

Dermal Effects of Nanomaterials

Skin penetration pathways

The robust skin barrier, especially the stratum corneum, generally prevents significant penetration of nanoparticles (NPs) into the deeper, living layers of the skin. However, small NPs can enter via several pathways:

- **Follicular pathway:** Nanoparticles can accumulate in the hair follicles and sweat glands. While these appendages make up only a small fraction of the skin's surface, they provide a direct route for NPs to reach deeper skin layers and potentially the circulatory system.
- **Intercellular pathway:** Very small and flexible NPs can navigate the lipid matrix between the flattened, dead skin cells (corneocytes) that make up the stratum corneum.
- **Transcellular pathway:** Nanoparticles can potentially pass directly through the corneocytes, though this route is less common for solid NPs.
- **Damaged skin:** A compromised skin barrier, due to conditions like sunburn, mechanical stress, or diseases such as psoriasis and atopic dermatitis, significantly increases the amount and depth of nanoparticle penetration.

Mechanisms of dermal toxicity

Once nanomaterials breach the skin barrier, they can cause a cascade of toxicological effects at the cellular and tissue levels.

- **Oxidative stress:** A primary mechanism of nanotoxicity is the generation of reactive oxygen species (ROS), which can lead to cell damage, apoptosis (programmed cell death), and DNA and mitochondrial damage in skin cells like keratinocytes.
- **Inflammatory response:** The presence of nanoparticles can trigger immune responses, causing dermal inflammation. Activated immune cells in the skin may proliferate and release cytokines, leading to conditions like erythema, edema, and more severe inflammatory skin diseases.
- **Allergic sensitization:** Certain metallic nanoparticles, particularly those that can release ions, may cause allergic contact dermatitis. This occurs when the metal ions act as haptens, binding to proteins and triggering a specific immune reaction. Nickel (Ni), cobalt (Co), and palladium (Pd) nanoparticles are known examples.
- **Cytotoxicity and genotoxicity:** Nanoparticles can directly cause damage to skin cells and their genetic material. This can impair cell viability, proliferation, and differentiation, and may contribute to carcinogenic processes in the long term, though robust human data are still emerging.

Factors influencing dermal nanotoxicity

The toxicological effects on skin are not universal across all nanomaterials but are heavily influenced by their specific physicochemical properties and the conditions of exposure.

- **Size and shape:** Smaller nanoparticles with a higher surface area-to-volume ratio tend to be more reactive and can penetrate deeper. The shape can also matter, with studies suggesting fibrous or rod-shaped nanoparticles may behave differently from spherical ones.
- **Surface chemistry and coatings:** The surface charge, coatings, and functional groups of NPs dictate their interactions with biological molecules and cell membranes. For example, positively charged NPs may be more likely to be taken up by skin cells.
- **Aggregation:** Nanomaterials often aggregate in biological fluids, which can alter their effective size and limit or change their penetration and toxic potential.
- **Dose and duration of exposure:** A higher dose and longer exposure time typically correlate with a greater risk of adverse effects. Chronic exposure may cause different toxicological outcomes than acute exposure.
- **Matrix:** The product formulation in which the nanoparticles are embedded (e.g., creams, sprays) can alter their aggregation state and bioavailability, thereby affecting dermal absorption.
- **Skin integrity:** As noted, damaged skin has a compromised barrier function, leading to significantly higher and deeper penetration of nanoparticles compared to healthy, intact skin.

Regulatory aspects and risk mitigation

Given the potential risks associated with dermal exposure, especially via cosmetics and other consumer products, regulatory oversight and careful risk assessment are critical.

- **Regulations:** The EU Cosmetics Regulation mandates labeling for products containing nanomaterials and has restricted or banned the use of certain NPs in cosmetics. This regulatory approach requires robust safety data, including dermal penetration studies.
- **Risk assessment:** Evaluating the risk of dermal nanotoxicity involves assessing the probability of exposure and the potential for harm. For consumers, this focuses on products like sunscreens, while for workers, it addresses occupational exposure scenarios.
- **Product safety:** Manufacturers are encouraged to follow "Safe-by-Design" principles, which involve designing nanomaterials with minimal toxic potential. For

consumer products, encapsulating NPs in nanocarriers can prevent penetration into deeper skin layers.

- **Protective measures:** In occupational settings, personal protective equipment (PPE), particularly chemical-resistant gloves, is crucial for preventing direct skin contact and subsequent exposure to potentially hazardous nanoparticles.