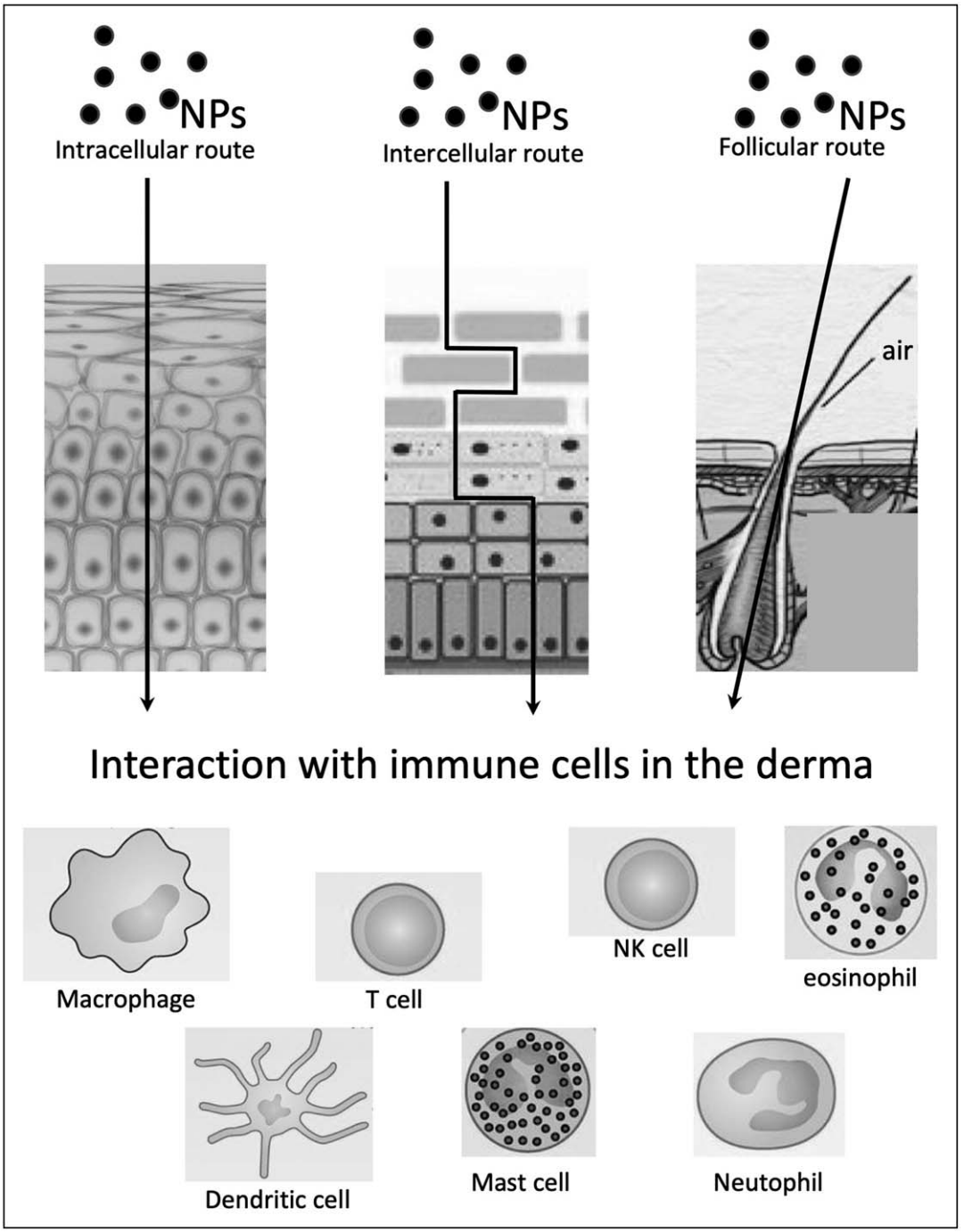

FIGURE 3. Nanoparticles and skin barrier. Nanoparticles can overcome the skin barrier through 3 pathways: the intracellular route, with the conditions and modalities described in Figure 1; the intercellular route for smaller nanoparticles, which interfere with the tight intercellular junctions; the follicular pathway, characteristic of metal-nanoparticles. Upon reaching the dermis, nanoparticles react with immune cells causing inflammation with the appearance or worsening of skin lesions characteristic of ACD or atopic dermatitis.

In the atopic dermatitis model, intradermal injection of amorphous SiO_2-nanoparticles [104], the application of TiO_2-nanoparticles [105], and other metal-nanoparticles [106] induced an aggravation of clinical skin manifestations, depending on the particle size: the smaller the particles the more important the effects [104,107,108].

ACD are induced and worsen by nanoparticles [78], depending on nanoparticle morphology [105], carboxylation [109], and other characteristics as

dimension, shape, surface, potential to penetrate epithelial layer, and interference with cytokine producing immune cells [9–11,20,44,64,110,111]. Interestingly, Au- nanoparticles are unlikely to induce ACD, but in case of skin sensitization to Au-ions, the bronchial exposure to Au- nanoparticles induced increase in bronchoalveolar lavage lymphocyte number, expansion of CD8+ T-cells and exposure-dependent increases in serum IgE [112].

DISCUSSION

Nanoparticles have a wider biodistribution and a greater tissue accumulation compared to their bulk counterparts as consequence of their physicochemical properties. Such wide biodistribution could be particularly important from an allergic point of view because of a possible direct interaction with innate, adaptive immune system and effector cells such as mast cells, basophils, and eosinophils. It is conceivable that these interactions may likely develop in already hypersensitive populations, such as individuals with respiratory or cutaneous allergic diseases with exacerbation of these preexisting allergic conditions.

It is challenging to assess the ability of nanomaterials to induce/worsen allergies to safely develop nanotechnology and nanowork. However, human data demonstrating the potential for nanoparticles to induce or exacerbate allergic diseases are very few. On the contrary, experimental studies *in vitro* and in *in vivo* in animals demonstrated that nanoparticles can act as haptens, become a complete antigen when linked to protein and induce an immune reaction. Moreover, nanoparticles have adjuvant proprieties favoring the sensitization to carried allergens and worsen preexisting allergic conditions. Data collected from experimental studies are affected by a bias due to the extremely undefined characterization of nanomatter once it reaches the human biologic matrixes. In fact, although a precise chemical-physical characterization can be obtained for the standing alone nanomaterials, they do not apply upon interaction of nanoparticles with the organism and the newly acquired properties are virtually not predictable and rather complex to measure. This makes difficult to confidently demonstrate an unequivocable cause-effect relationship. Moreover, to achieve an experimental result, high doses and short time of exposure are applied, whereas the level of contamination is expected to be rather low in the workplace for a chronic mode of exposure.

Despite these limitations, the few human and the many in vitro and animal studies suggest the immunogenic potential of nanoparticles. Therefore, the precautionary principle by limiting exposure to the minimum in the workplace is mandatory. Mitigation measures should be tailored due to the broad variety of potential sources and activities in industrial scenarios. Limited exposure data and the relatively short period since the first exposure may have influenced the incidence of adverse effects found in epidemiological studies. Therefore, exposed workers should be carefully monitored, promoting the collection of all possible adverse events to have as much data as possible on the appearance/worsening of pathological conditions in relation to all morpho/chemical and environmental characteristics of nanoparticle exposure.

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Conflicts of interest

There are no conflicts of interest.

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