Cosmetics, nanotoxicity and skin penetration – a brief summary of the toxicological and skin penetration literature

Summary

There is a growing body of evidence that nanomaterials commonly found in sunscreens, cosmetics and personal care products can be toxic. We do not yet know whether or not nanomaterials in these products are likely to penetrate skin and in what circumstances. It does appear that penetration of intact skin by some nanomaterials will be possible in some circumstances. Furthermore, broken skin is an ineffective particle barrier, suggesting that the presence of acne, eczema, shaving wounds or severe sunburn may enable nanoparticle uptake more readily.

The risks of engineered nanomaterials have been recognised at the highest scientific levels, but remain effectively unregulated

The world's oldest scientific organisation, the United Kingdom's Royal Society, has warned that we should not continue to release products containing engineered nanomaterials until we have vastly improved requirements for safety testing[1]. In 2004 the Royal Society recommended that nanomaterials should be assessed as new chemicals[2], and that "ingredients in the form of nanoparticles should undergo a full safety assessment by the relevant scientific advisory body before they are permitted for use in products"[3]. The Royal Society also recommended that products containing nanoscale ingredients should be clearly labelled, to enable people to make an informed decision about using these products[4].

But despite recognition at the highest scientific levels that nanomaterials present new risks that require new types of safety testing, there are as yet no regulations anywhere in the world that require nanomaterials to undergo new safety assessments prior to their inclusion in products. There is similarly no requirement anywhere in the world for labelling of nano-scale ingredients to allow the public to make an informed choice about using products that contain engineered nanomaterials.

There is a growing body of scientific evidence that nanomaterials commonly found in sunscreens, cosmetics and personal care products can be toxic

The toxicity risks of nanomaterials remain poorly studied and poorly understood. However a growing number of peer-reviewed scientific studies have demonstrated both the potential for nanomaterials currently used in sunscreens, cosmetics and personal care products to present serious toxicity risks for human health[5] and the capacity for nanomaterials to penetrate the skin in at least some circumstances[6] (see below).

Research has shown that many types of nanomaterials can be toxic to human tissue and cell cultures, resulting in increased oxidative stress, inflammatory cytokine production, DNA mutation and even cell death[7]. Nanomaterials are more readily taken up by the human body than larger sized particles and are able to cross biological membranes that larger sized particles normally cannot[8]. Once in the blood stream, nanomaterials are transported around the body and can be absorbed into vital organs including the heart, kidney, liver and spleen[9]. Unlike larger particles and materials, nanomaterials may be transported within cells and be taken up by cell mitochondria[10] and the cell nucleus[11], where they can cause major structural damage.

The small size, greater surface area and greater chemical reactivity of nanomaterials results in increased production of reactive oxygen species, including free radicals[12]. Production of reactive oxygen species has been found in a diverse range of nanomaterials including nanoparticle metal oxides[13] commonly used in sunscreens and cosmetics and carbon fullerenes[14] that are used in some face creams and moisturisers. Reactive oxygen species

and free radical production is one of the primary mechanisms of nanotoxicity; it may result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA[15].

Exposure to nanoparticle titanium dioxide, used in large numbers of sunscreens, cosmetics and personal care products, has been shown to cause far greater cell damage than larger particles of titanium dioxide. It has been demonstrated that whereas 500nm titanium dioxide particles have only a small ability to cause DNA strand breakage, exposure to 20nm particles of titanium dioxide causes complete destruction of supercoiled DNA, even at low doses and in the absence of exposure to UV[16]. Also in the absence of UV light, *in vitro* exposure to nanoparticle titanium dioxide resulted in the production of reactive oxygen species in human brain cells[17] although it is not yet known whether these reactive oxygen species damage brain neurons. Pilot data indicate that nanoparticle titanium dioxide results in cell death in cultured neurons at concentrations >20ppm after 24 hours exposure[18]. These data also indicate that in addition to the production of reactive oxygen species, both nanoparticle titanium dioxide and nanoparticle zero valent iron affect ATP levels and result in mitochondrial depolarization[19].

Silver nanoparticles are highly toxic to pathogens and bacteria[20]. They are now used in some toothpaste, soaps and face creams, and are used widely in antimicrobial formulations and wound dressings[21]. However recent studies demonstrate that silver nanoparticles are also highly toxic to mammalian cells *in vitro*, in the absence of photo-activation. Exposure of rat neuronal cells to nanoparticle silver led to a decrease in their size, irregularities in their shape and a significant dose-dependent decrease in mitochondrial function[22]. Silver nanoparticles were also demonstrated to be highly toxic to *in vitro* mouse germline stem cells, "drastically reducing mitochondrial function and cell viability" even at low concentrations[23]. Silver nanoparticles were similarly highly toxic to *in vitro* rat liver cells; low level exposure resulted in oxidative stress, cellular shrinkage and impaired mitochondrial function[24]. In the same experiment, exposure to higher concentrations of nanoparticle titanium dioxide, iron oxide and aluminium each caused significant oxidative stress mediated damage to the rat liver cells.

The toxicity of fullerenes, currently being used in some face creams and moisturisers, remains poorly understood. However some early experiments have demonstrated the potential for some forms of fullerenes to be toxic. Carbon fullerenes (buckyballs) have been found to cause brain damage in fish[25], kill water fleas and have bactericidal properties[26]. Even low levels of exposure to water soluble fullerenes have been shown to be toxic to human liver cells carcinoma cells and dermal fibroblasts *in vitro*[27]. Fullerene-based amino acid nanoparticles have been found to decrease the viability of human epidermal keratinocytes and initiate a pro-inflammatory response[28]. Toxicity appears to be a function of both surface structure[29] and also the extent of aggregation, where different solvents or emulsion bases are key variables in the formation of aggregates[30].

The potential for nanomaterials in sunscreens and cosmetics to result in harm is made greater as production of reactive oxygen species and free radicals increases with exposure to UV light[31]. Photo-activated nanoparticle titanium dioxide and zinc oxide have been demonstrated to cause oxidative damage to DNA in cultured human fibroblasts[32]. Photo-activated titanium dioxide nanoparticles have also been shown to cause oxidative stress-mediated toxicity in *in vitro* skin fibroblasts and nucleic acids[33] and in human colon carcinoma cells[34]. In the presence of biological reducing agents (eg NADH) similar to the concentrations found in biological systems, reactive oxygen species generated by photo-activated fullerenes C_{60} and C_{70} resulted in cleavage of supercoiled DNA *in vitro*[35].

We do not yet know whether penetration of intact skin by nanomaterials commonly found in sunscreens and cosmetics is possible, or likely, although we do know that broken skin is an ineffective particle barrier

If nanoparticles are able to penetrate the stratum corneum (outer layer of dead skin cells) and gain access to the living cells within the epidermis and the dermis, they can join the blood stream and circulate around the body with uptake by cells, tissues and organs[36]. Some

cosmetics manufacturers, and even the Australian Therapeutic Goods Administration[37], claim that the potential for nanomaterials in sunscreens and personal care products to be toxic to living cells and tissues is not a serious concern because nanoparticles remain in the outer layers of dead skin. The problem is that no one knows if this assertion is accurate.

We do know that broken skin is an ineffective barrier and enables particles up to 7,000nm in size to reach living tissue[38]. This suggests that the presence of acne, eczema or shaving wounds is likely to enable the uptake of nanoparticles. The Royal Society has called for additional research into the influence of skin condition, including sun burn, on the uptake of nanomaterials, especially in the assessment of nanomaterials found in sunscreens and cosmetics[39]. However the fact that many cosmetics and personal care products are used on blemished skin or following shaving has been largely ignored in the discussion about skin uptake of nanomaterials found in personal care products to date.

Penetration of intact skin is in part dependent on particle size, meaning that skin uptake of nanomaterials is comparably more likely than uptake of larger particles[40]. However we still have a poor understanding of the other key variables that influence skin penetration. These variables include: physicochemical properties of nanomaterials (eg shape, surface charge, surface coatings, composition, solubility); the presence of other substances or solvents that act as penetration enhancers; and the condition of skin (eg abrasions, blemishes, age).

Penetration of intact pig skin by “quantum dots” of a diameter of 6nm and 10nm, three different surface coatings, and neutral, positive and negative surface charge has been demonstrated in a recent study[41]. The authors of the study state: “our findings indicate that skin is permeable to nanomaterials with diverse physicochemical properties. If true, skin would serve as a portal of entry for occupational and consumer exposures to a diversity of engineered nanostructures”[42].

However despite the fact that many sunscreens, cosmetics and personal care products are designed to be applied directly to the skin on a daily basis, there are few published, peer-reviewed studies that investigate the ability of engineered nanomaterials commonly found in these products to penetrate the skin[43]. Studies investigating the skin penetration of metal oxides, for example titanium dioxide and zinc oxide, do not adequately investigate key variables that influence skin penetration as described above. There are many metal oxides commonly used in sunscreens and cosmetics for which no skin penetration studies appear to have been published (eg nanoparticle silver oxide, nanoparticle aluminium oxide, nanoparticle iron oxide). There are still no published studies relating to skin penetration of fullerenes[44], despite the increasing incidence of fullerenes in face creams and moisturisers.

Preliminary study of the ability of zinc oxide and titanium oxide nanomaterials to penetrate the skin has produced conflicting results. Most studies found that these nanomaterials did not penetrate the stratum corneum[45]. Conversely, a pilot study suggested that skin absorption of titanium dioxide nanomaterials took place[46], a further pilot study suggested skin absorption of larger particles of both zinc oxide and titanium dioxide occurred from both a water and oily base[47], and one study demonstrated that nanoparticle titanium dioxide penetrated into the deeper layers of the stratum corneum in oily and liposome test emulsion bases[48]. This latter finding is of note even though penetration to the epidermis and dermis was not demonstrated; given the likely underestimation of skin penetration by *in vitro* models, “evidence of dermal penetration in a diffusion cell model should be of concern, regardless of the dermal depth observed *in vitro*[49]”. Pilot data indicates that amino-acid substituted fullerenes can penetrate intact skin to reach all epidermal layers, and that this penetration was “greatly enhanced” in the presence of surfactant[50].

The limitations of the skin penetration studies conducted to date mean that we cannot yet draw conclusions about whether or not engineered nanomaterials commonly used in sunscreens and cosmetics can penetrate the skin, and in what circumstances. It does appear that skin penetration by some nanomaterials will be possible in at least some circumstances. Publicly funded research into the interactions between nanomaterials and the skin is being

undertaken, in the European Union, the United States and elsewhere. However little of this information has yet been published in peer-reviewed, publicly accessible literature, and most studies are likely to continue for several years before publishing their results.

The limitations of existing skin penetration studies mean that we cannot draw conclusions about whether skin penetration by nanoparticles is possible and in what circumstances

The limitations of skin penetration studies carried out to date in part reflect the nascent scientific understanding of nanomaterials and of how to design studies to measure their interactions with human skin. Understanding of the large number of variables that influence skin penetration by nanomaterials is growing. However, as one study noted recently: "Major problems now exist in assessing skin absorption and skin toxicity of nanomaterials, the first being how to actually conduct the experiments"[51].

Key requirements of future skin penetration studies to overcome existing limitations include:

- Detailed characterisation of test nanomaterials. Many existing studies provide incomplete information about nanoparticle size and physicochemical properties (eg shape, surface coatings, charge etc)[52]
- Inclusion of nanomaterials <30nm in size, as commonly used in sunscreens and cosmetics. Many studies currently include particles around 100nm in size[53]
- Investigation of a range of test emulsion bases that could influence skin uptake of nanomaterials by altering skin structure or increasing the solubility of the nanomaterial in the skin[54]
- Testing in whole product assays, or with other substances or product ingredients that could act as penetration enhancers. *Skin Deep*, a recent report by US-based Environmental Working Group on the health risks of commercially available cosmetics and personal care products, found that more than half of all cosmetics contained ingredients that act as "penetration enhancers"[55]. As noted in the literature: "It is essential to the validity of any dermal exposure study that experiments be conducted using the same solvents in which human exposures occur"[56]
- Investigation of the influence of skin flexing or massage on skin penetration of nanomaterials, despite the fact that flexing[57] and massage[58] has been demonstrated to increase skin uptake of larger particles, drugs and dyes
- Investigation of penetration by nanomaterials of compromised skin (eg in the presence of acne, shaving wounds, eczema or severe sunburn), even though broken skin is an ineffective barrier and enables particles up to 7,000nm in size to reach living tissue[59]

It is also important to recognise that all skin penetration studies are likely to underestimate skin penetration. *In vitro* cell diffusion experiments[60] are likely to underestimate skin uptake as nanoparticle penetration occurs via passive diffusion only, rather than facilitated by an intact vasculature as is present *in vivo*[61]. However *in vivo* experiments also present limitations; because of their small size, nanomaterials could be difficult to locate in skin, and if systemically absorbed would be diluted throughout the whole body or lodged in major organs, further reducing the ability to detect them[62].

Skin penetration research continues, but conclusive findings remain years away

The Australian government has not yet recognised formally the need to fund nanotechnology research into health and environmental risks of nanomaterials. Earlier this year the Therapeutic Goods Administration published a literature review of existing studies into the potential for nanomaterials in sunscreens to be absorbed through the skin[63]. However the review lacked a critical assessment of the literature available, failing to critique the

inadequacies of studies conducted to date. The review also neglected to emphasise the need for more thorough research.

The European Union has launched a research project called “Nanoderm” to investigate the quality of the skin as a barrier to formulations containing nanoparticles[64]. In one of the few concrete responses from governments to the Royal Society’s 2004 recommendations, last year the European Union requested its Scientific Committee on Consumer Products to review its previous decisions to allow nanoparticle titanium dioxide and zinc oxide to be permitted for use in sunscreens without new safety assessments[65].

In the USA, government agencies including the Food and Drug Administration and the National Institute of Environmental Health Sciences are cooperating through the National Toxicology Program (NTP) to study the skin absorption and phototoxicity of nanoparticles of titanium dioxide and zinc oxide preparations used in sunscreens and cosmetics. The NTP is also looking at the uptake and toxicity of fullerenes. The Food and Drug Administration is currently conducting public hearings in response to the petition filed earlier in the year by the International Center for Technology Assessment, Friends of the Earth and others, to recall sunscreens that use nanoparticle ingredients until new safety assessments are required for these products.

Most of these studies will take years before results are published and much further work will then be required before reliable conclusions can be drawn to inform regulations to protect public health and the environment. Civil society groups such as Friends of the Earth and others have argued that the sensible response to a situation where the risks of nanotoxicity have been clearly identified, but remain poorly understood, is to place a moratorium on the commercialisation of nanoproducts until the necessary safety research has been conducted and regulations enacted.

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