Safety aspects of skin penetration of nanoparticles in topically applied cosmetics / pharmaceuticals

A. Patzelt, H. Richter, W. Sterry, J. Lademann

Center of Experimental and Applied Cutaneous Physiology (CCP)
Safety aspects of skin penetration of nano-sized particles

RISK??!!
Safety aspects of skin penetration of nano-sized particles

Potential risks of NP – a public debate

Principal human health risk may be from inhalation of NP!

Potential dangers may be from contact of NP with skin?
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Key questions

Do topically applied NP pose new risks when compared to traditional cosmetic products?

→ Material versus Size?

Do topically applied NP remain on the skin or do they pass the skin barrier and gain access to systemic compartments?

Which biological effects can be induced when NP enter the organism?
Are nano-sized particles able to cross the skin barrier?
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Penetration pathways

- intercellular
- follicular
- intracellular
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Investigation of intercellular penetration of titanium dioxide by tape stripping

Application of the emulsion  Homogeneous distribution

Pressing the tape with a roller  Removal of the adhesive film
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Penetration profile of titanium dioxide

Tape number

Relative thickness of the stratum corneum [%]

Concentration TiO$_2$ [µg/cm$^2$]
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Skin after removal of 25 tape strips
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Position of hair follicles on tape strips with OsO₄ staining
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Detection of titanium dioxide on the removed tape strips in follicular areas
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Biopsy after application of titanium dioxide
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No penetration of titanium dioxide via the intercellular pathway into the living tissue

Tan et al., 1996
Landsdown and Taylor, 1997
Dussert and Gooris, 1997
Lademann et al., 1999
Pflücker et al. 2001
Schulz et al, 2002
Gottbrath and Müller-Goymann, 2003
Grontier et al. 2004
Mavon et al. 2007
Nohynek et al, 2007
etc.
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Penetration profile of titanium dioxide

Concentration TiO₂ [µg/cm²]
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Investigation of follicular penetration of NP
Safety aspects of skin penetration of nano-sized particles

Investigation of follicular penetration of NP

320 nm NP formulation  non-particle containing formulation

Lademann et al., *Eur J Pharm Biopharm*, 2007, 66, 159
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Size dependency of follicular penetration of NP

Toll et al.

Lademann et al.

Vogt et al.
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Size dependency of follicular penetration of NP

![Graph showing the size dependency of follicular penetration of NP. The x-axis represents particle size in nanometers (nm), and the y-axis represents penetration depth in micrometers (µm). There are bars for particle sizes of 860 nm, 643 nm, 470 nm, 300 nm, 230 nm, and 122 nm. The bars show the penetration depth for each particle size. There are asterisks (*) indicating statistical significance with p-values. (*) p = 0.07, * p < 0.05.]
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Hair follicle pump
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Size dependency of follicular penetration of NP

Terminal hair follicle

Vellus hair follicle

Penetration depth [µm]

Particle size [nm]

860 nm  643 nm  470 nm  300 nm  230 nm  122 nm

0  200  400  600  800  1000  1200  1400

(*) p = 0.07

(*) p < 0.05
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Hair follicle targeting

Infundibulum:
1. transfollicular penetration
2. immunotherapy
topical vakzination

Sebaceous gland
1. Acne
2. Androgenetic Alopecia

Stem cells
1. regenerative medicine
2. wound healing
3. gene therapy

Matrix cells
1. control of hair growth
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Size dependency of follicular penetration of NP

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Size dependency of follicular penetration of NP

Microparticles
750 nm
1500 nm

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Size dependency of follicular penetration of NP

<table>
<thead>
<tr>
<th>Author</th>
<th>Particle size</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryman-Rasmussen et al., 2006</td>
<td>4.6 and 12 nm</td>
<td>QD penetrated through porcine skin, applied in alkaline solution</td>
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<tr>
<td>Gopee et al., 2006</td>
<td></td>
<td>QD penetrated only through mouse skin after dermabrasio</td>
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<tr>
<td>Baroli et al, 2007</td>
<td>5.9 nm</td>
<td>Metallic NP penetrated through skin, experiments in diffusion cell</td>
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<tr>
<td>Rouse et al, 2007</td>
<td>Fullerene particles</td>
<td>Fullerenes penetrated through porcine skin after skin flexing, experiment in diffusion cell</td>
</tr>
<tr>
<td>Vogt et al, 2006</td>
<td>40 nm</td>
<td>NP penetrated into the living tissue, after CSSS</td>
</tr>
<tr>
<td>Gopee et al, 2007</td>
<td>10, 30, 100 nm</td>
<td>No penetration in healthy porcine skin in vivo but in damaged skin</td>
</tr>
<tr>
<td>Zhang et al., 2008</td>
<td>ca. 40 nm</td>
<td>QD penetrated into upper SC layers in intact skin, reached living cells in damaged skin</td>
</tr>
</tbody>
</table>
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Skin damage enables skin penetration of NP

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Skin damage enables skin penetration of NP

Diffusion cell

NP

Receptor fluid

2500 µm

500 µm
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Summary

NP > 100 nm seem not penetrate through the intact skin barrier

NP < 100 nm: up to now, no evidence for penetration through intact skin

additional investigations have to be performed especially for NP < 10 nm
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NP as carriers for drug delivery
Thank you very much for your attention!

CHARITÉ

Department of Dermatology
Center of Experimental and Applied Cutaneous Physiology
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Long-term reservoir of NP in hair follicles

Fluorescence intensity [arb. units]

Particles
Non particle containing formulation

1st day
4th day
7th day
10th day
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Long-term reservoir of NP in hair follicles

Fluorescence intensity [arb. units]

- NP in stratum corneum
- NP in hair follicles

30 min | 1st day | 4th day | 8th day | 10th day

30 min: 100
1st day: 80
4th day: 55
8th day: 40
10th day: 20

Lademann et al., Eur Jour Pharm and Biopharm 2007, 66, 139