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REVIEW ARTICLE

Nanoparticle dermal absorption and toxicity: a review of the literature

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Abstract
Introduction Nanotechnologies are among the fastest growing areas of scientific research and have important applications in a wide variety of fields. The data suggest that in the future workers and consumers exposed to nanoparticles will significantly increase.
Dermal absorption and toxicity of nanoparticles At now there are gaps in understanding about the human and environmental risk that manufactured nanoparticles pose for occupational exposed people and for consumers. There is a need for assessing the health and environmental impacts, the nanoparticles life cycle, the human exposure routes, the behavior of nanoparticles in the body, and the risk for workers. Possible routes of entry into the body include inhalation, absorption through the skin or digestive tract, injection, and absorption or implantation for drugs delivery systems. In particular, dermal absorption and skin penetration of nanoparticles needs a better evaluation because few and contradictory data are present in the literature, mainly on titanium dioxide.
Conclusions There are limited data on carbon-based nanoparticles and very few data on other metal nanoparticles increasingly used in industry. The article reviews the literature on the percutaneous absorption of nanoparticles and their effect on skin.

Keywords Skin absorption · Nanoparticles · Review

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Introduction

Nanomaterials are defined as materials that have at least one dimension <100 nm (1 nm = 10^{-9} m) and they can be divided into two large groups: ultrafine nanosized particles not intentionally produced and engineered nanoparticles produced in a controlled, engineered way (Oberdörster et al. 2005a).

Nanotechnologies are among the fastest growing areas of scientific research and have important applications in a wide variety of fields. The corresponding industries would require about two million workers in nanotechnology, and about three times as many jobs in supporting activities (Roco 2005). Nanoscale materials are already being introduced for use in many commercially available products like cosmetics and sunscreens, pharmaceuticals, stain resistant clothing, sports equipment, automobile catalytic converters, dental bonding, cleanings products, dressings for specific wound care strategies, but many are the fields of possible future applications of nanotechnologies as drug delivery systems, nanomedicine, environmental remediation, and cell imaging.

Engineered nanoparticles, because of their big surface-to-volume ratios, exhibit chemical, physical, and biological

properties distinctly different from the same materials in the bulk form, but such properties may lead to adverse effects on human health and environmental systems.

Every year new products containing nanomaterials enter in the market (Woodrow Wilson International Center for Scholars 2007) and in the next future more workers and costumers will come in contact with nanoproducts. Since the toxicological and environmental effects of these compounds are not fully known, there is a need to understand better the health and environmental impacts, the nanoparticles life cycle, the human exposure routes, the behavior of nanoparticles into the body, and the risk for workers in order to use these new materials in a safe way (Dreher 2004; EPA 2007; Gwinn and Vallyathan 2006; Hoet et al. 2004; Nasterlack et al. 2008; Nel et al. 2006; NIOSH 2007; Oberdörster et al. 2005a, b).

Nanotoxicology is an emerging discipline (Oberdörster et al. 2005a) and there is a gap between the nanomaterials safety evaluation and the nanotechnology development that daily produce new materials, new synthesis, new applications, and new products ready for the market. According to the Royal Society & the Royal Academy of Engineering report (2004), nanoparticles should be treated as new chemicals from a risk-point of view because they can overcome the body's normal protective barrier given their size (Nasterlack et al. 2008; NIOSH 2007; Schulte et al. 2008).

Moreover, ultrafine particles, different in sources and composition (Geller et al. 2002), are a component of the airborne particulate matter (Ntziachristos et al. 2007; Pakkanen et al. 2001) and their absorption through inhalation and skin routes must be better studied (Ayres et al. 2008).

Dermal absorption and toxicity of nanoparticles

Possible routes of entry include inhalation, absorption through the skin or digestive tract (Chen and Schluesener 2008), but also voluntary injection, absorption, or implantation for drug delivery systems (Bianco et al. 2005; Guterres et al. 2007; Klumpp et al. 2006; Lademann et al. 2007).

Dermal absorption of chemicals must be considered as risk evaluation (Fiserova-Bergerova et al. 1990; Nielsen and Grandjean 2004; Sartorelli et al. 2007). In particular, the skin is the largest organ of the body accounting for more than 10% of body mass and has an important role of barrier versus the external environment with function of protection, homeostasis maintaining, metabolism, synthesis, and deposition.

Four pathways of penetration across the skin have been identified depending on physicochemical properties of the compound: intercellular, transcellular, and two transappendageal, through hair follicles and sweat glands (Scheuplein 1967).

It is well known that small (<600 Da) lipophilic molecules can easily penetrate the skin passively (Barry 2001), but a variety of factors can influence the extent of the dermal uptake: the skin barrier integrity, the contaminate surface, the anatomical side, and the presence of skin diseases such as allergic and irritant contact dermatitis, atopic eczema, and psoriasis. Moreover, mechanical flexions, irritant detergents, and chemicals (Larese Filon et al. 2006; Nielsen et al. 2007) can increase skin absorption.

There are few studies on nanoparticles skin penetration (Bronaugh 2008; Chen and Schluesener 2008; EPA 2007; Kielhorn et al. 2006; Oberdörster et al. 2005a; SCCP 2007) with discrepancies in results likely related to differences in techniques and methods employed, laboratory conditions, and absence of standardized evaluation protocols. In addition, the respiratory route of entry is every time a matter of concern, while the skin is often considered less permeable and the risk perception by this route is very low (Donaldson et al. 2006; Geiser et al. 2003; Geys et al. 2006, 2007; Lam et al. 2004a; Limbach et al. 2007; Magrez et al. 2006; Muller et al. 2005; Nel et al. 2006; Oberdörster et al. 2005a; Rotoli et al. 2008; Shimada et al. 2006; Shvedova et al. 2005). However, in the literature there are studies which suggest that the skin is an important route of entry for nanoparticles both in occupational and consumer setting.

Alvarez-Roman et al. (2004) have used confocal laser scanning microscopy to visualize the distribution of non-biodegradable, fluorescent, polystyrene nanoparticles (diameters 20 and 200 nm) across porcine skin after 0.5, 1, and 2 h of exposure in vertical diffusion cells. The surface images revealed that polystyrene nanoparticles accumulated preferentially in the follicular openings increasing in a time-dependent manner, and that the follicular localization was favored by the smaller particle size. Tinkle et al. (2003) studied the effects of flexing movement on normal skin nanoparticles uptake showing that mechanical flexion facilitated the penetration of fluorescent dextran micrometer-sized particles that were observed in deeper dermal layers. Kim et al. (2004) found that nanoparticles administered in the dermis migrated to regional lymph nodes, potentially via skin macrophages and Langerhans cells, raising potential concern for immunomodulation.

Carbon-based nanoparticles

Carbon nanomaterials are one of the most important new classes of multifunctional nanoparticles because of their large variety of applications. This class include: (1) carbon nanotubes (CNTs), single-walled (SWCNTs) and multi-walled (MWCNTs), which have diameters ranging from a few to hundreds of nanometers, whereas their length can be

up to a few micrometers, and (2) fullerenes, that have a size less than 100 nm. Modifications and derivatizations of these compounds promise a number of applications in many fields (Tasis et al. 2006).

Actually no data on dermal absorption of CNTs are present in literature while, regarding fullerenes, Rouse et al. (2007) investigated the influence of mechanical flexion on dermal absorption of fullerene amino acid-derivatized peptide nanoparticles using dermatomed porcine skin fixed to a flexing device. Confocal microscopy showed dermal penetration of the nanoparticles at 8 h in skin flexed for 60 and 90 min, while there was no evidence of penetration into the dermis of unflexed skin until 24 h.

Concerning cytotoxicity, in the last few years some studies (Tables 1, 2) have reported possible negative effects of carbon nanomaterials on dermal cells and their possible absorption through the cutaneous barrier. Shvedova et al. (2003) investigated adverse effects of unrefined SWCNTs on cell cultures of immortalized human epidermal keratinocytes, HaCaT, finding that they can cause oxidative stress and cellular toxicity by formation of free radicals, accumulation of peroxidative products, antioxidant depletion, and loss of cell viability. Exposure to nanotubes also resulted in ultrastructural and morphological changes in cultured skin cells. Manna et al. (2005) found an increased oxidative stress and inhibition of cell proliferation in response to treatment of keratinocytes with SWCNTs and suggest that nanotubes can activate Nuclear Factor-kappa B (NF-κB) in a dose-dependent manner. Zhang et al. (2007) investigated the effect of human epidermal keratinocytes exposure to different concentrations of 6-Aminohesanoic acid-derivatized SWCNTs. Results showed an increase of interleukin(IL)-8 release and a decrease in cell viability, suggesting a dose-dependent irritation response.

Sayes et al. (2006a) found that the cytotoxic response of human dermal fibroblasts in culture was dependent on the degree of functionalization of the SWCNTs: as the degree of sidewall functionalization increased, the SWCNTs sample became less cytotoxic. Sarkar et al. (2007) found that SWCNTs-induced oxidative stress in human BJ Foreskin cells with an increase of the products of stress responsive genes. In another study (Tian et al. 2006), the toxic effects of five carbon nanomaterials (SWCNTs, active carbon, carbon black, MWCNTs, and carbon graphite) on human fibroblast cells in vitro was compared. The surface area of the carbon nanomaterials was found to be the best predictor for their potential toxicity. SWCNTs induced the strongest cellular apoptosis/necrosis response. In addition, the refined SWCNTs were more toxic than their unrefined counterpart.

Herzog et al. (2007) studied the toxicity of carbon-based nanomaterials using the clonogenic assay, also called colony formation assay, in order to prevent any interaction with colorimetric indicator dyes normally used. They applied this method to test three types of carbon nanoparticles (two types of SWCNTs and one type of carbon black nanoparticles) on three different cell models including the HaCaT cells. The two types of SWCNT elicit a stronger cytotoxic response than carbon black, but all three particle types were highly effective in inhibiting cell proliferation in all three cell lines. Moreover, HaCaT cells showed decreased cell viability.

Ding et al. (2005) performed the whole genome expression array analysis based on phenotypic measurements on human skin fibroblast cell populations exposed to MWCNTs and multi-walled carbon nano-onions (MWCNOs), showed that exposure to these nanomaterials at cytotoxic doses induced cell cycle arrest and increased apoptosis/necrosis. Multiple cellular pathways were perturbed with material-specific toxigenomic profiles.

Additional studies conducted with proteomic analysis in human epidermal keratinocytes exposed to MWCNTs showed differences in expression and alterations of several proteins, suggesting alteration of intermediate filament expression, cell cycle inhibition, altered vesicular trafficking/exocytosis, and membrane scaffold protein down-regulation (Monteiro-Riviere et al. 2005b). Further two studies showed that MWCNTs, neither derivatized nor optimized for biological applications, were capable of both localizing within and initiating an irritation response in human epidermal keratinocytes (Monteiro-Riviere et al. 2005a) and that MWCNTs were able to alter the expression of protein associated with metabolism, cell signaling, stress, cytoskeletal elements, and vesicular trafficking in human epidermal keratinocytes (Witzmann and Monteiro-Riviere 2006).

Fullerene cytotoxicity seems to depend on their surface derivatization. In two different human cell lines, the lethal dose of fullerene changed over seven orders of magnitude with relatively minor alterations in fullerene structure. Oxidative damage to cell membranes was observed in all cases where fullerene exposure led to cell death (Sayes et al. 2004).

Sayes et al. (2005) found that nano-C60 colloidal suspension disrupts normal cellular functions through lipid peroxidation studying the biological effects of water-soluble fullerene aggregates on human dermal fibroblasts.

Quantum dots

Quantum dots (QDs) are semiconductor nanocrystals consisting of a colloidal core surrounded by one or more surface coatings that give specific characteristics to this nanoparticles. These heterogeneous fluorescent nanoparticles have great potential for use as diagnostic and imaging agents in biomedicine and as semiconductors in the

Table 1 Nanoparticles (NPs) skin absorption studies

Study (year)	Compound (dimensions)	Study type	Outcome
Alvarez-Roman et al. (2004)	Polystyrene NPs (20 and 200 nm)	In vitro: vertical diffusion cells with full-thickness porcine ear skin	NPs accumulation in follicular openings
Baroli et al. (2007)	Two different types of iron-based NPs (<10 nm)	In vitro: vertical diffusion cells with full-thickness human skin	NPs was detected into deepest layers of the epidermis, stratum granulosum, and into the hair follicles
Bennat and Müller-Goymann (2000)	Titanium Dioxide (*)	In vivo: human volunteers—tape stripping In vitro: penetration cells with human skin and cultivated skin	Differences in penetration between different formulations. Microfine titanium dioxide penetrated probably via hair follicles and hair
Cross et al. (2007)	Zinc Oxide (15–40 nm)	In vitro: Franz diffusion cells with human epidermis	No NPs could be detected in the lower stratum corneum or viable epidermis
Gamer et al. (2006)	Titanium Dioxide (80 nm)	In vitro: Franz diffusion cells with porcine skin	Neither microfine zinc oxide nor microfine titanium dioxide was able to penetrate through porcine skin, and that most of the applied material was recovered in the first five tape strips
Kertész et al. (2005)	Titanium Dioxide (*)	In vivo: penetration via human foreskin grafts transplanted to immunodeficient mice	NPs were observed having penetrated into the corneocyte layers of stratum corneum
Kiss et al. (2008)	Titanium Dioxide (*)	In vivo: penetration via human skin transplanted to immunodeficient mice	No evidence of penetration through the intact epidermal barrier
Lademann et al. (1999)	Titanium Dioxide (*)	In vivo: human volunteers—tape stripping	No penetration of microparticles into viable skin tissue. Little amount was found into the hair follicles
Larese et al. (2009)	Silver (25 nm)	In vitro: Franz diffusion cells with full-thickness human skin	Some evidence of penetration through damaged skin
Mavon et al. (2007)	Titanium Dioxide (20 nm)	In vivo: human volunteers—tape stripping In vitro: static diffusion cells with human skin	In vivo and in vitro penetration study showed no titanium dioxide penetration into the viable skin layers
Menzel et al. (2004)	Four different formulations containing Titanium Dioxide.	In vivo: pig skin biopsies	NPs penetrated into the stratum granulosum via intercellular space
NANODERM (2007)	Many different formulations of Titanium Dioxide (*)	In vivo: pig skin biopsies, human healthy and psoriasic skin biopsies, human skin transplanted to immunodeficient mice	The final report concluded that no health effects are expected for topical application of sunscreens containing titanium dioxide NPs (especially when coated) on healthy skin. The situation with psoriatic, sunburned or atopic skin is less clear
Rouse et al. (2007)	Fullerenes (0.7 nm before functionalization)	In vitro: dermatomed porcine skin fixed to a flexing device	Skin flexion increased NPs dermal penetration
Ryman-Rasmussen et al. (2006)	Spherical Quantum Dots (4.6 nm) and ellipsoid Quantum Dots (12 × 6 nm)	In vitro: Porcine skin in flow-through diffusion cells	QDs of different sizes, shapes, and surface coatings could penetrate intact skin in an occupationally relevant dose
Sonavane et al. (2008)	Gold (15 nm, 102 nm and 198 nm)	In vitro: Franz diffusion cells with rat skin	Gold NPs showed size dependent permeation As the size of the NPs increased, permeability coefficient and diffusion coefficient was found to be decreased

Table 1 continued

Study (year)	Compound (dimensions)	Study type	Outcome
Schulz et al. (2002)	Three different type of titanium dioxide formulations (10/15, 20, 100 nm)	In vivo: Human volunteers—skin biopsies	Micronized titanium dioxide was solely deposited on the outermost surface of the stratum corneum but not in deeper stratum corneum layers, in the human epidermis and dermis
Tan et al. (1996)	Titanium dioxide (*)	In vivo: Human volunteers—Tape stripping and skin biopsies	After excision, skin analysis showed that the concentration of titanium in the subjects exposed were higher than in the controls
Trop et al. (2006)	Silver (15 nm)	Case report: one patient treated with silver-coated wound dressing	After 1 week of local treatment in a young, previously healthy, man with 30% mixed depth burns, hepatotoxicity, argyrialike symptoms, and grayish discoloration of the patient's face appeared. Silver levels in plasma and urine were elevated
Zhang et al. (2008)	Quantum dots (39/40 nm)	In vitro: Porcine skin—flow-through diffusion cells	Minimal skin penetration and limited primarily to the outer Stratum Corneum layers

NPs nanoparticles, *SWCNTs* single-walled carbon nanotubes, *MWCNTs* multi-walled carbon nanotubes, *MWCNOs* multi-walled carbon nano-onions, *QDs* quantum dots, (*) characterization not reported or too long to be reported in the tables

electronic industry, but their potential human toxicity and cytotoxicity have to be evaluated (Hardman 2006).

Ryman-Rasmussen et al. (2006) carried out a study in which soluble QDs of two sizes with three different surface coatings were applied to porcine skin in flow-through diffusion cells. Their findings showed that QDs of different sizes, shapes, and surface coatings could penetrate intact skin in an occupationally relevant dose within the span of an average-length work day. Zhang et al. (2008) obtained different results using another type of QDs: their conclusions suggest that porcine skin penetration of QD621 is minimal and limited primarily to the outer stratum corneum layers and near hair follicles (see Table 1).

Ryman-Rasmussen et al. (2007) used human epidermal keratinocytes to assess if soluble QDs of two sizes with three different surface coatings (polyethylene glycol (PEG), PEG-amines, or carboxylic acids), induced toxic effects on skin cells. Exposure of keratinocytes to QDs significantly increased cell release of IL-1b, IL-6, and IL-8. These findings suggest that surface coating of QDs does not influence the uptake by keratinocytes but is a primary determinant of cytotoxicity and immunotoxicity. Similar results were found by Zhang et al. (2008) using a different type of water-soluble QDs with a cadmium/selenide core and a cadmium sulfide shell coated with PEG. Another study carried out by Rouse et al. (2008) investigated the effects of applied strain on QDs uptake by human keratinocytes. Their data indicated that addition of strain resulted in an increase in cytokine production and QDs uptake, with irritation and reduction of cell viability. These data suggest that application of physiological load conditions can increase cell membrane permeability, thereby increasing nanoparticle concentration in cells.

Titanium dioxide and zinc oxide

Titanium dioxide (TiO_2) and zinc oxide (ZnO) are largely present in many sunscreens formulations to protect against UV-induced skin damage. When exposed to UV radiation, TiO_2 and ZnO do not undergo any chemical decomposition and for that reason they represent an alternative to chemical agents. Moreover, they offer a wider range of protection compared to other organic compounds. Actually, in many formulations TiO_2 and ZnO are included as nanosized particles because in this form they are transparent and more esthetically acceptable to the consumers. Furthermore, TiO_2 nanoparticles are used in other several products (sport clothes, surface cleaning agents, computer devices) of the everyday life and the exposure occasions are increasing day-by-day.

Tan et al. (1996) performed a pilot study on percutaneous absorption of microfine TiO_2 from sunscreens applying the formulation to the skin for 2–6 weeks to 13

Table 2 Nanoparticles (NPs) cells toxicity studies

Study (year)	Compound (dimensions)	Type of cells	Outcome
Berry et al. (2004)	Iron Oxide (10 nm)	Human dermal fibroblasts	NPs caused disruption to cell cytoskeleton and reduced proliferation
Ding et al. (2005)	MWCNTs and MWCNOs (*)	Human dermal fibroblasts	Exposure to NPs at cytotoxic doses induced cell cycle arrest and increased apoptosis/necrosis
Herzog et al. (2007)	Two types of SWCNTs and Carbon Black NPs (*)	Human epidermal keratinocytes	NP inhibited cell proliferation and decreased cell viability
Kiss et al. (2008)	Titanium Dioxide (9 nm)	Human epidermal keratinocytes human dermal fibroblasts primary human melanocytes human immortalized sebaceous gland cells	NPs exerted significant and cell-type dependent effects on cellular functions, such as viability, proliferation, apoptosis and differentiation
Lam et al. (2004b)	Silver (*)	Human epidermal keratinocytes	Proliferation was significantly inhibited and cell morphology affected
Manna et al. (2005)	SWCNTs (*)	Human epidermal keratinocytes	NPs increased oxidative stress and inhibited cell proliferation
Monteiro-Riviere et al. (2005a)	MWCNTs (*)	Human epidermal keratinocytes	NPs localized within the cells and initiated an irritation response, inducing the release of proinflammatory cytokine
Monteiro-Riviere et al. (2005b)	MWCNTs (*)	Human epidermal keratinocytes	NPs caused alteration of several protein expression
Paddle-Ledinek et al. (2006)	Silver (*)	Human epidermal keratinocytes	NPs reduced cell proliferation and affected cell morphology
Papageorgiou et al. (2007)	Cobalt chrome alloy (30 nm)	Human dermal fibroblasts	NPs induced DNA damage, aneuploidy and cytotoxicity. NPs appeared to disintegrate within the cells with the creation of electron dense deposits which were enriched in cobalt
Poon and Burd (2004)	Silver (*)	Human epidermal keratinocytes - human dermal fibroblasts	The contact between cells and silver released from a type of wound dressing determined a reduction in cell metabolism and vitality. Fibroblasts appeared to be more sensitive to silver than keratinocytes
Rouse et al. (2008)	Quantum Dots (6 × 12 nm)	Human epidermal keratinocytes	Applied strain caused an increase in cytokine production and QDs uptake, resulting in irritation and decreasing cell viability
Ryman-Rasmussen et al. (2007)	Two types of Quantum Dots (4.6 nm and 6 × 12 nm, before coating)	Human epidermal keratinocytes	Exposure to QDs significantly increased cell release of interleukines. Surface coating of QDs did not influence the uptake but was a primary determinant of cytotoxicity and immunotoxicity
Sarkar et al. (2007)	SWCNTs (*)	Human BJ Foreskin cells	NPs inducted oxidative stress and increased the expression of stress responsive genes
Sayes et al. (2004)	Fullerenes (60 nm)	Human dermal fibroblasts	The lethal dose of NPs changed depending on their surface derivatization. Oxidative damage to cell membranes was observed in all cases where NPs exposure led to cell death
Sayes et al. (2005)	Fullerenes (60 nm)	Human dermal fibroblasts	NPs colloidal suspension disrupted normal cellular functions through lipid peroxidation

Table 2 continued

Study (year)	Compound (dimensions)	Type of cells	Outcome
Sayes et al. (2006a)	SWCNTs (*)	Human dermal fibroblasts	Cytotoxic response was dependent on the degree of functionalization of the NPs: as the degree of sidewall functionalization increased, the NPs became less cytotoxic
Sayes et al. (2006b)	Three types of Titanium Dioxide (10.1 nm, 3.2 nm, 5.2 nm)	Human dermal fibroblasts	Cytotoxicity and inflammation were observed only at relatively high concentrations. The extent to which NPs affected cellular behavior did not depend on surface area. Cytotoxicity was related to the phase composition of NP
Shvedova et al. (2003)	SWCNTs (*)	Human epidermal keratinocytes	Exposure to NPs resulted in oxidative stress and cellular toxicity, with formation of free radicals, accumulation of peroxidative products, antioxidant depletion, loss of cell viability and ultrastructural and morphological changes.
Tian et al. (2006)	SWCNTs, active carbon, carbon black, MWCNTs and carbon graphite (*)	Human dermal fibroblasts	SWCNTs induced the strongest cellular apoptosis/necrosis. Surface area was the best predictor for the potential toxicity of these refined carbon nanomaterials
Witzmann and Monteiro-Riviere (2006)	MWCNTs (*)	Human epidermal keratinocytes	NPs were able to alter the expression of proteins associated with metabolism, cell signaling, stress, cytoskeletal elements and vesicular trafficking
Zhang et al. (2007)	SWCNTs (*)	Human epidermal keratinocytes	Exposure resulted in a dose-dependent irritation response with an increase in IL-8 release and a decrease in cell viability
Zhang et al. (2008)	Quantum Dots (39/40 nm)	Human epidermal keratinocytes	Cell viability decreased, and IL-6 and IL-8 release increased, both significantly. NPs were found in cytoplasmic vacuoles and at the periphery of the cell membranes

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selected volunteers scheduled to have skin surgery for a total of 16 skin biopsies. After excision, the stratum corneum was removed from the skin samples by tape stripping and the concentration of titanium after digestion of the skin was evaluated. The titanium concentration on the skin biopsies of the subjects exposed to the microfine TiO_2 was higher than the controls.

These findings were not confirmed by other researchers who did not observe penetration of nanoparticles in the viable layers of the epidermis using different TiO_2 nanoparticle formulations and different investigative techniques. A small amount of metal oxide was only detected into the hair follicles following application to volunteers (Lademann et al. 1999).

Mavon et al. (2007) used the tape stripping method in in vivo experiments on volunteers after exposure to a sunscreen formulation containing TiO_2 nanoparticles. Transmission electron microscopy (TEM) and particle-induced X-ray emission (PIXE) techniques were used to localize the TiO_2 in skin sections in in vitro experiments by the same Authors. In this in vivo and in vitro permeation study no TiO_2 was detected in the follicle, viable epidermis or dermis, and more than 90% of the applied sunscreen was recovered in the first 15 tape strippings while the remaining 10% was localized in the furrows and in the opened infundibulum.

Schulz et al. (2002), using optical and electron microscopy, proved that neither surface characteristics and particle size nor shape of the micronized pigments result in any dermal absorption of this substance. Micronized TiO_2 was solely deposited on the outermost surface of the stratum corneum, but not in deeper stratum corneum layers, the human epidermis and the dermis.

The three-year European project NANODERM involved a great number of research groups in the evaluation of skin permeation of different TiO_2-based sunscreens. The project provided many data from in vivo and in vitro experiments with human and porcine skin, with human foreskin transplanted to immunodeficient mice, and with dermal cells in culture.

Some Authors involve in the project detected a little amount of titanium dioxide in the deeper viable epidermal layers using spatially resolved ion beam analysis (PIXE, RBS, STIM, and secondary electron imaging) on freeze-dried cross sections of pig skin biopsies (Menzel et al. 2004), while other Author reported that TiO_2 nanoparticles do not penetrate through the stratum corneum of human skin transplants (Kertész et al. 2005; Kiss et al. 2008).

The project report confirmed the safety of the sunscreens formulation containing TiO_2 nanoparticles, reporting no evidence of nanoparticle transcutaneous penetration (NANODERM 2007).

Instead, Bennat and Müller-Goymann (2000) found that different formulations had different penetration: according with their experiments, microfine TiO_2 penetrated deeper into human skin from an oily dispersion than from an aqueous one, and encapsulation of the pigments into liposomes caused a higher penetration into the skin. Furthermore, penetration was greater when applied to hairy skin, suggesting a surface penetration through hair follicles or pores.

Also Gamer et al. (2006) investigated the in vitro absorption of microfine ZnO and TiO_2 in cosmetic formulations through porcine skin. One ZnO formulation and two TiO_2 formulations were tested in modified Franz static dermal penetration cells. In their conclusions Authors observed that neither microfine ZnO nor microfine TiO_2 was able to penetrate through porcine skin, and that most of the applied material was recovered in the first five tape strips, indicating that the material did not penetrate into the deeper layers of the skin.

ZnO skin absorption was investigated by Cross et al. (2007) using Franz-type diffusion cells. Two different formulations of 26–30 nm ZnO particles and one placebo cream base formulation containing no ZnO nanoparticles were compared. Authors found that less than 0.03% of the applied zinc content was detected in the receptor phase (not significantly different following application of a placebo formulation). No particles could be detected by in the lower stratum corneum or viable epidermis by electron microscopy, suggesting that minimal nanoparticle penetration occurs through the human epidermis (see Table 1).

Some Authors suggested that nanoparticles can elicit a photocatalytic activity into the dermal layers causing formation of free radicals in skin cells, damaging DNA (Cai et al. 1992; Dunford et al. 1997; Wamer et al. 1997; Serpone et al. 2001), disrupting normal cell functions and cell viability (Sayes et al. 2006b). So the debate is just open about their safety use.

Silver and gold nanoparticles

Owing to their strong antibacterial activity, silver nanoparticles are largely used as a component of various commercially available products such as textiles, medical devices, contraceptives, water disinfectants, and room spray (Woodrow Wilson International Center for Scholars 2007). Moreover, nanosilver is used for treatment of wounds and burns, as well as for coating on implants.

Some Authors suggested an increased dermal penetration of nanosilver associated with damaged skin in in vitro experiments (Larese Filon et al. 2009) or following the use of nanosilver coated dressings in case of extensive burns (Trop et al. 2006).

Traditionally, silver is relatively non-toxic to mammalian but can cause argyria or argyrosis in subjects with chronic occupational exposure. Because of the extensive presence of nanosilver in textiles, wound dressing, sport clothes, and other products which come in direct contact with the skin, dermal exposure must be carefully evaluated.

Keratinocytes and fibroblasts in culture were used to assess the cytotoxic effects of nanosilver released from several types of silver containing dressings (Table 2) although some laboratory and clinical studies suggested their dermal biocompatibility (Leaper 2006; Supp et al. 2005; Muangman et al. 2006; Wright et al. 2002). The results of these studies showed that keratinocytes proliferation was significantly inhibited and cell morphology affected after exposure to extracts of nanocrystalline coated dressings (Paddle-Ledinek et al. 2006; Lam et al. 2004b). Poon and Burd (2004) found that nanosilver crystallines were toxic to both keratinocytes and fibroblasts, and that fibroblasts appeared to be more sensitive to silver than keratinocytes.

Nanogold is also an interesting nanomaterial for its applications in cell imaging, cancer therapy, tissue welding, and nanomedicine. Sonavane et al. (2008) investigated the in vitro cutaneous penetration of three types of gold nanoparticles differing in size (15, 102, and 198 nm) using the Franz diffusion cell method with rat skin. Gold nanoparticles showed size-dependent permeation through rat skin. Fifteen nanometers of gold nanoparticles showed higher permeation compared to 102 and 198 nm gold nanoparticles. TEM study of rat skin revealed accumulation of smaller size gold nanoparticles in deeper region of skin whereas larger particles were observed mainly in epidermis and dermis.

Regarding the cytotoxicity of gold nanoparticles, a number of studies have argued its safe use because the uptake of gold clusters (1.4 nm) by different types of cells and their interaction with DNA have been demonstrated (Connor et al. 2005; Liu et al. 2003; Tsoli et al. 2005).

Pernodet et al. (2006) investigated the effects of citrate/gold nanoparticles at different concentrations and exposure times on human dermal fibroblasts. They found that, as a result of the intracellular nanoparticle presence, actin stress fibers disappeared, thereby inducing major adverse effects on cell viability. Properties such as cell spreading and adhesion, cell growth, and protein synthesis to form the extracellular matrix were altered dramatically, suggesting that the internal cell activities were damaged.

Other metals and metal oxides

Researchers are developing a number of metal and alloy nanoparticles for either various applications in industrial processes, such as catalyst, fillers, semiconductors, or for systemic drug administration, but very few data regarding their toxicity are available in literature.

It is well known that metal and metal oxide powders once placed in biologic media can release metal ions (Midander et al. 2007) that can subsequently pass through the skin (Larese Filon et al. 2007) but little is known about skin penetration of metal nanoparticles.

Berry et al. (2004) found that underivatized iron oxide nanoparticles (8–15 nm) were rapidly endocytosed into cultured human dermal fibroblasts causing disruption to the cell cytoskeleton and a decrease in proliferation. The same nanoparticles, transferrin derivatized, stimulated cell proliferation and were not internalized, but appeared to attach to the outside of the cell membrane, most likely to cell-expressed transferring receptors.

Baroli et al. (2007) demonstrated that iron-based rigid nanoparticles smaller than 10 nm were able to passively penetrate the skin through the SC lipidic matrix and hair follicle orifices, reaching the deepest layers of the SC, the stratum granulosum, and hair follicles. In rare cases, nanoparticles were also found in the viable epidermis.

Papageorgiou et al. (2007) compared the cytotoxic and genotoxic effects of nanoparticles and micron-sized particles of cobalt-chrome alloy in cultured human fibroblasts. Nanoparticles, which caused more free radicals in an acellular environment, induced more DNA damage than micron-sized particles using the alkaline comet assay. Nanoparticles appeared to disintegrate within the cells faster than microparticles with the creation of electron dense deposits, which were enriched in cobalt. The mechanism of cell damage appeared to be different after exposure to nanoparticles and microparticles.

Discussion and conclusions

Experimental findings on skin absorption and skin toxicity of nanoparticles are contradictory. More data are needed to better define and understand if skin represents a route of entry of nanoparticles into the body or a target tissue. In the final report of the project NANODERM it is stated that adverse health effects for the topical application of sunscreens containing TiO_2 nanoparticles (especially when coated) are not expected for healthy skin but several other studies on carbon-based nanoparticles and quantum dots confirm an interaction between human dermal cells and nanosized particles. The shortage of data about many types of new compounds, such as metals and metal oxides, calls for more studies to improve understanding of nanoparticle skin absorption. Quantitative data are needed because there is evidence that some nanoparticles can pass through the skin in particular conditions such as wounds, flexures sites and lesions.

Moreover, nanoparticles characterization should be essential in the future studies on dermal penetration and toxicity. Size, shape, coating, purity, presence of catalysts, extent of agglomeration and agglutination of the nanoparticles could influence the amount permeating the skin, and the toxicity of the nanomaterials.

Finally, to investigate the interaction between new nanocompounds and the human skin the researchers have to take into consideration several exposure variables, such as anatomical exposure sites, extension of the exposition area, time of exposition, chronic and repeated exposure, presence of skin diseases, and the role of cleanser and penetration enhancer.

The classic investigation protocols must be adapted and re-standardized to the new nanosized compounds. Cell cultures (Bernstein and Vaughan 1999), Franz diffusion cells (Franz 1975), tape stripping (Escobar-Chávez et al. 2008), human skin implantations on animals, remain powerful tools to study particle interaction with human dermal tissue. Furthermore new methods and new technique applications have to be developed (Monteiro-Riviere and Inman 2006; SCCP 2007). In particular microscopy techniques like Coherent anti-Stokes Raman Scattering (CARS), Transmission Electron Microscopy (TEM), Confocal Laser Scanning Microscope (CLSM), and other ion beam techniques are necessary to visualize nanoparticles into biologic structures (Moger et al. 2008).

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