Toxicity of zinc oxide particles in sunscreens: myth or fact?

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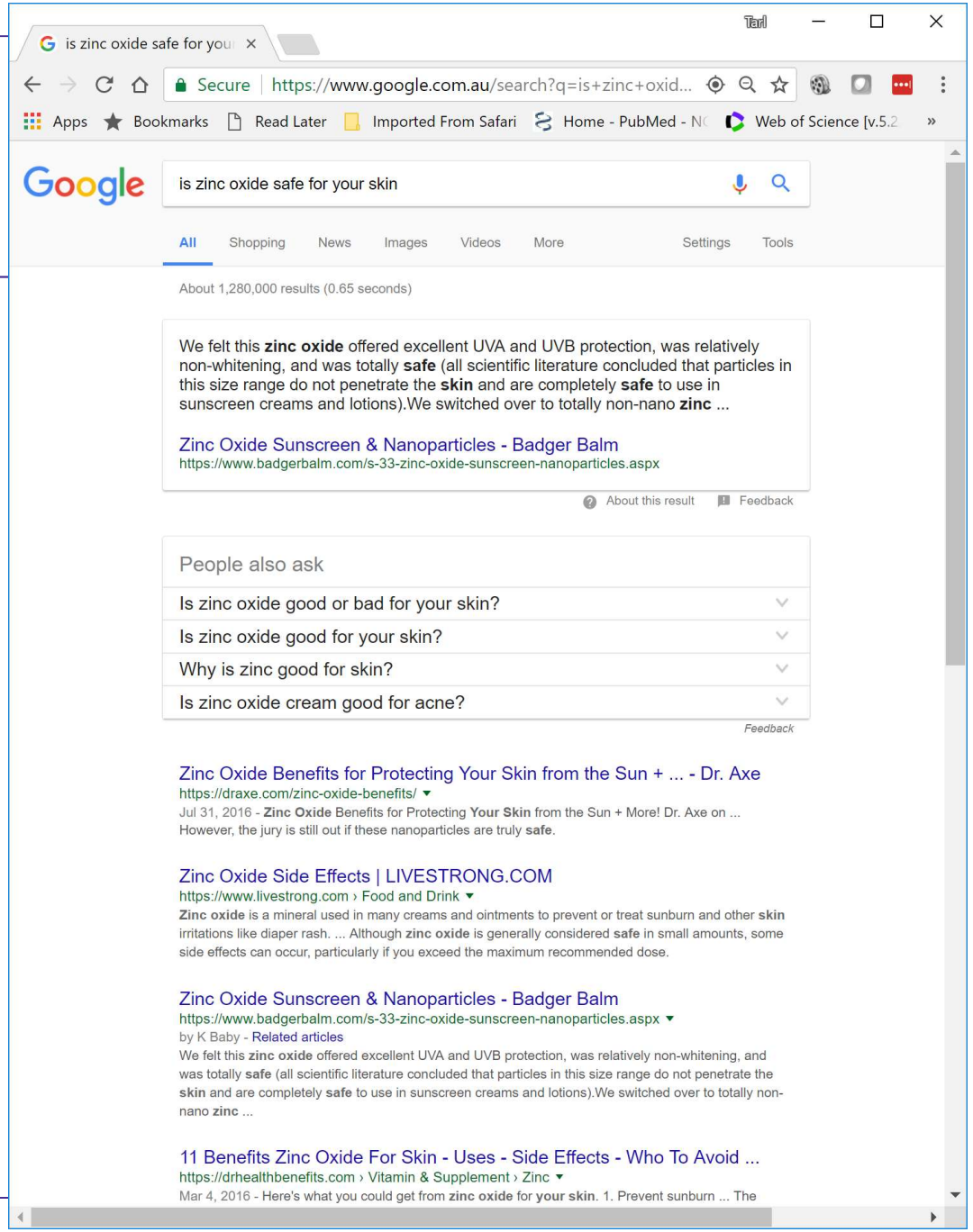
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We felt this zinc oxide offered excellent UVA and UVB protection, was relatively non-whitening, and was totally safe (all scientific literature concluded that particles in this size range do not penetrate the skin and are completely safe to use in sunscreen creams and lotions).We switched over to totally non-nano zinc ...
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https://draxe.com/zinc-oxide-benefits/
Jul 31, 2016 - Zinc Oxide Benefits for Protecting Your Skin from the Sun + More! Dr. Axe on ... However, the jury is still out if these nanoparticles are truly safe.
Zinc Oxide Side Effects | LIVESTRONG.COM
https://www.livestrong.com › Food and Drink
Zinc oxide is a mineral used in many creams and ointments to prevent or treat sunburn and other skin irritations like diaper rash. ... Although zinc oxide is generally considered safe in small amounts, some side effects can occur, particularly if you exceed the maximum recommended dose.
Zinc Oxide Sunscreen & Nanoparticles - Badger Balm
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We felt this zinc oxide offered excellent UVA and UVB protection, was relatively non-whitening, and was totally safe (all scientific literature concluded that particles in this size range do not penetrate the skin and are completely safe to use in sunscreen creams and lotions).We switched over to totally non-nano zinc ...
11 Benefits Zinc Oxide For Skin - Uses - Side Effects - Who To Avoid ...
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Mar 4, 2016 - Here's what you could get from zinc oxide for your skin. 1. Prevent sunburn ... The

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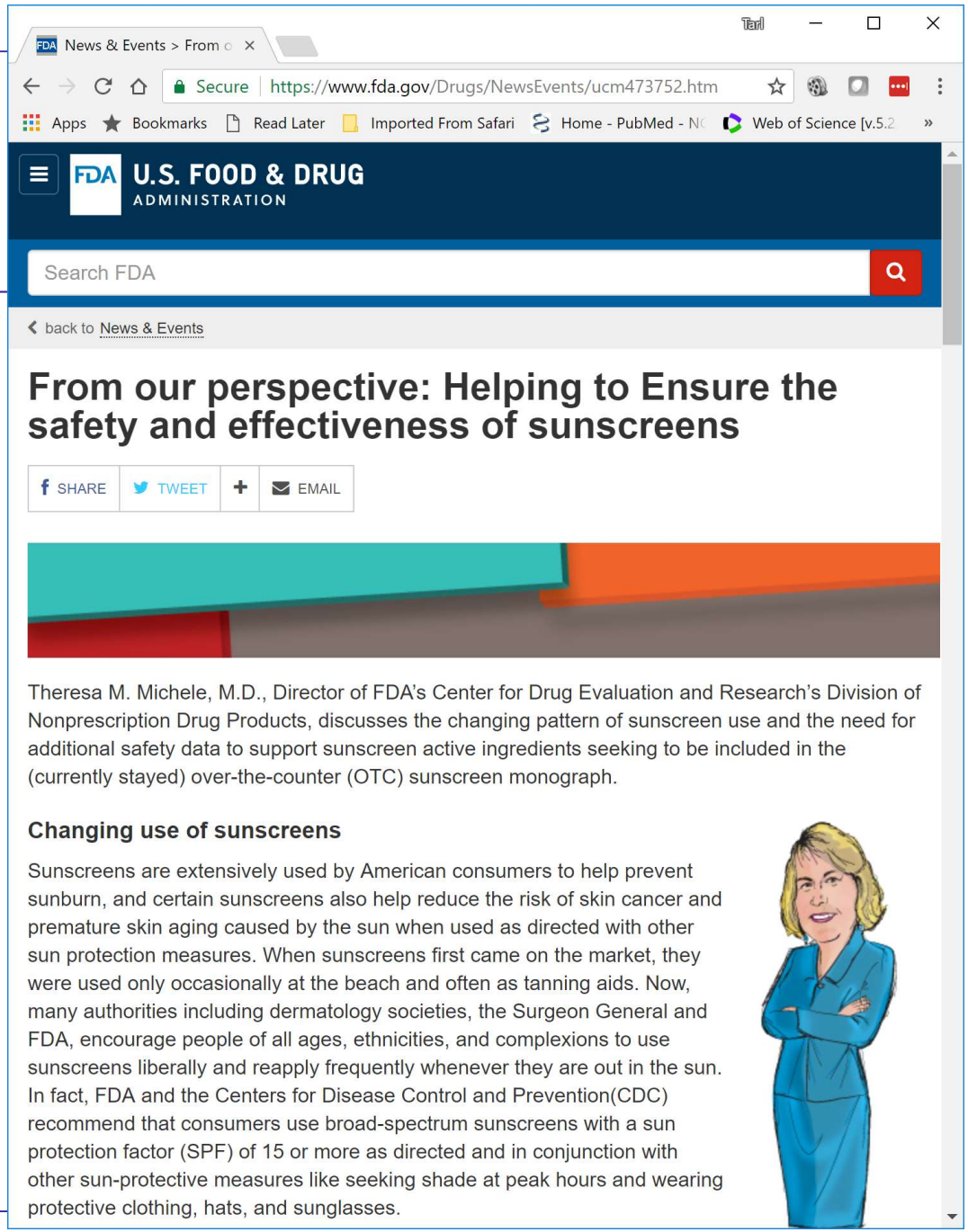


Protection from UV
Stability

My Perspective on Sunscreen Safety

- Does the formulation reach living cells?
- Does the formulation maintain homeostasis before, during and after UV exposure?

- *Is the formulation easily removed?

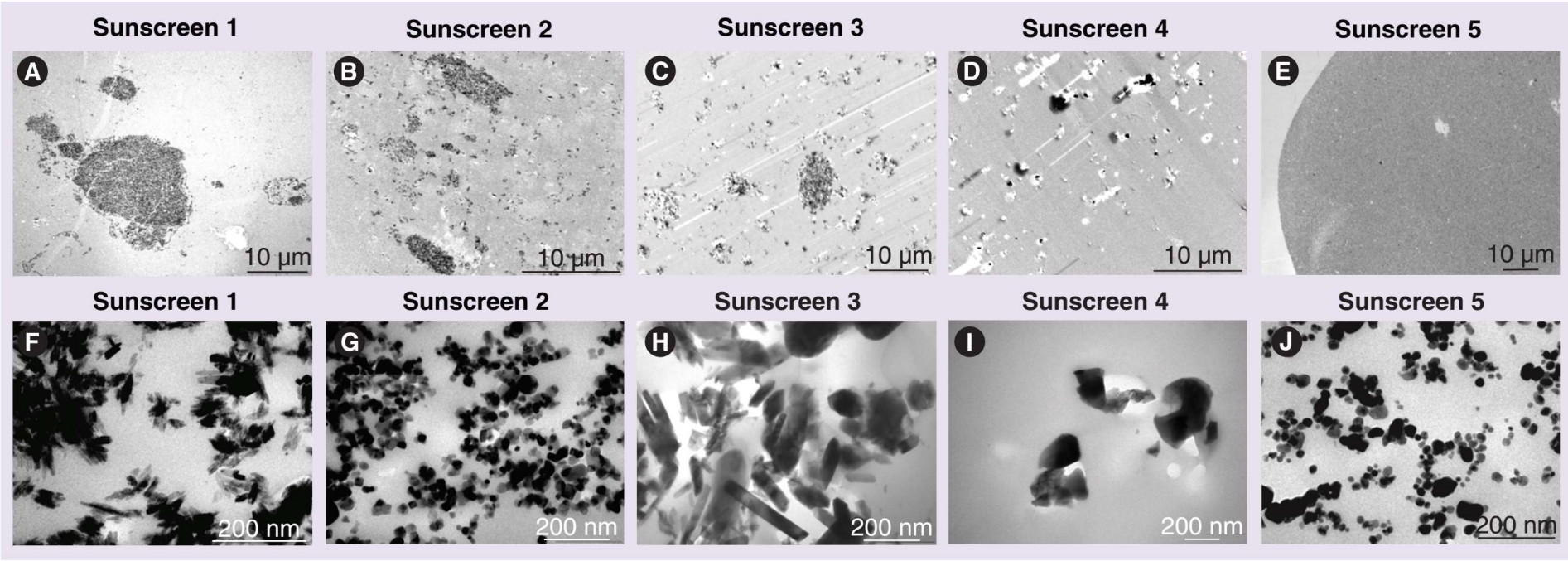
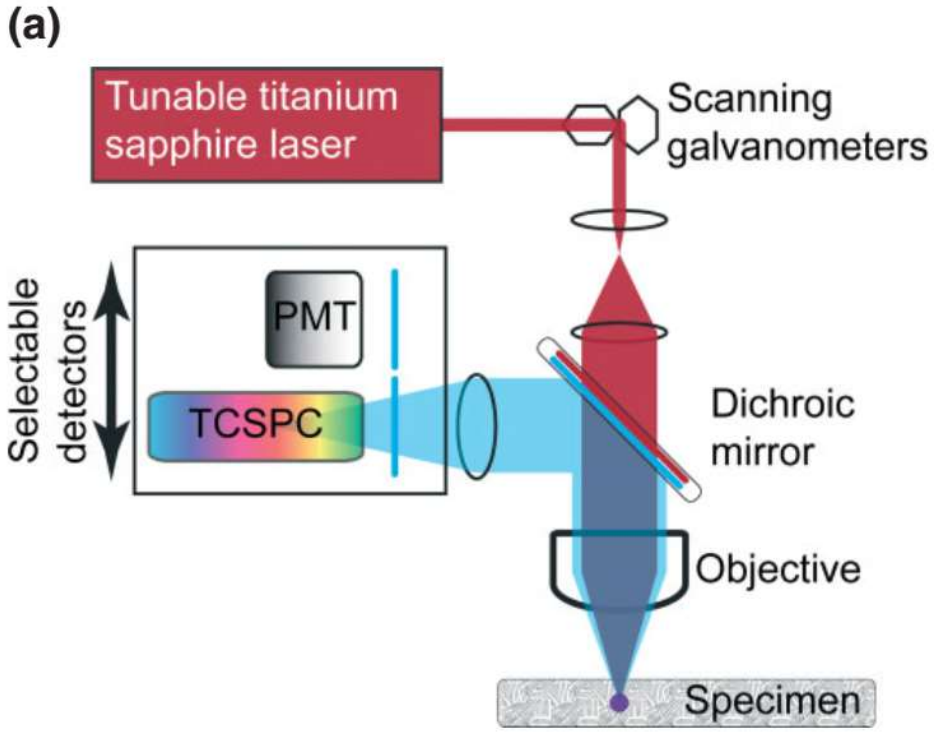
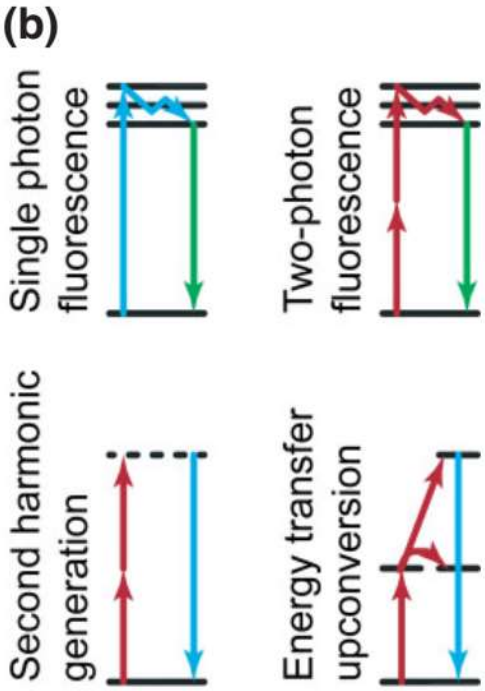


Table 1. Sunscreen samples used in this study and their listed ingredients.

Sunscreen number	Product	Listed metal oxide	Active ingredients (%w/w)	Preservatives (%w/w)
1	NIVEA Visage Moisturising Fluid SPF 15	TiO_2	Octyl methoxycinnamate 6.0%, butyl methoxydibenzoyl-methane 2.0%, 4-methylbenzylidene camphor 1.8%, TiO_2 3.0%	Methyl hydroxybenzoate 0.07%, bronopol 0.002%
2	NIVEA SUN Sun Spray	TiO_2	Octyl methoxycinnamate 9.0%, Octyl triazone 4.5%, 4-methylbenzylidene camphor 4.0%, butyl methoxydibenzoyl-methane 2.5%, phenylbenzimidazole, sulfonic acid 2.0%, TiO_2 1.0%	Phenoxyethanol, methyl hydroxybenzoate, alcohol
3	CG Smoothers	ZnO	Octyl methoxycinnamate 6.0%, ZnO 3.0%	Not listed/disclosed
4	Banana Boat Sport	ZnO	Octyl methoxycinnamate 7%, 4-methylbenzylidene camphor 1%, ZnO micronized 6%	Phenoxyethanol, diazolidinyl urea, hydroxybenzoates
5	Antaria ZinClear-S_60CCT	ZnO	Siliconate coated ZnO 60%, Caprylic capric triglycerides	None

TiO_2: Titanium dioxide; ZnO: Zinc oxide.


(a)
Tunable titanium sapphire laser
Scanning galvanometers
Selectable detectors
PMT
TCSPC
Dichroic mirror
Objective
Specimen


(b)
Single photon fluorescence
Two-photon fluorescence
Second harmonic generation
Energy transfer upconversion

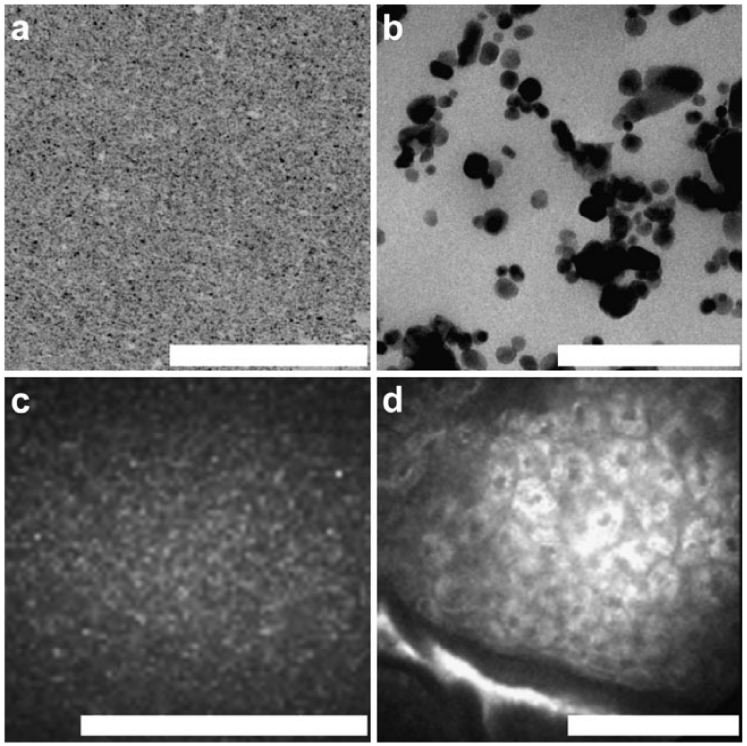
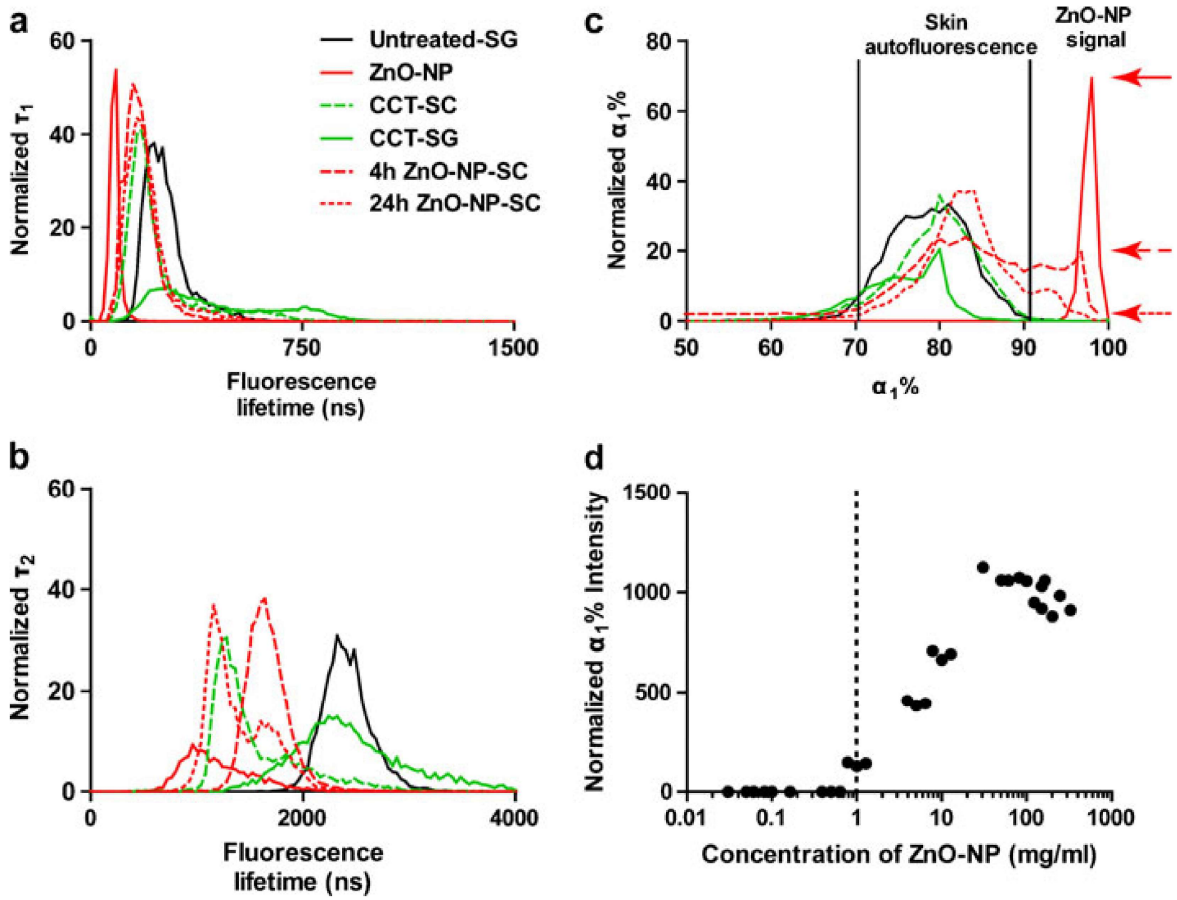
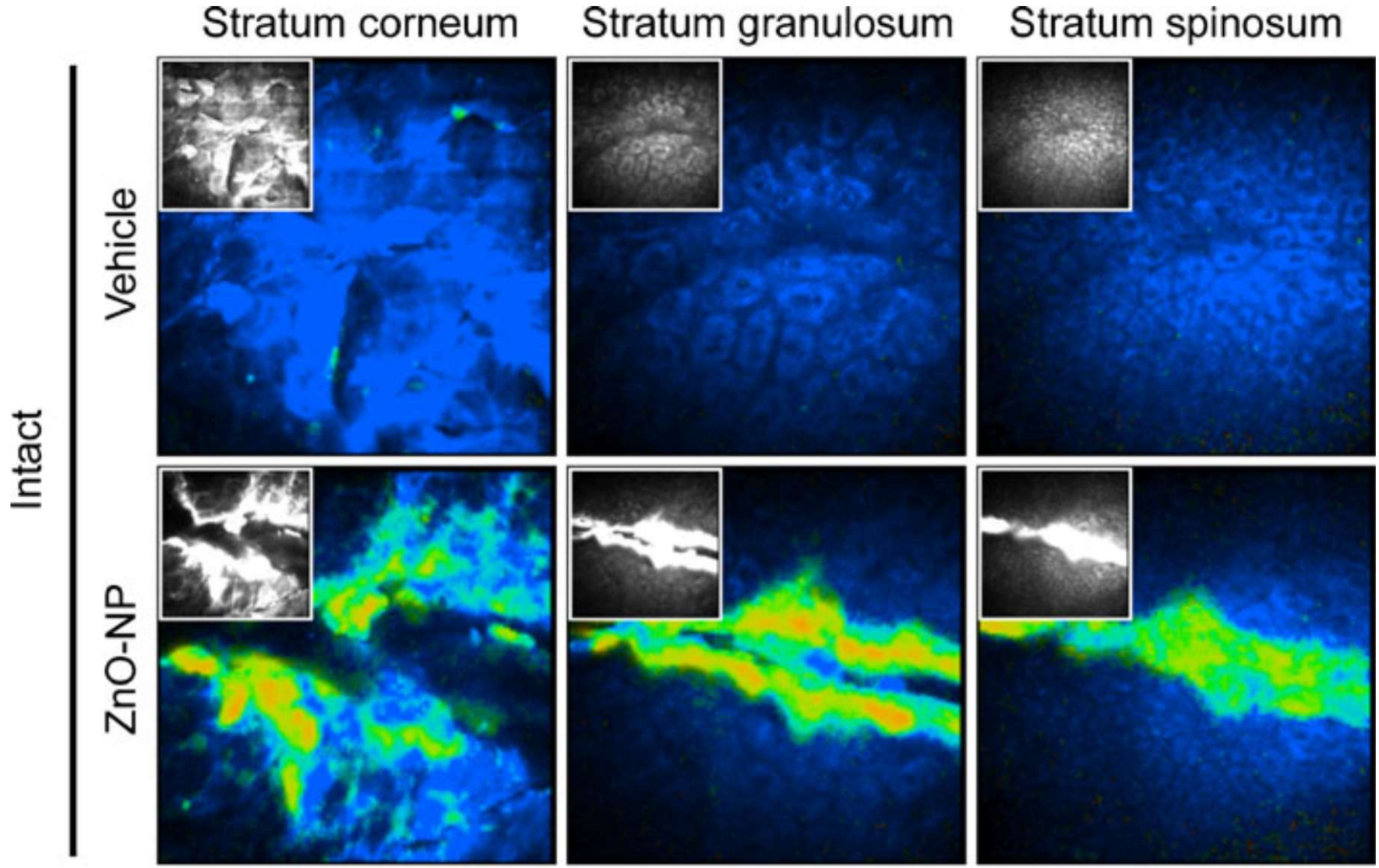
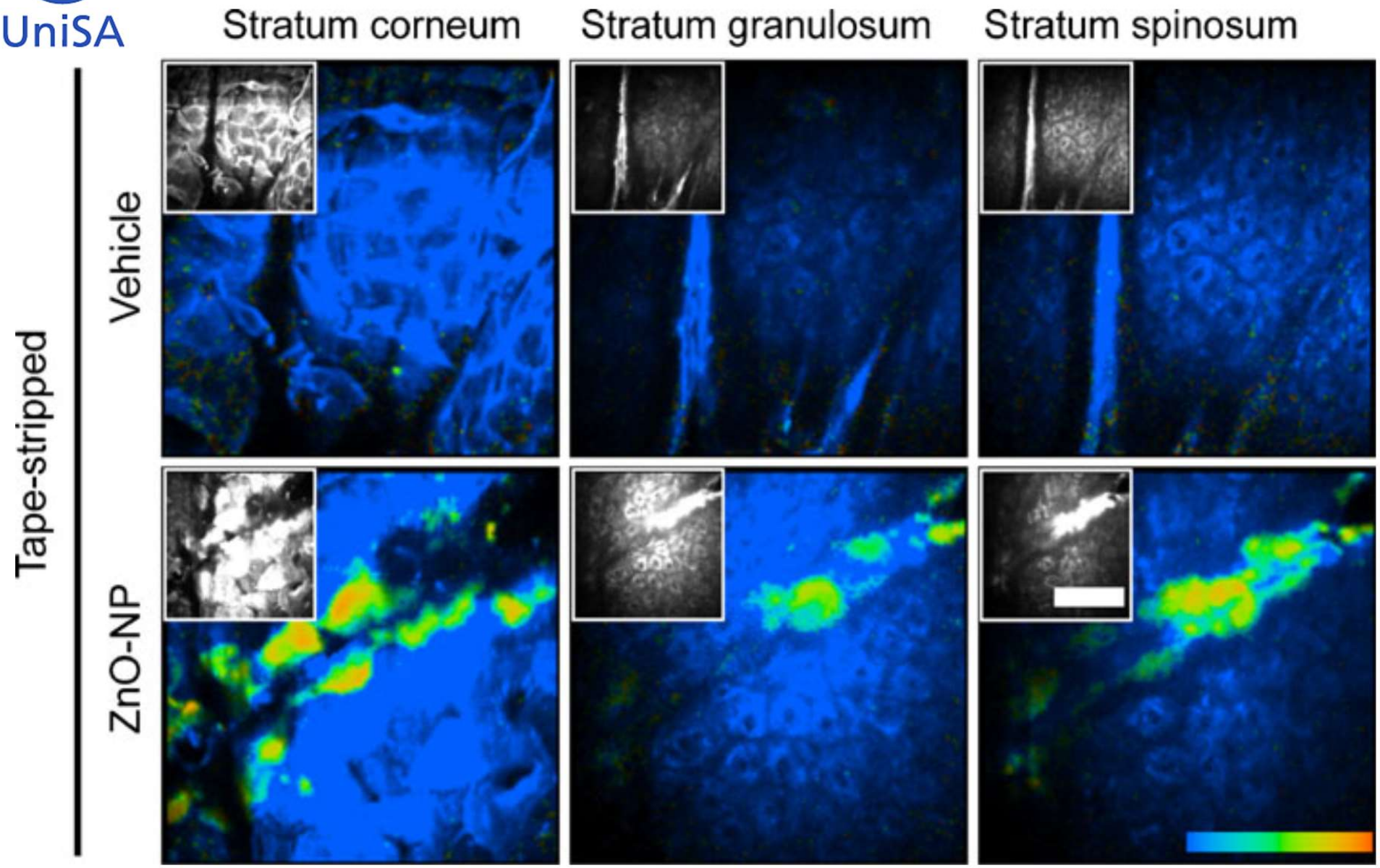


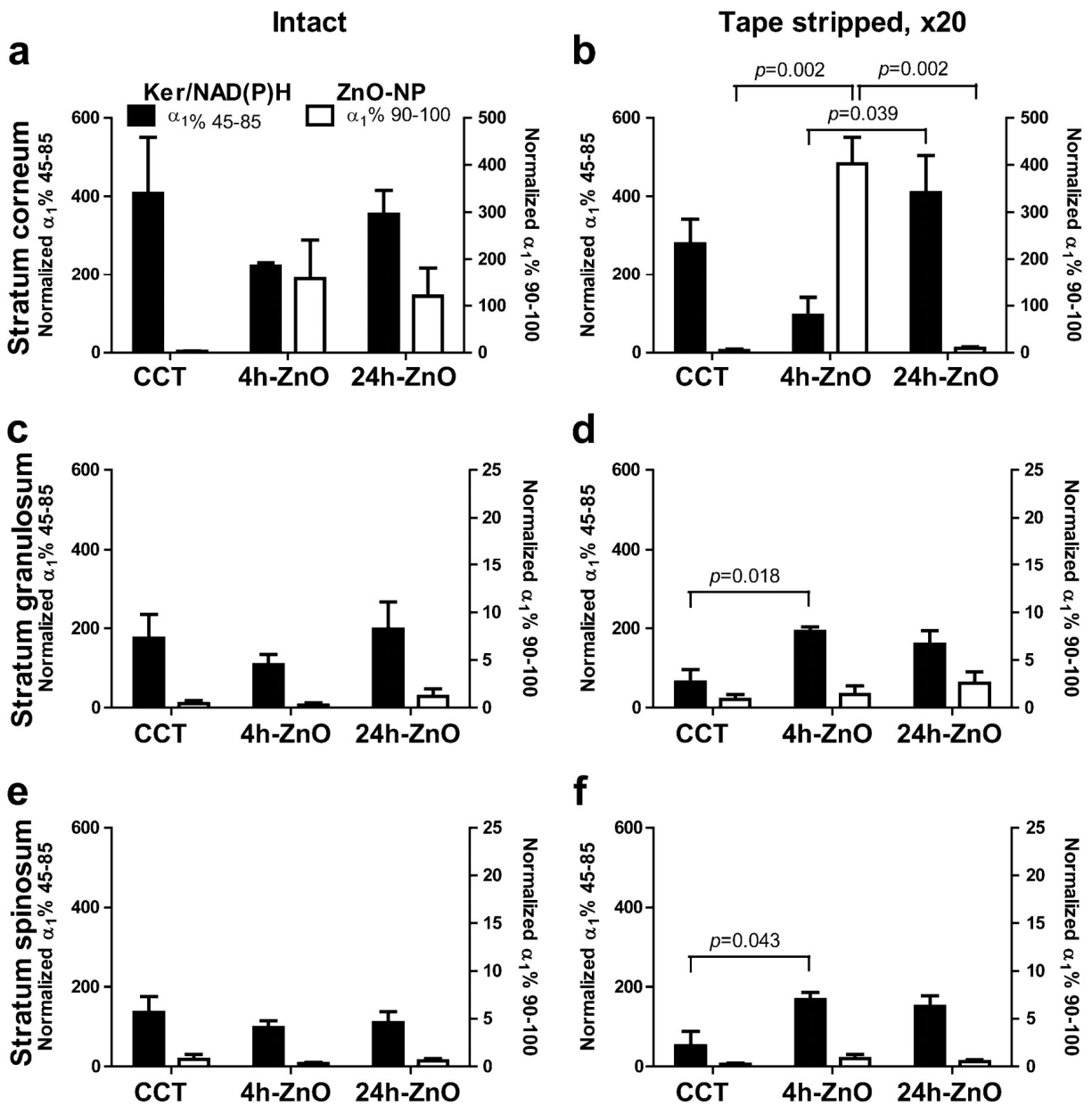
Fig. 2 TEM images of ZnO-NP and MPM ZnO-NP and the viable epidermis. TEM images of 1 mg/mL ZnO-NP show the 35 nm nanoparticles at low (**a**) and high magnification (**b**). MPT intensity image of a 1 mg/mL ZnO-NP solution (**c**) and untreated volunteer viable epidermis (**d**). The MPT images in (**c** and **d**) were taken with 740 nm excitation. The *scale bars* indicate 10 μm (**a**), 200 nm (**b**), and 50 μm (**c** and **d**).

How deep do topically applied zinc oxide nanoparticles penetrate?

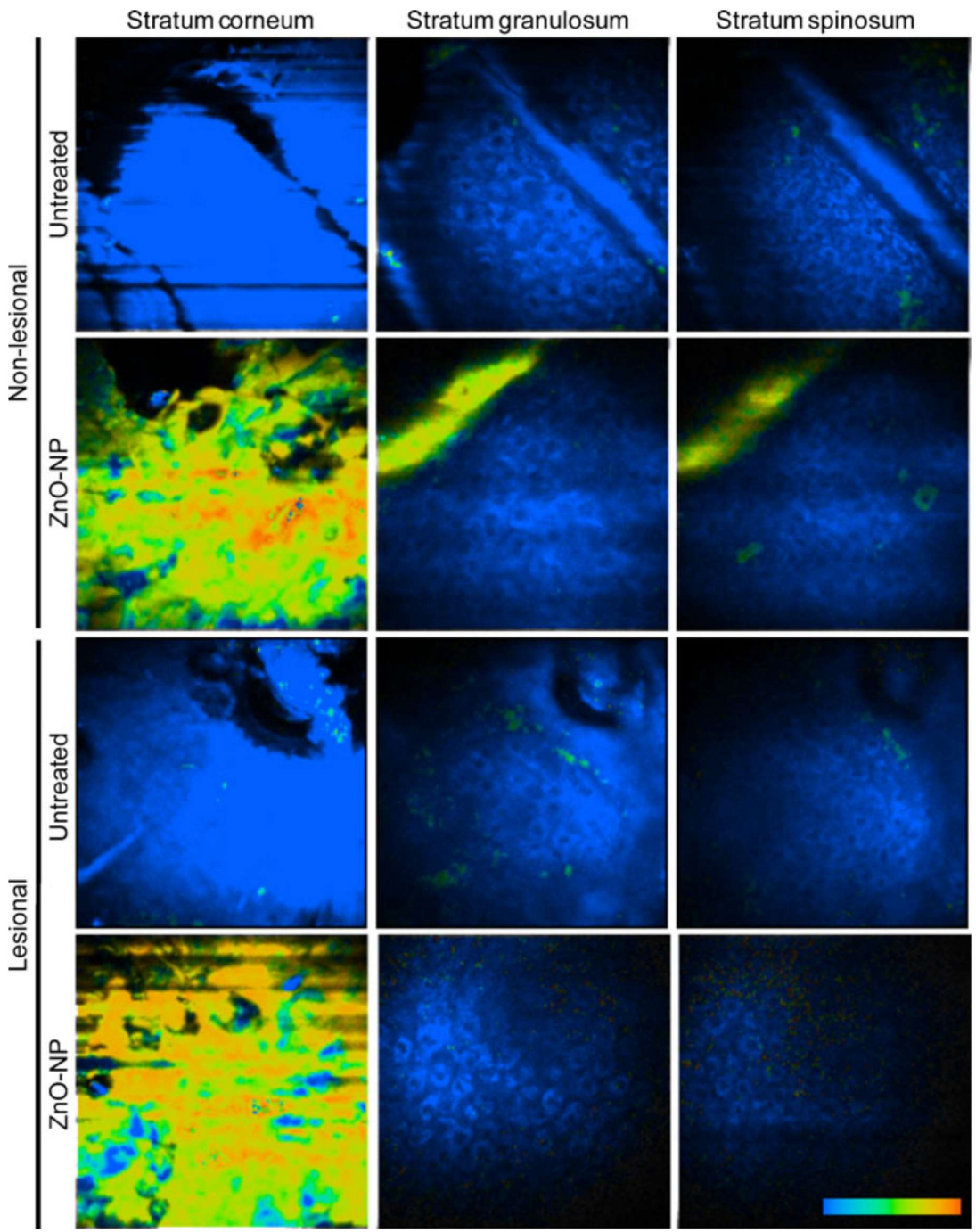


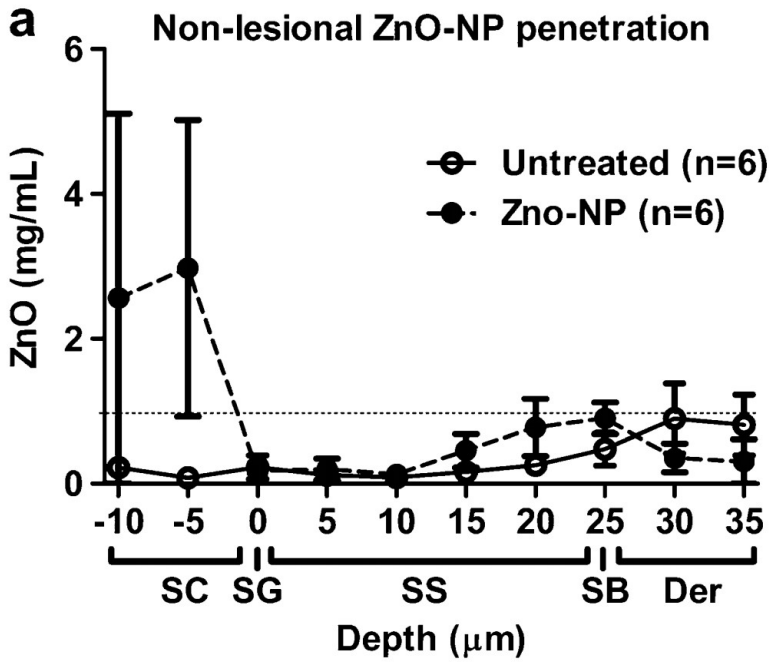

Stratum corneum
Stratum granulosum
Stratum spinosum
Intact
Vehicle
ZnO-NP

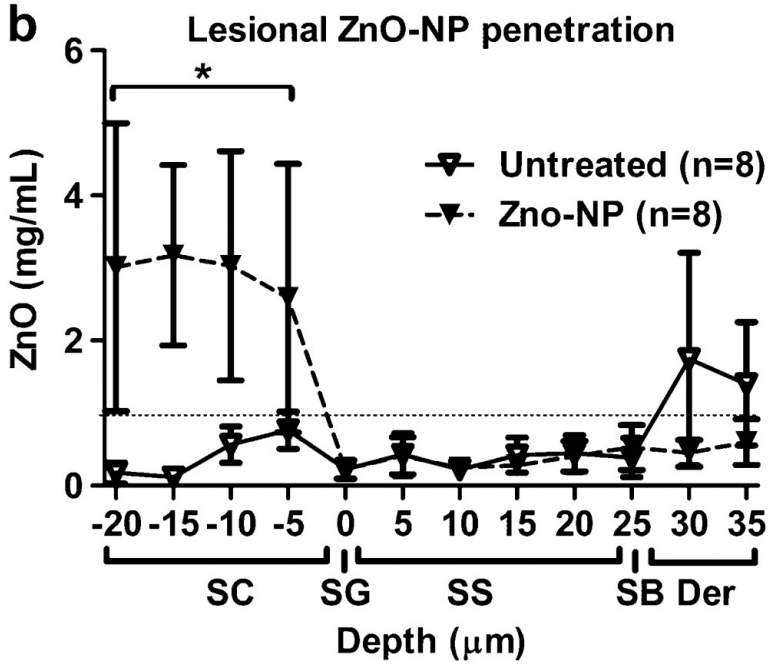

Stratum corneum
Stratum granulosum
Stratum spinosum
Tape-stripped
Vehicle
ZnO-NP

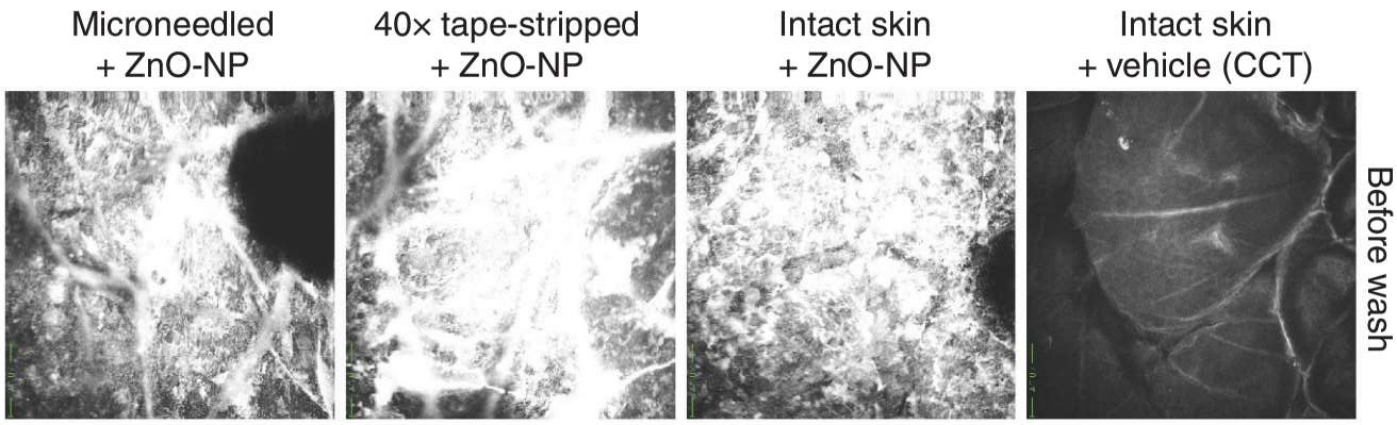

Intact
Tape stripped, x20
a
b
c
d
e
f
Ker/NAD(P)H
ZnO-NP
α1% 45-85
α1% 90-100
Stratum corneum
Stratum granulosum
Stratum spinosum
Normalized α1% 45-85
Normalized α1% 90-100
p=0.002
p=0.002
p=0.039
p=0.018
p=0.043
CCT
4h-ZnO
24h-ZnO

Quantification of ZnO-NP Penetration and Metabolic State In Volunteers With Psoriatic and Atopic Dermatitis Lesions




a
Non-lesional ZnO-NP penetration
ZnO (mg/mL)
6
4
2
0
Untreated (n=6)
Zno-NP (n=6)
-10 -5 0 5 10 15 20 25 30 35
SC SG SS SB Der
Depth (μm)


b
Lesional ZnO-NP penetration
*
ZnO (mg/mL)
6
4
2
0
Untreated (n=8)
Zno-NP (n=8)
-20 -15 -10 -5 0 5 10 15 20 25 30 35
SC SG SS SB Der
Depth (μm)


Microneedled
+ ZnO-NP
40× tape-stripped
+ ZnO-NP
Intact skin
+ ZnO-NP
Intact skin
+ vehicle (CCT)
Before wash

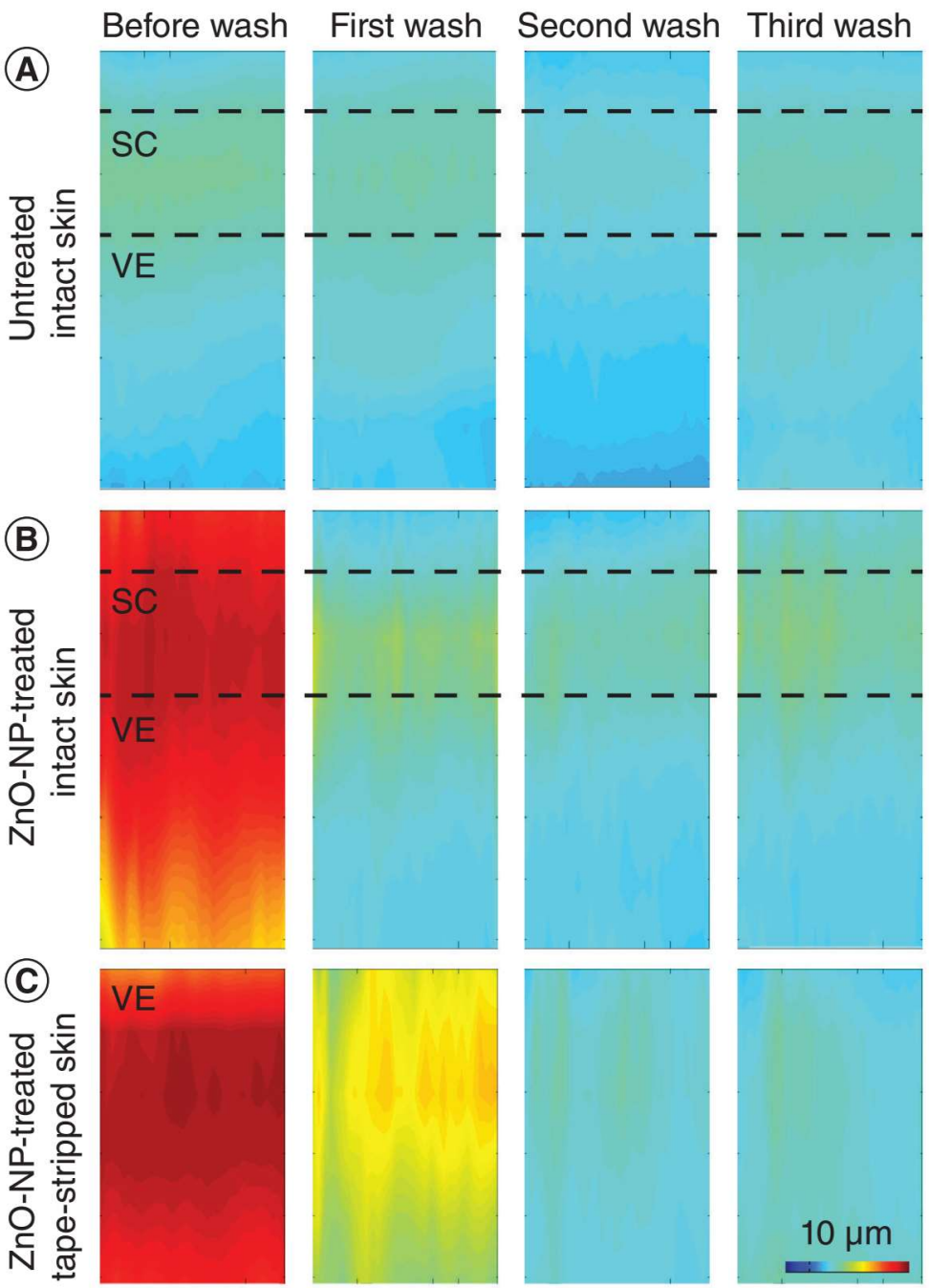
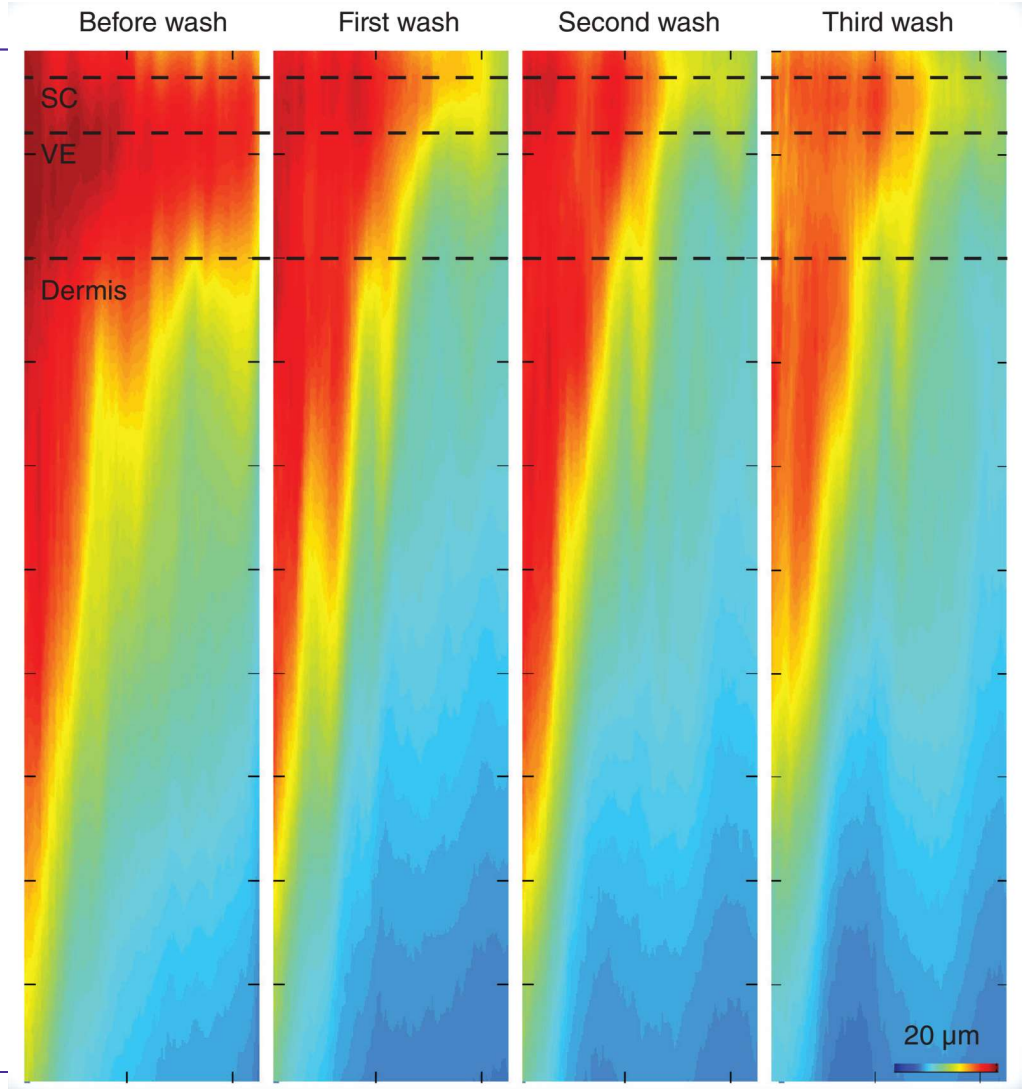
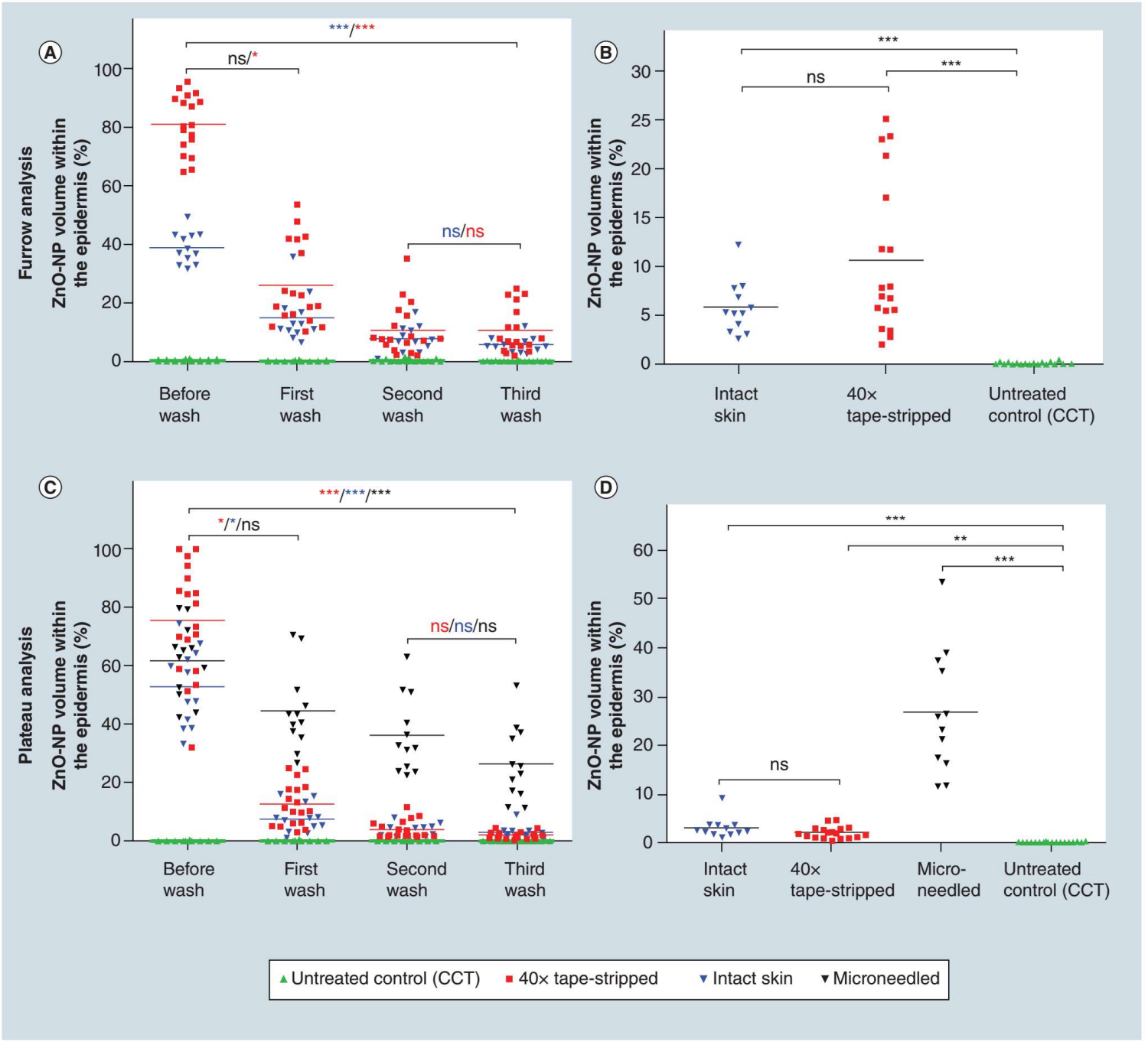

Before wash
First wash
Second wash
Third wash
A
Untreated intact skin
SC
VE
B
ZnO-NP-treated intact skin
SC
VE
C
ZnO-NP-treated tape-stripped skin
VE
10 µm

Figure 6. Average cross-sectional heat map of *ex vivo* microneedled skin with zinc oxide nanoparticle treatment before washing and after one, two and three washes. Color bar: 0–255 pixel intensity (blue to red). Color bar also corresponds to a scale bar as indicated in the figure.
SC: Stratum corneum; VE: Viable epidermis.




A
Furrow analysis
ZnO-NP volume within the epidermis (%)
/
ns/*
ns/ns
Before wash
First wash
Second wash
Third wash
B
ZnO-NP volume within the epidermis (%)
***
***
ns
Intact skin
40× tape-stripped
Untreated control (CCT)
C
Plateau analysis
ZnO-NP volume within the epidermis (%)
//***
//ns
ns/ns/ns
Before wash
First wash
Second wash
Third wash
D
ZnO-NP volume within the epidermis (%)
***
**
***
ns
Intact skin
40× tape-stripped
Micro-needled
Untreated control (CCT)
Untreated control (CCT)
40× tape-stripped
Intact skin
Microneedled

Executive summary

Topical nanoparticle exposure

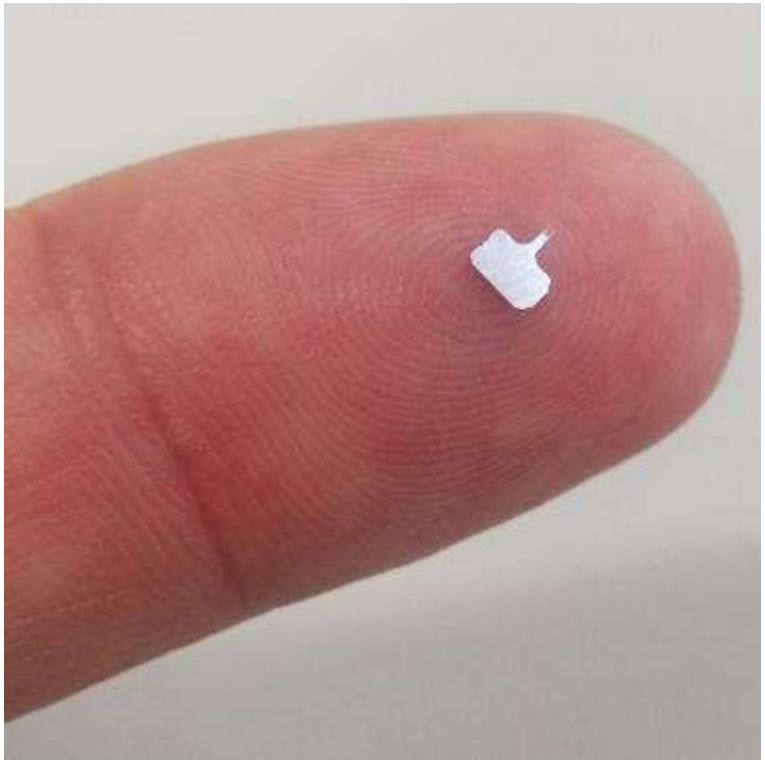
- Improved manufacturing methods have led to the fabrication and incorporation of nanoparticles into many consumer products.
- Zinc oxide nanoparticles (ZnO-NPs) are one of the most common nanoparticles used in topical products (sunscreens and daily moisturizers, among others).
- Owing to knowledge gaps in the field of nanoparticle–biological interaction there is increasing pressure to specifically regulate nanoparticle-containing products.
- Specifically, there is a significant knowledge gap in our understanding of how nanoparticles interact with human skin.

Removal of ZnO-NPs from injured skin

- Damaged skin is prone to ZnO-NP uptake, although the penetration of these nanoparticles is more limited than predicted by animal models and *in vitro* data.
- Removal of ZnO-NPs from intact and tape-stripped skin can be achieved by washing with soap and water.
- ZnO-NPs cannot be removed from small wounds (microneedle puncture sites) even after three washing steps with soap and water.

Future perspective

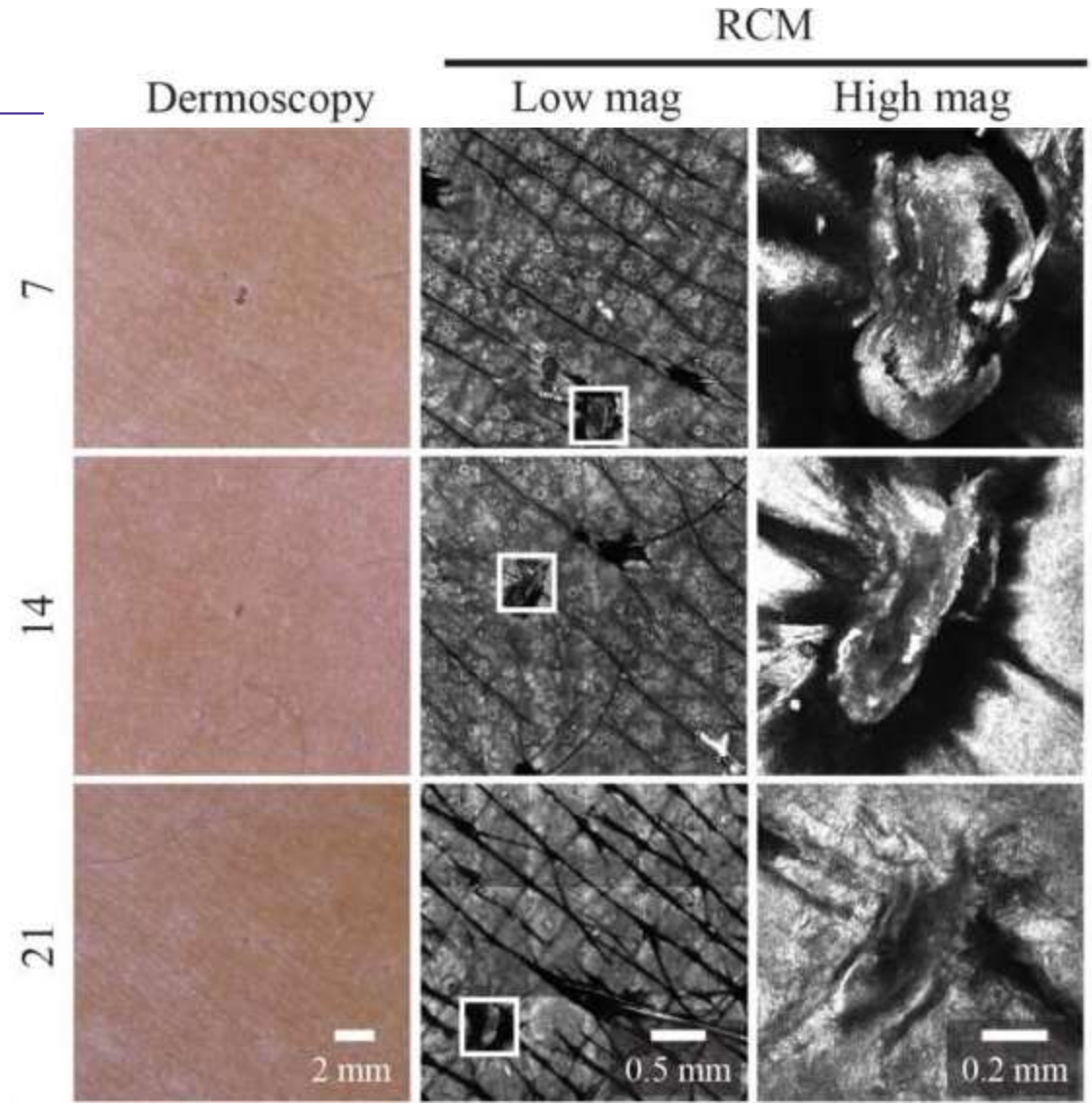
- Exposing ZnO-NPs to injured volunteer skin will bridge between the current data on *in vitro*, *ex vivo* and *in vivo* ZnO-NP toxicology and penetration, this will provide industry with a framework for testing topical products and help regulators make decisions on the safety and health risks associated with topical products containing nanomaterials.



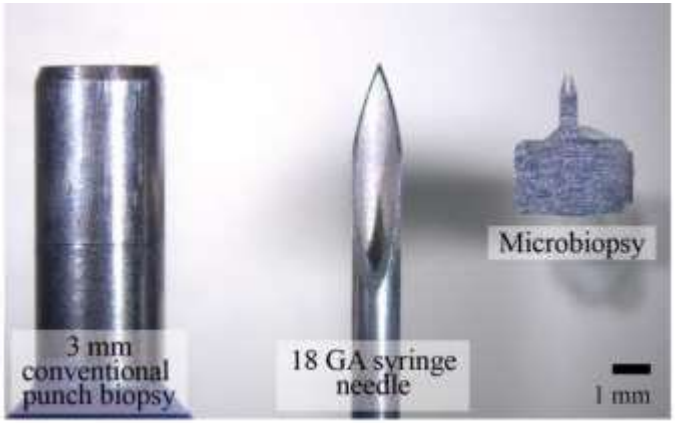
Microbiopsy

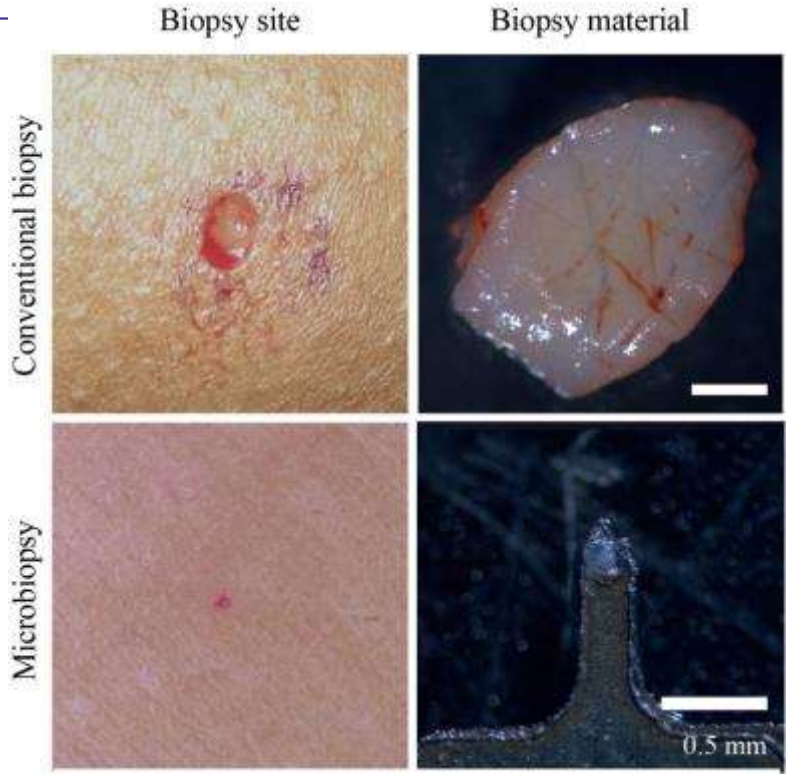
Micro-device for rapid, minimally invasive skin sampling

Clinical follow-up of microbiopsy site



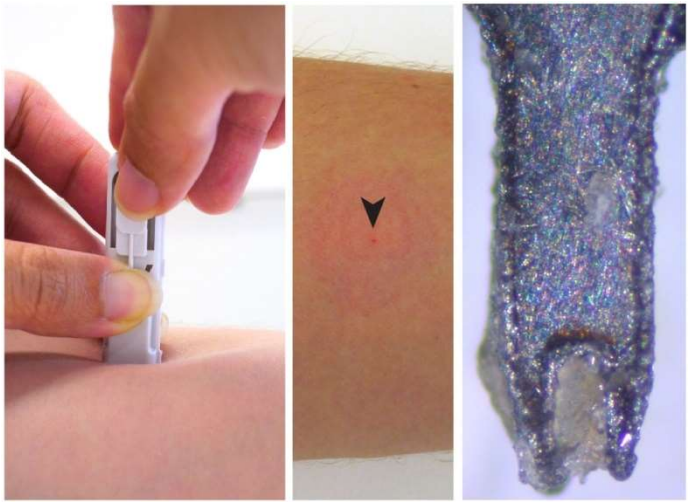
Conventional punch biopsy and Microbiopsy™





Sunscreen Study Design

Volunteer's forearm was tape-stripped (asterisk). Barrier-disrupted skin was treated with ZnO-NP on a separate arm to prevent cross-contamination.



Microbiopsy samples were collected for live cell assays.

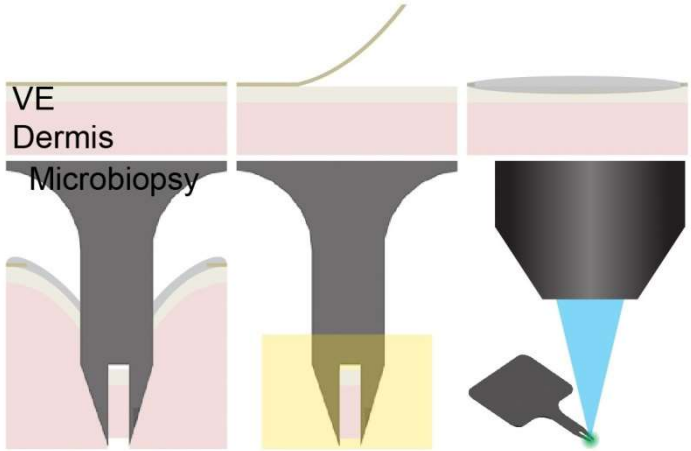


Illustration of microbiopsy collection to staining of oxidative stress biomarker reagents to imaging with confocal microscopy.

Conclusions

- Microbiopsy is a quick and suture-free approach to perform live cells assays using tissue obtained from human volunteers.

Acknowledgements

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