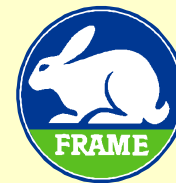


The limitations of animal models in safety assessment:

A case study on transdermal exposure to nanomaterials and medical devices



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Nanoparticles

Nanoparticles are elements, chemicals or complexes that are smaller than 100 nm in every dimension whereas ultrafines are smaller than 100 nm in at least one dimension. Due to their small size, both nanoparticles and ultrafines can possess unusual physicochemical characteristics that are distinct from their bulk material counterparts.

Nanoparticles do not obey the laws of classical physics but instead follow the laws of quantum physics

The importance of testing nanomaterials

There is currently no regulatory oversight that is specific for the safety evaluation of nanomaterials. A decrease in particle size, with a corresponding increase in surface area, can result in more extensive and different interactions than made by the bulk material equivalents. Indeed, parameters that determine the potential biological effects of nanoparticles include:

- Chemical composition
- Porosity
- Surface structure
- Surface area
- Shape
- Solubility

The impact of each of these parameters on the biological activity and bioavailability safety of nanomaterials must be assessed. One of the greatest challenges refers to the heterogeneity of composition and size. Not only can stable nanoparticles leach away from devices in a reactive form but nanodelivery devices (e.g. liposomes) can also be subjected to varying degrees of degradation. The latter can alter the rate and site of drug delivery.

Nanomaterials may pose problems for risk assessment since they may require animal testing of each new nanomaterial variant. Whether animal models are able to predict human health effects is questionable.

Dermal exposure to nanoparticles

Nanomaterials are increasingly found in subcutaneous monitoring devices or used to deliver therapeutics through the skin. If nanoparticles are able to cross the innermost layer of the skin, the dermis, they can reach the systemic blood circulation. It is therefore important to establish the internal level of nanoparticles acquired through the transdermal route.

Nanomaterials in medicine

Nano-scale restoratives and delivery devices (hereafter referred to as nanodevices) are composed or coated with a nanomaterial. On the whole they are classified as devices since they are not intended to have a biological function, only to have a physical interaction with the body, enhance drug delivery or reduce drug toxicity.

Toxicity testing of dermal nanomaterials

Most information about chemical's toxicity results from animal studies. The ability of topically applied nanomaterials to penetrate into living tissue is often tested using animal skin. Due to physiological differences, animals may not be relevant models to predict harmful exposure to humans.

The follicular route of dermal penetration, for instance, is likely to be a major route of absorption of metal and lipid based nanomaterials. The former are present in sensor devices as well as in sun screens. Liposomes are increasingly commonly found in toiletry products and used to deliver therapeutics across biological barriers such as the skin.

The cross-sectional diameter of a human hair follicle is larger than in most commonly used test species. Thus, animal models are likely to underestimate transcutaneous uptake of nanomaterials. Furthermore, human skin is more densely innervated, vascularised and occupied by inflammatory mediators and cells than most test species. These differences can result in a greater inflammatory mediation and distal effects than anticipated by animal studies. Comparisons of skin structure are made in Table 1.

| | Human | Marmoset | Rat | Rabbit | Pig |
|-----------------------------|--------|----------|-----|--------|--------|
| Stratum (μm) | 20 | 10 | 16 | 10 | 18 |
| Epidermis (μm) | 25 | 18 | 18 | 15 | 47 |
| Dermis (μm) | > 2000 | 740 | 780 | 1000 | > 2000 |
| Follicles (back) | | | | | |
| Diameter (μm) | 70 | 16 | 18 | 18 | - |
| Density (mm^2) | 0.06 | 20 | 80 | - | 0.9 |
| Total skin | | | | | |
| thickness (mm) | 2-4 | 1-3 | 1 | 1.8 | 1-2 |

Table 1. Differences in animal skin characteristics

In vitro models and cadaveric skin

Ideally, skin for *in vitro* tests would come from healthy human donors and cadavers. However, the availability of human skin is an issue due to logistic and regulatory matters. Furthermore, cadaveric skin often lacks the levels of hydration seen in living skin.

Artificial skin models, some of which are already in the market, present an alternative for skin penetration experiments. The advent of innervated skin models and those which incorporate an immune cell component are likely to prove useful for the toxicological assessment of nanomaterials. However, since many models lack barrier integrity and follicles, it is likely that cadaveric skin and artificial models would need to be used in conjunction to provide a clearer picture of nanomaterial uptake and toxicity.

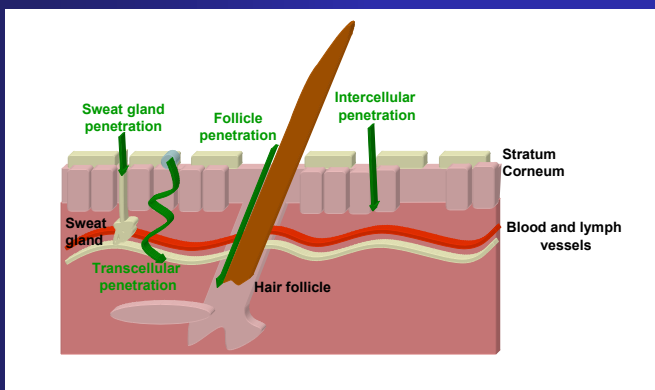


Figure 1. Diagram of human skin and potential routes of transdermal nanoparticle entry

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