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Occupational dermal exposure to nanoparticles and nano-enabled products: Part I—Factors affecting skin absorption

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ABSTRACT

The paper reviews and critically assesses the evidence on the relevance of various skin uptake pathways for engineered nanoparticles, nano-objects, their agglomerates and aggregates (NOAA). It focuses especially in occupational settings, in the context of nanotoxicology, risk assessment, occupational medicine, medical/epidemiological surveillance efforts, and the development of relevant exposure assessment strategies.

Skin uptake of nanoparticles is presented in the context of local and systemic health effects, especially contact dermatitis, skin barrier integrity, physico-chemical properties of NOAA, and predisposing risk factors, such as stratum corneum disruption due to occupational co-exposure to chemicals, and the presence of occupational skin diseases. Attention should be given to: (1) Metal NOAA, since the potential release of ions may induce local skin effects (e.g. irritation and contact dermatitis) and absorption of toxic or sensitizing metals; (2) NOAA with metal catalytic residue, since potential release of ions may also induce local skin effects and absorption of toxic metals; (3) rigid NOAA smaller than 45 nm that can penetrate and permeate the skin; (4) non rigid or flexible NOAA, where due to their flexibility liposomes and micelles can penetrate and permeate the intact skin; (5) impaired skin condition of exposed workers.

Furthermore, we outline possible situations where health surveillance could be appropriate where there is NOAA occupational skin exposures, e.g. when working with nanoparticles made of sensitizer metals, NOAA containing sensitizer impurities, and/or in occupations with a high prevalence of disrupted skin barrier integrity. The paper furthermore recommends a stepwise approach to evaluate risk related to NOAA to be applied in occupational exposure and risk assessment, and discusses implications related to health surveillance, labelling, and risk communication.

1. Introduction

The potential for nanoparticles, nano-objects, their agglomerates and aggregates, (NOAA, defined as having at least one dimension <100 nm) to enter the body through intact skin has been a controversial issue, with some authors asserting that nanoparticles can pass through the stratum corneum, while others disputing this conclusion (Oberdörster et al., 2005; SCCP 2007; Crosera et al., 2009; Labouta and Schneider 2013; Larese Filon et al., 2015).

The skin is a complex organ system comprising the epidermis and dermis, with hair follicles and sweat glands providing pathways across these layers, and peripheral blood flowing into the dermis. The epidermis mainly comprises keratinocytes that migrate from the basal layer towards the skin surface forming the outer protective layer (stratum corneum). The intact stratum corneum provides an effective barrier against bacteria, viruses and most exogenous chemicals. However, the barrier is not completely impervious and it is possible for relatively small molecules, and in theory very small particles, to diffuse across the stratum corneum via cellular and/or inter-cellular pathways. If the barrier is damaged (disrupted) then permeation may be enhanced.

The focus of this work is to review and critically assess the evidence on the relevance and relative significance of various skin

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uptake pathways for NOAA, especially in occupational settings, in the context of nanotoxicology, risk assessment, occupational medicine, medical and epidemiological surveillance efforts, and in development of relevant exposure assessment strategies. Skin uptake of nanoparticles is presented in the context of local and systemic health effects, especially contact dermatitis, skin barrier integrity, physico-chemical properties of NOAA, and predisposing risk factors, such as stratum corneum disruption due to work, co-chemical exposures, and presence of occupational skin diseases. In the accompanying paper by Brouwer et al. (2016) these findings are integrated in an approach for evaluating occupational dermal exposure to nanoparticles. Dermal exposure is approached both conceptually and from the perspective of evidence for exposure, by linking the use of NOAA and nano-enabled products in industrial sectors to job titles. In addition, we flagged specific job titles where there is often a high incidence rate of skin barrier disruption and skin disease. We conclude with recommendations for occupational health practitioners and risk assessors.

In this paper, the term nanoparticle includes both engineered and incidental nanoparticles, as well as their agglomerates and aggregates (ISO, 2011). Nanoparticles embedded in nano-enabled products, such as pastes, paints, glues, etc., are potential sources of dermal exposure to nanoparticles (Aitken et al., 2004, 2006). The term NOAA (nano-objects, and their aggregates and agglomerates) is used throughout the paper to refer inclusively to such nanoparticles. The terms penetration and permeation are used throughout the paper to mean that NOAA can reach the skin layers and pass through the skin respectively.

2. Methods

2.1. Literature review

An extensive literature search was conducted in major databases, including Pubmed, Thompson Reuters Web of Science (ISI), and Google Scholar using search terms “skin absorption nanoparticles” or “skin penetration nanoparticles” or “skin exposure nanoparticles”, “sensitizer and nanoparticles”, “engineered nanoparticles and skin” and similar terms. The period taken into consideration was from 1999 to 31st-12-2015. A total of 810 papers were selected and 132 analysed. The skin absorption data were presented in detail an earlier paper by the authors (Larese Filon et al., 2015) and are summarized here for completeness.

The search for available studies on contact dermatitis in workers was performed on the same database using the term “occupational contact dermatitis” and epidemiology, “irritant contact dermatitis” and epidemiology. A total of 176 papers were selected and 127 were analysed. Additional searches on these same databases and internal databases available at co-authors’ institutions were performed for occupational skin disorders and occupational disease burden by industry sectors. Additional relevant information not available in the peer-reviewed literature (such as reports, white papers, personal communications) from authors’ bibliographies were also analysed.

The abstracts of all studies were reviewed and only papers that were deemed relevant to the current objectives were analysed in detail.

2.2. Summary data on physico-chemical (PC) properties of NOAA and impurities

Certain metals (e.g. nickel Ni) are known to cause allergic contact dermatitis and such metals can be found as engineered nanomaterials, or as impurities in NOAA (Bello et al., 2009). For this reason, we conducted a detailed analysis for metals in NOAA. In generating summary data on PC properties of NOAA and their impurities, authors conducted summary statistical analysis using a large dataset of their own ENM (Hsieh et al., 2013). Some data on PC properties of subclasses of NOAA have been presented in earlier work in the context of exploring links between PC properties and biological oxidative damage, in vitro nanotoxicology, and exposure assessment (Bello et al., 2009; Hsieh et al., 2013). The summary analysis across all available NOAA is new, and utilizes in part a substantial subset of unpublished PC data. The methods for chemical analysis of metals (total and water soluble), organic and elemental carbon, and polycyclic aromatic hydrocarbon (PAHs) have been presented elsewhere (Bello et al., 2009) and includes sector field inductively coupled plasma mass spectrometry (SF ICP-MS), thermogravimetric analysis for carbon speciation into organic and elemental (OC/EC), and gas chromatography mass spectrometry GC–MS for PAHs.

3. Results

3.1. Penetration of NOAA through the skin

NOAAs on the skin may penetrate stratum corneum reaching viable epidermis using different pathways, namely: (a) via sweat glands and hair follicles (Lademann et al., 2009), which are probably the most efficient way for penetration and permeation of large molecules and nanoparticles; (b) via the intercellular route, which is likely only possible for very small NOAAs (<1 to 4 nm, the size of intercellular keratinocyte space) or under conditions where the skin barrier is disrupted. The intracellular pathway (Scheuplein, 1965, 1967) used by chemical substances and ions is not relevant for NOAAs. Skin properties per body parts are relevant for one of the pathways mentioned above. Follicular density varies greatly between different body parts, highly in forehead and lower in calf and thigh. The surface density of hair follicles, which varies by anatomical site and ethnicity, can cover up to 13.7% of skin surface on the forehead but only 0.95% on the forearm (Otberg et al., 2004). Thickness of the skin also varies by body parts. The stratum corneum is thicker in palms and soles (up to 175 and 500 μm, respectively), and much thinner in other anatomical sites (e.g. 22.6–6.4 μm on the abdomen with differences related to the method used; Holbrook and Odland, 1974; Egawa et al., 2007; Robertson and Rees, 2010; Huzaira et al., 2001).

Watkinson et al. (2013) considered that NOAAs behave like large molecules and modelled their rate of penetration using diffusion theory. They concluded that only particles of 1 nm or less are small enough to pass through intact skin. One would further assume that in healthy, intact skin, nanoparticles larger than ~4 nm (maximum intercellular space) cannot normally penetrate. However, there are experimental data that show that NOAAs larger than this size can pass through disrupted skin where intercellular gaps are larger than in normal skin (Labouta and Schneider, 2013; Monteiro-Riviere and Larese Filon, 2012; Monteiro-Riviere and Riviere, 2009; Larese Filon et al., 2009, 2011, 2013; Poland et al., 2013).

The skin penetration and permeation of NOAAs is affected by many factors, including NOAA primary size, NOAA physico-chemical properties (such as rigidity/flexibility of the nanostructure, dissolution rate in water/sweat, and morphology), and skin health. Such factors have been analysed and presented in the following sections.

3.1.1. NOAA size

NOAAs characteristics may change considerably when they interact with physiological media. .Airborne NOAAs, which are emitted as individual nanoparticles, can subsequently agglomerate and settle on the skin and or surfaces. Therefore, the skin will