Nondecisional radiation protection remarks on nanoparticles

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Disclaimer

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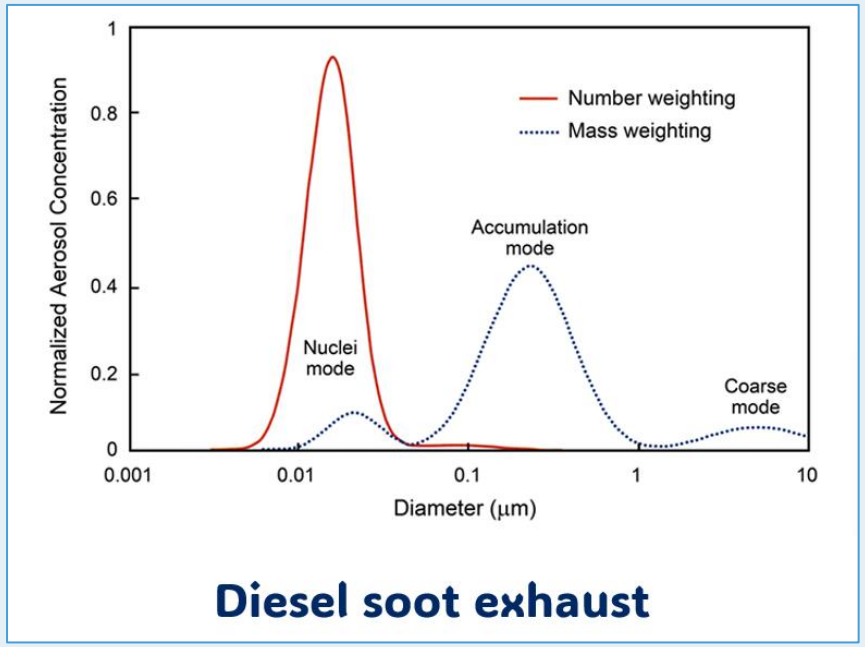
Nanoparticle exposure assessments

- Emphasize radioactive nanoparticles here
- Acknowledge broader field of study for nonradioactive nanoparticles



Kittelson, D. "Engines and nanoparticles: A review." *J. Aerosol Sci.* 29(5–6): 575–588; 1998.

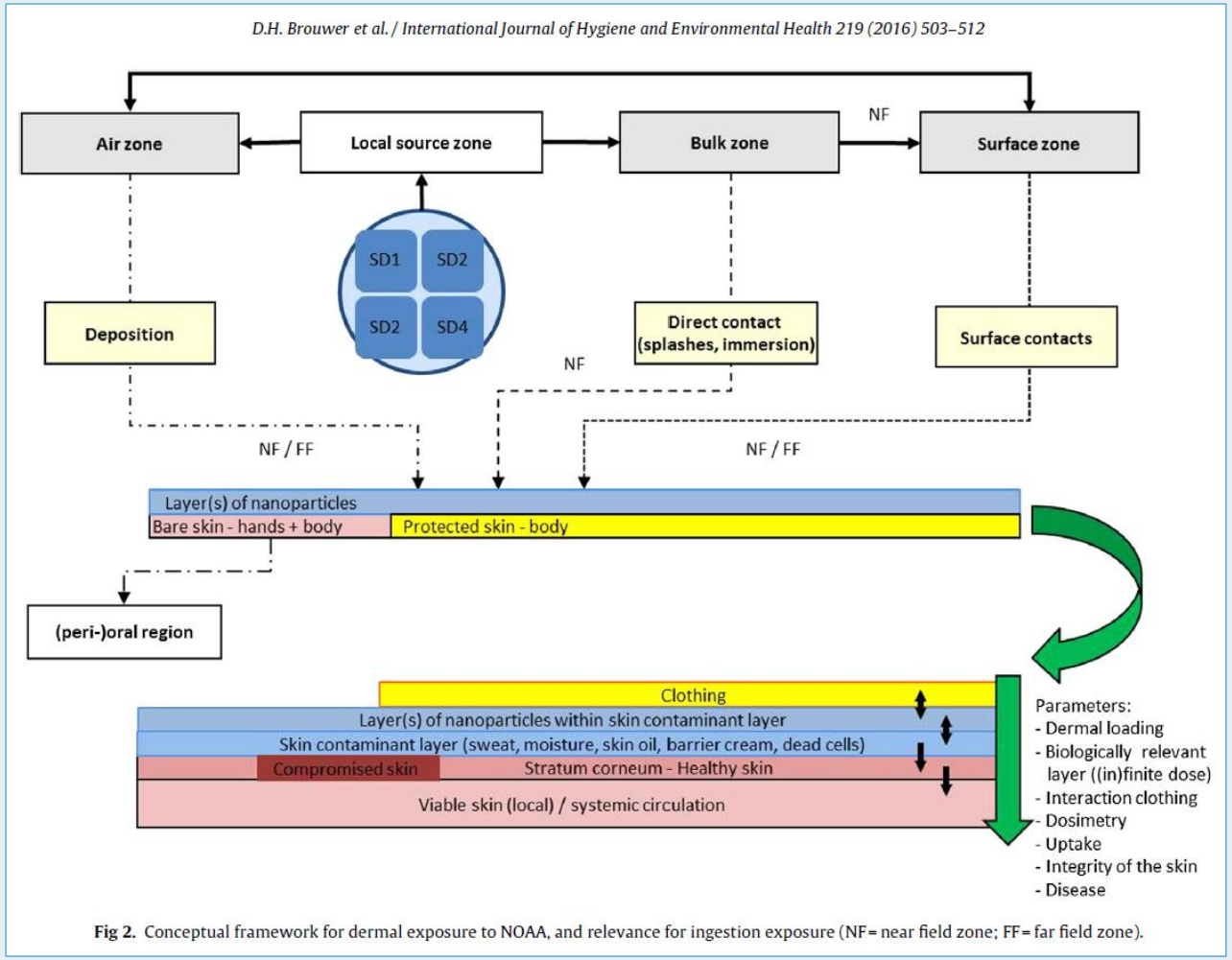
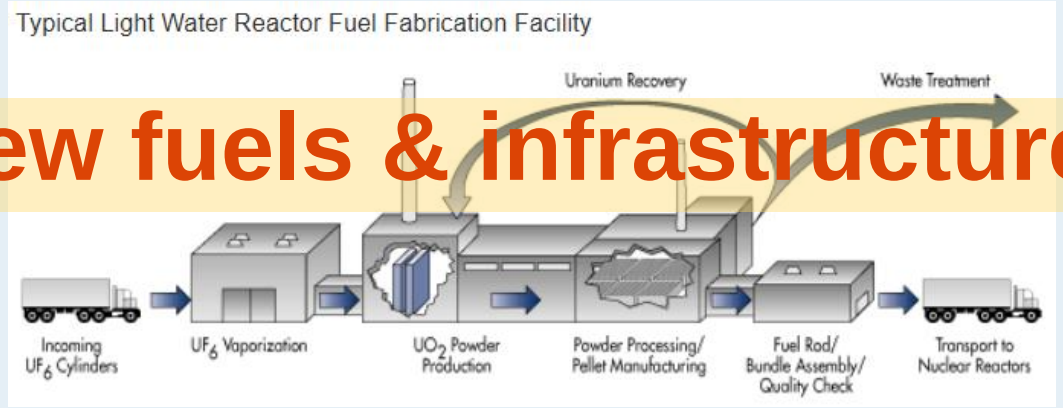


Fig 2. Conceptual framework for dermal exposure to NOAA, and relevance for ingestion exposure (NF = near field zone; FF = far field zone).

Motivation

Advanced reactors & new nuclear fuels



nrc.gov

New fuels & infrastructure

nrc.gov

Objective

Introduce technical discussion points

Nondecisional, no prejudgement

Risk triplet

- What can go wrong?
- How likely is it?
- What are the consequences?

Radiation protection considerations

Potential Impacts

If new technologies significantly increase the likelihood of

human exposure to radioactive nanoparticles…

What are the challenges to existing regulatory frameworks and dosimetric models?

Discuss four nanoparticle topics

- Increased nanoparticle solubility $\xrightarrow{?}$ soluble uranium definition
- Dominant ICRP-66 deposition in deep lung $\xrightarrow{?}$ revised inhalation dose coefficients
- Influences of particle agglomeration & degradation after deposition
- Small nanoparticle absorption by intact skin $\xrightarrow{?}$ enhanced skin or effective doses

Nanoparticle solubility

Remarks by NCRP

National Council on Radiation Protection and Measurements (NCRP) cites nanoparticle potential:

- More reactive in biological systems from large $\frac{\text{surface area}}{\text{mass}}$ ratio
- Unique particle cell interactions including cell entry and translocation across cell membranes

Sufficiently similar to soluble behavior?

Yes & No

Nanoparticles reach the blood stream, but translocation rates & tissue distributions are very different.

- Not amenable to existing systemic biokinetic models
- New approaches likely needed

Soluble Uranium Implications

Based older ICRP-26/30 dosimetry

INHALATION CLASS	BLOOD UPTAKE FRACTION, f_1	REGULATORY POSITION
D	0.05	Soluble
W	0.05	Soluble
Y	0.002	Insoluble

Benke et al. "Soluble Uranium Definition for Regulatory Compliance." ADAMS Accession No. ML14175A565. Conference presentation. July 2014.

Regulatory Guide 8.34, Rev. 1 (NRC, 2022)

- Class D and W compounds are considered "soluble" uranium compounds.
- Class Y compounds are considered insoluble.

Inhaling mixtures of uranium compounds

- Radiotoxicity more limiting when Class Y abundance greater than approx. 9%
- Chemotoxicity more limiting when Class Y abundance less than approx. 9%

For micrometer-sized aerosols.

Nanoparticle behavior could change these conclusions.

Renal toxicity, a concern for some elements

in NCRP-176 (2017)

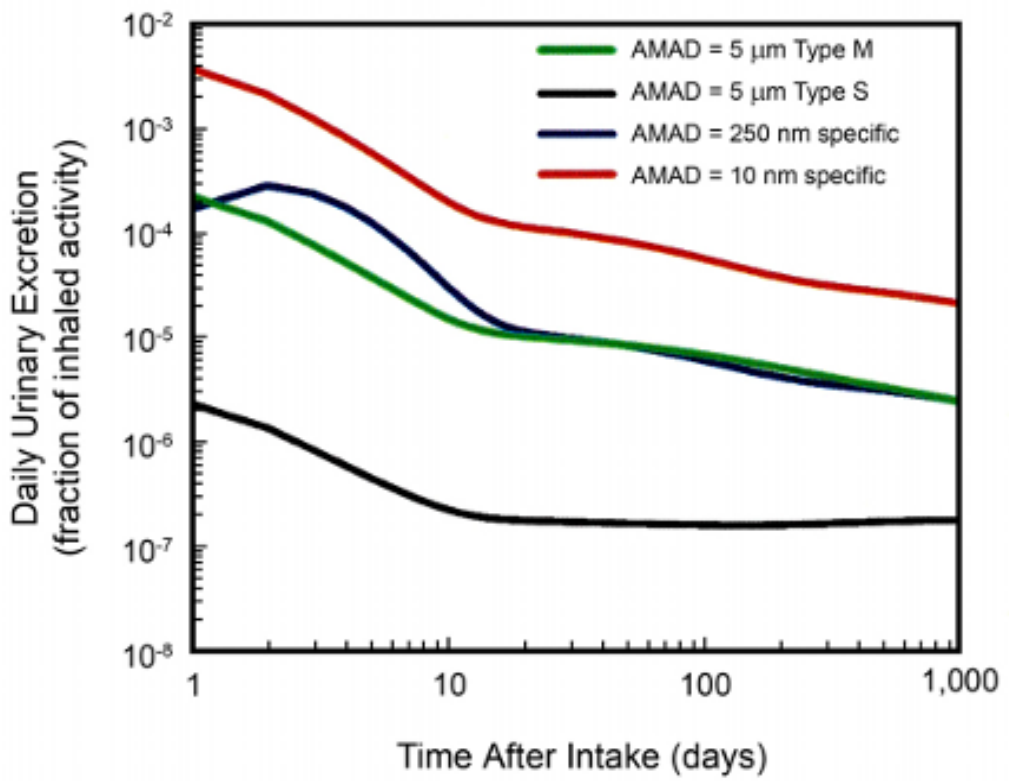


Fig. 7.1. Comparison of calculated daily ^{239}Pu urinary excretion rates in humans based on default particle size and blood absorption parameters to rates based on material-specific solubility parameters derived from plutonium NP studies (Cash, 2014; Cash *et al.*, 2016).

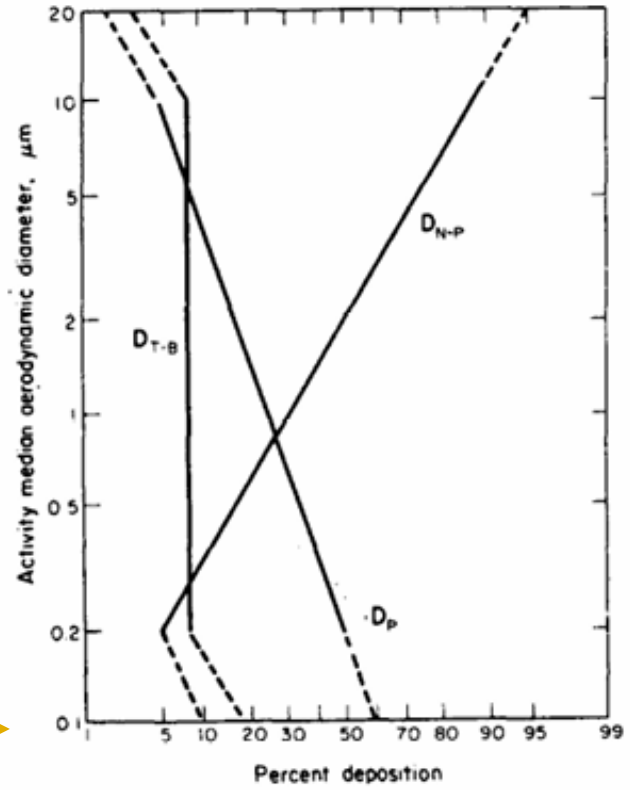
- Correlate greater urinary excretion rates to kidney concentrations
- Chemotoxicity driven by persistent elemental concentrations in the kidney
- Combined nanotoxic & chemotoxic effects have not been ruled out

When addressed, radiotoxicity limitations for nanoparticles could be more restrictive

- Potential saving grace?
- Caution: Physicochemical toxicity of radioactive nanoparticles may be potentially greater than radiotoxicity alone
- Significant uncertainty remains

Deep lung deposition

The figures 5.1 and 5.2 published on pages 24 and 25 of ICRP Publication 30 are amended as follows:



?→

Nanoparticles not addressed by ICRP-30 (1979)

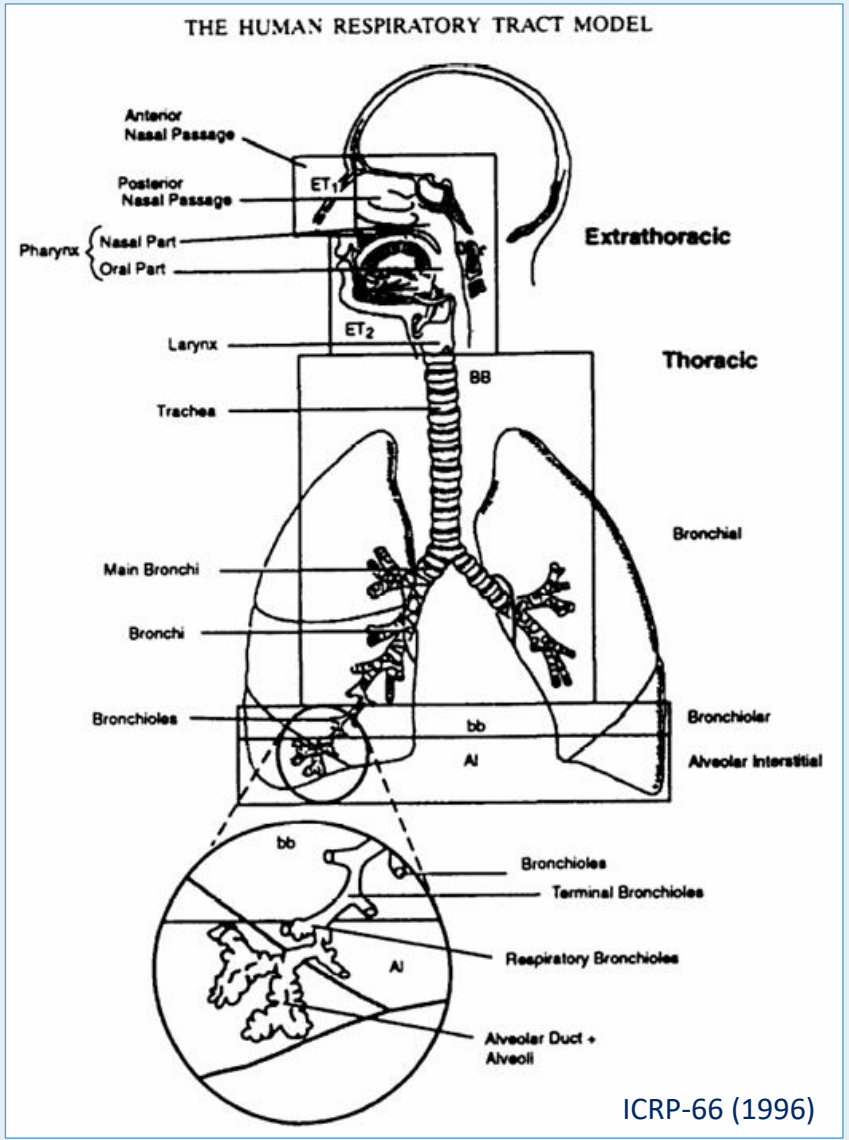
Fig. 5.1. Deposition of dust in the respiratory system. The percentage of activity or mass of an aerosol which is deposited in the N–P, T-B and P regions is given in relation to the Activity Median Aerodynamic Diameter (AMAD) of the aerosol distribution. The model is intended for use with aerosol distributions with AMADs between 0.2 and 10 μm and with geometric standard deviations of less than 4.5. Provisional estimates of deposition further extending the size range are given by the dashed lines. For an unusual distribution with an AMAD of greater than 20 μm, complete deposition in N–P can be assumed. The model does not apply to aerosols with AMADs of less than 0.1 μm.

Lung deposition

– Severe data gap with old lung modeling…

– filled by newer model?

Differences in biokinetic behavior



ICRP-66 (1996)

NCRP-176 (2017)

– Compared to micrometer-sized particles, differences in biokinetic/dose distributions for radioactive nanoparticles in lung microstructure are not accounted for by current models.

– Unclear if ICRP-66 (1996) model is adequate.

ICRP models greater sensitivity to nanoparticles vs. NCRP models

ICRP Publication 66 (1994) Lung Model

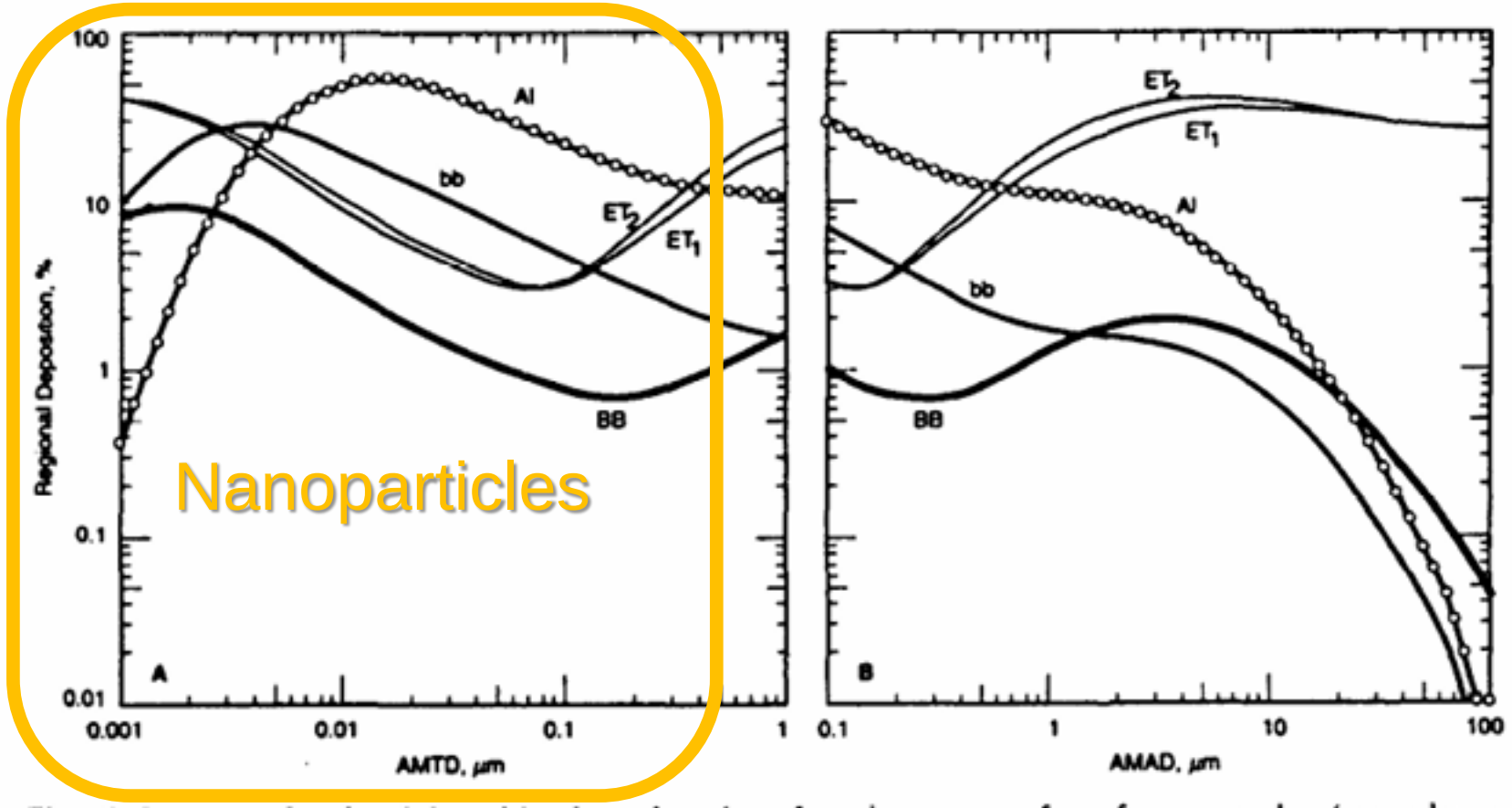


Fig. 43. Summary: fractional deposition in each region of respiratory tract for reference worker (normal nose breather). Deposition is expressed as a fraction of activity present in volume of ambient air that is inspired, and activity is assumed to be log-normally distributed as function of particle size (for particles of density 3.00 g cm^{-3} and shape factor 1.5).

Nanoparticles

- Very high deep lung deposition
- Agglomeration shifts behavior to the right
- Borderline nanosizes, notionally factors of 2 to 4 times higher Pu inhalation dose coefficients
- Small nanosizes, notionally factors of 6 to 11 times higher Pu inhalation dose coefficients
- Unique distribution kinetics absent

Particle agglomeration & degradation

$$\text{surface transfer to skin} \propto \frac{1}{\text{particle size}}$$

Much greater transfer from surfaces to skin

- Inverse particle size relationship
- Smaller particles → greater skin transfer

Potential implications for fixed vs. removable contamination

Table 1
Summarized results of the transfer experiments with nano-ZnO.

Surface	Particle Size	N	Transfer Efficiency (%)		
			Range	GM	GSD
Metal	micron	4	3.5–27	12	2.4
	nano	4	53–106	77	1.4
Wood	micron	4	0.9–10	2	3.2
	nano	4	14–40	20	1.6

Brouwer et al. Occupational dermal exposure to nanoparticles and nano-enabled products: Part 2, exploration of exposure processes and methods assessment. *Int. J. Hyg. Environ. Health*. 219: 503–512; 2016.

Agglomeration

Brouwer et al. (2016)

- Nanoparticles attached to large particles expected to constitute main deposition for aerosol skin deposition.
- Increases in surface deposition observed for aerosols with particle sizes < 200–300 nm, for which diffusion and Brownian motion are more important.

NCRP-176 (2017)

- Mass concentration data may be insufficient for characterizing radioactive nanoparticle contributions
- Nanoparticle aerosols consist of *very large* particle-number & *small* particle-mass concentrations
- Substantial coagulation within seconds for initial aerosol concentrations >10^7 particles cm^{-3} in air
  - Constrained upper bound for nanoparticle concentrations
  - Maximal concentrations for longer-term exposures likely below 5×10^5 particles cm^{-3} in air

Skin absorption

Skin pathway for nanoparticles (NP)

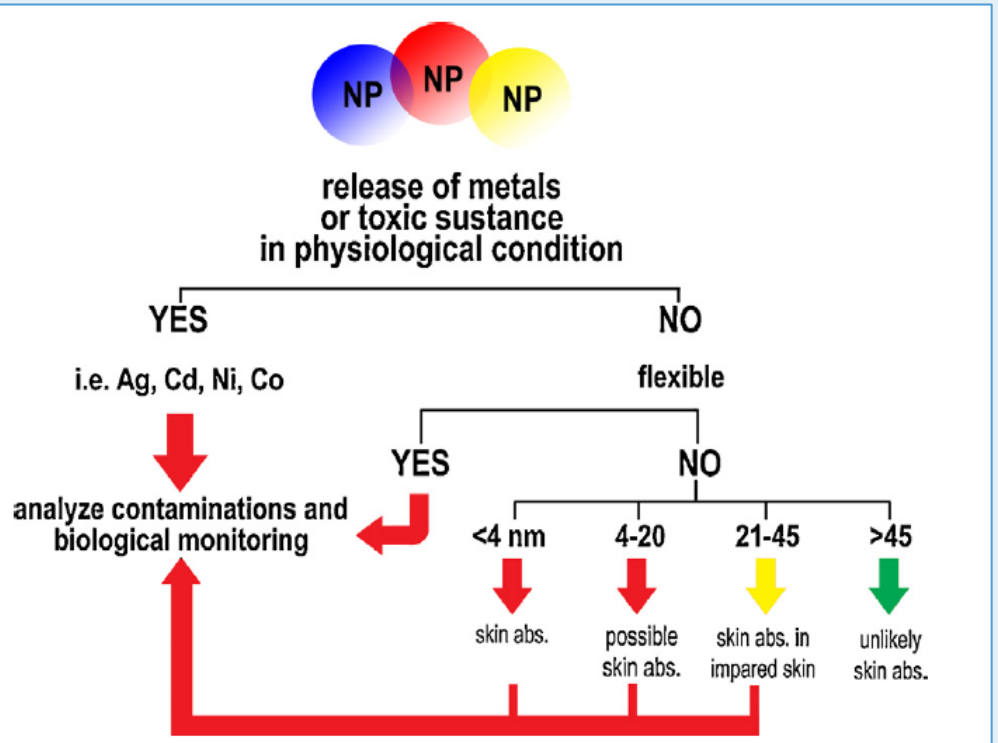


Fig. 1. Skin absorption of NOAA considered available knowledge.

Filon et al. Occupational dermal exposure to nanoparticles and nano-enabled products: Part I—Factors affecting skin absorption. *Int. J. Hyg. Environ. Health*. 219: 536–544; 2016.

Nanoparticles

- At least one dimension <100 nm
- Skin absorption more feasible
- Various studies published in the literature
  - Some studies for & some against a viable skin pathway
  - More intense debate for intermediate nanoparticle sizes

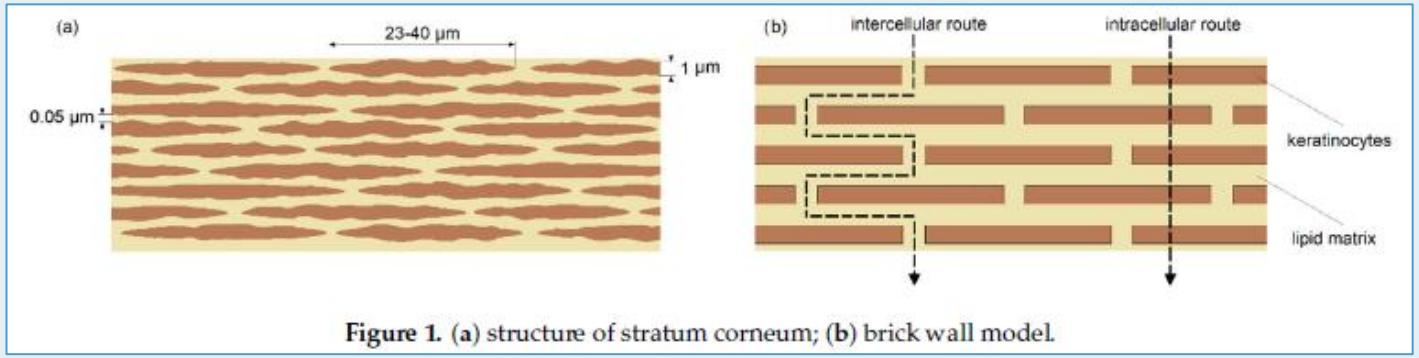


Figure 1. (a) structure of stratum corneum; (b) brick wall model.

Błaszczyk et al. The combined diffusion and adsorption concept for prediction of nanoparticles transport through dermal layers based on experiments in membranes. *Int. J. Mol. Sci*. 23: 6419; 2022.

Penetration into skin is very important to alpha particle dose delivery.

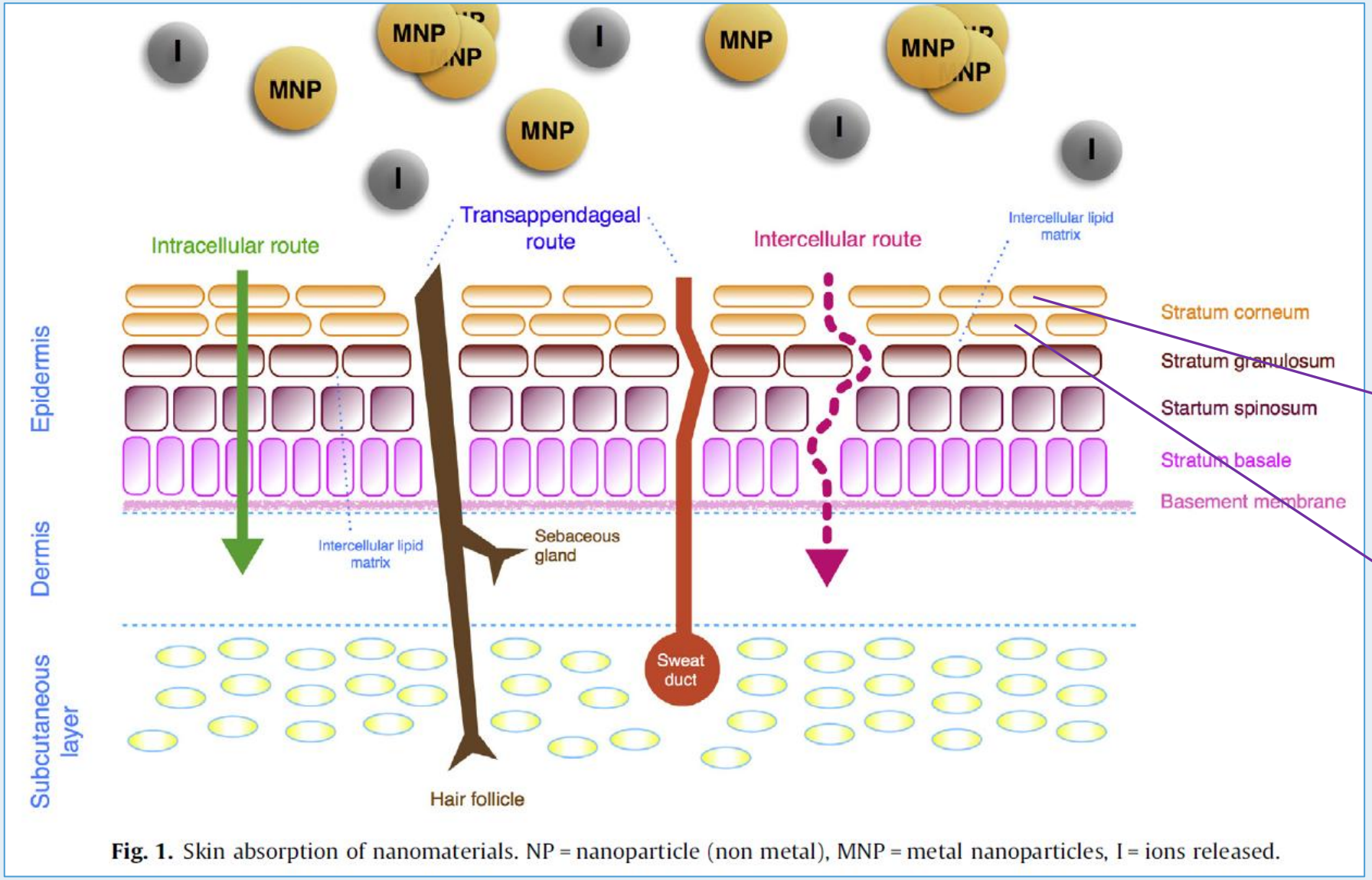


Fig. 1. Skin absorption of nanomaterials. NP = nanoparticle (non metal), MNP = metal nanoparticles, I = ions released.

Filon et al. Nanoparticles skin absorption: New aspects for a safety profile evaluation. *Reg. Toxicology and Pharmacology*. 72: 310–322; 2015.

Multiple potential routes

Some are less viable

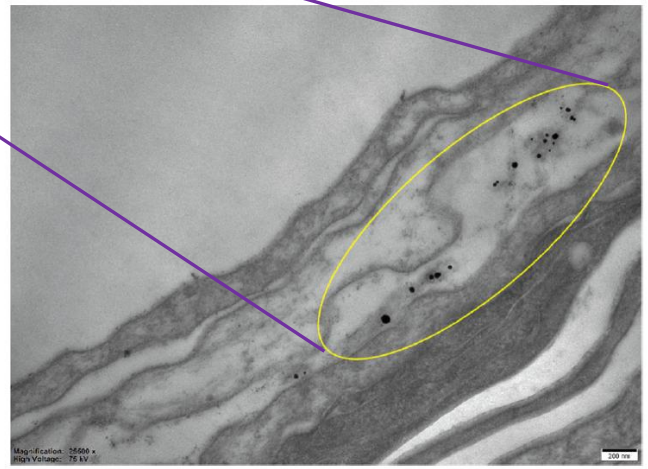
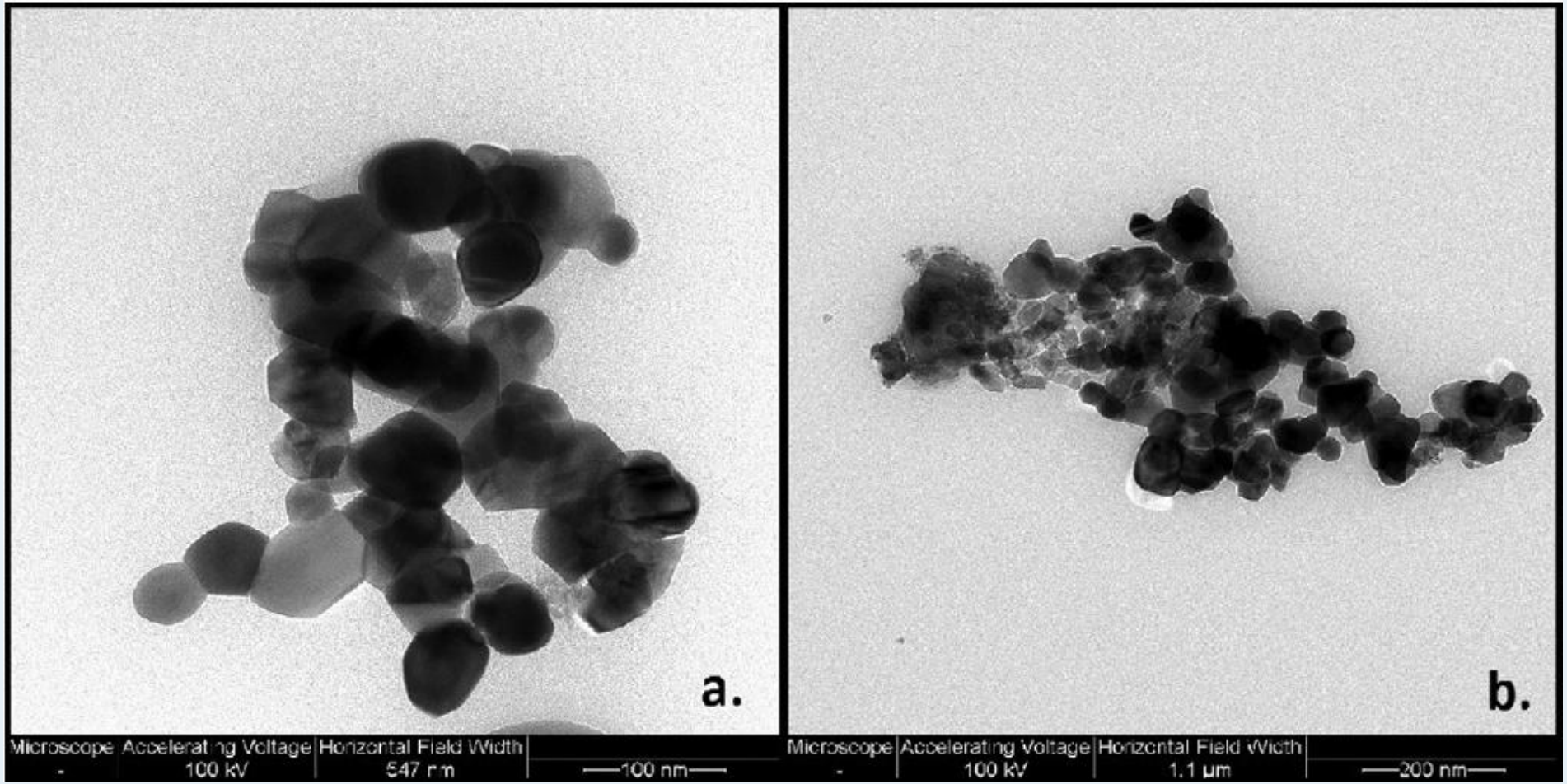


Fig. 6. TEM images of CS-AuNPs in the SC layer (shown as small particles in the circled area).

Singpanna et al. Chitosan capped-gold nanoparticles as skin penetration enhancer for small molecules: A study in porcine skin. *Int. J. Pharmaceutics*. 640: 123034; 2023.

Al_2O_3 nanoparticles on human skin (1 of 2)



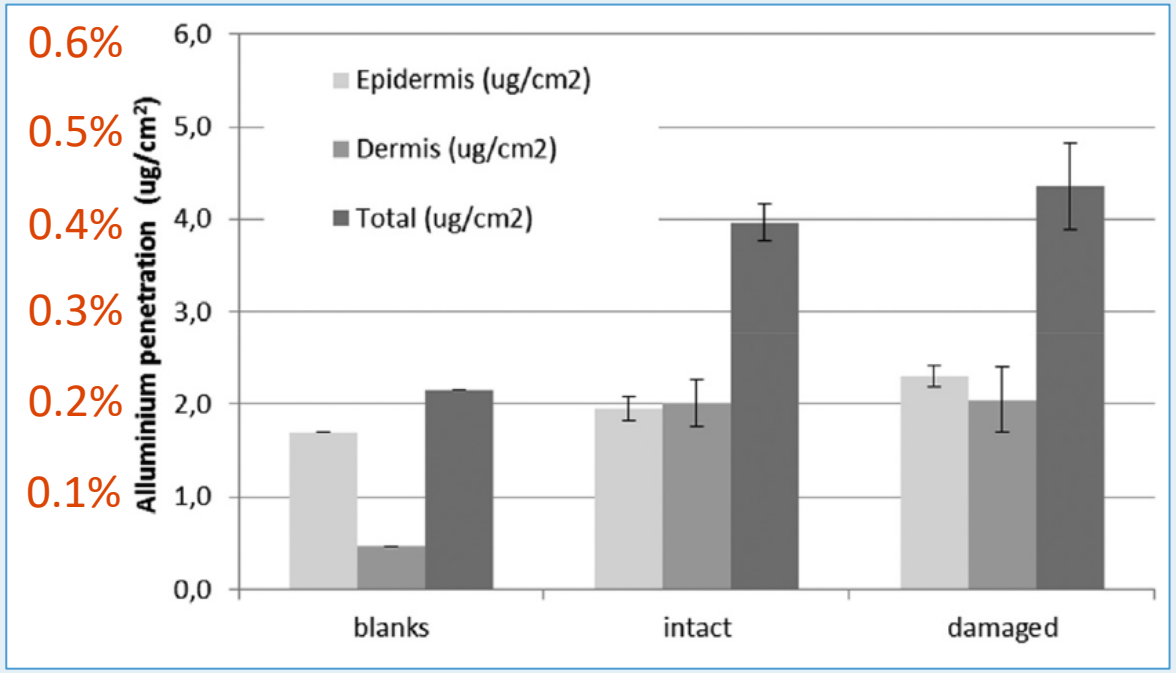
Significant clustering

Mauro et al. Oin vitro transdermal absorption of Al_2O_3 nanoparticles. *Toxicology in Vitro* 59: 275–280; 2019.

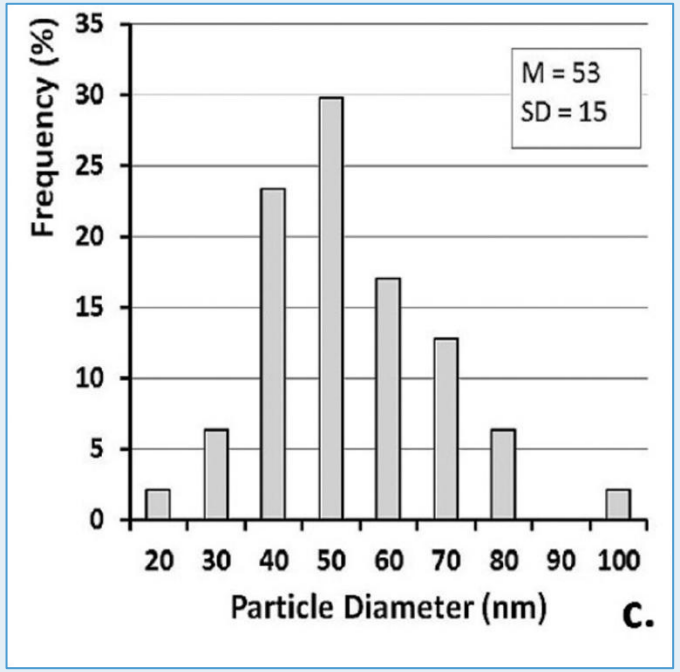
In vitro Al_2O_3 skin penetration (2 of 2)

Percent of surface exposure

Nonradioactive experimental data



Nanoparticle size distribution



Mauro et al. *In vitro* transdermal absorption of Al_2O_3 nanoparticles. *Toxicology in Vitro* 59: 275–280; 2019.

In vitro CeO_3 nanoparticle penetration

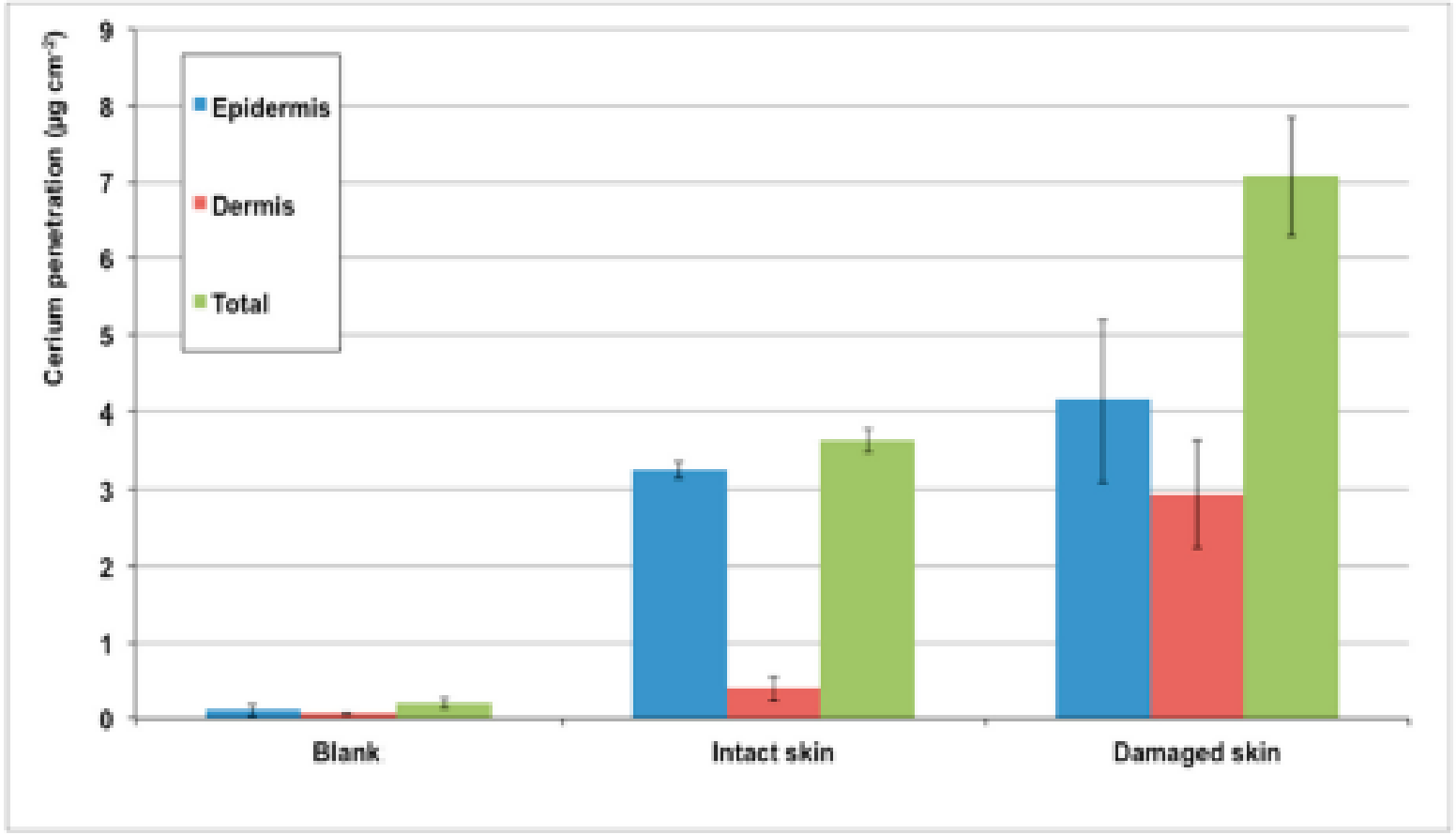


Figure 3. Cerium penetration (μg cm^{-2}) into the skin layers (epidermis, dermis, and total skin) after 24 h of exposure to a dispersion of CeO_2 NPs in synthetic sweat.

Skin integrity can affect NP penetration beyond epidermis into dermis.

Mauro et al. Cerium oxide nanoparticles absorption through intact and damaged human skin. *Molecules* 24, 3759; 2019.

Nanoparticle distribution

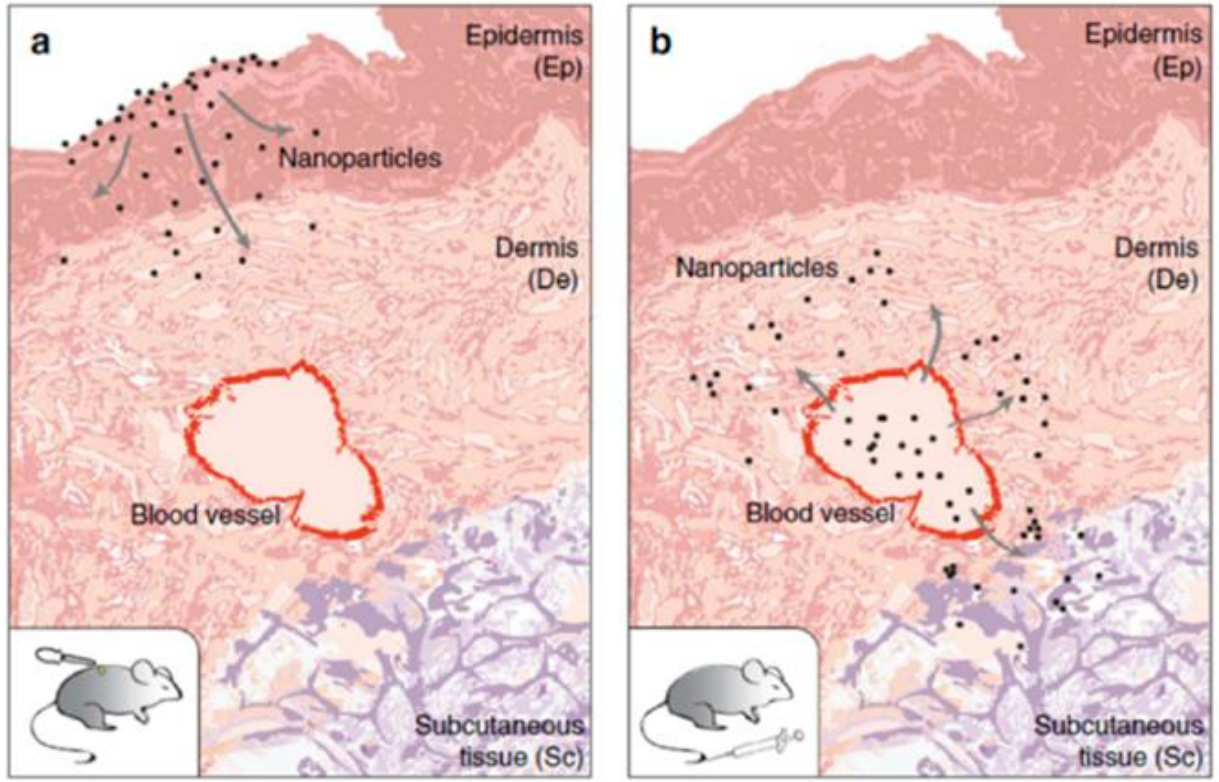


Figure 4. Route of entry of NPs in mice after topic dermal application (a) and tail-vein injection (b). When NPs were applied topically, they spread in the epidermis and dermis. The subcutaneus tissue (hypodermis) was reached by NPs only after the injection. Reprinted by permission from Macmillan Publishers Ltd. Nature Communication copyright (2014) [78].

78. Sykes, E.A.; Dai, Q.; Tsoi, K.M.; Hwang, D.M.; Chan Warren, C.W. Nanoparticle exposure in animals can be visualized in the skin and analysed via skin biopsy. *Nat. Commun.* **2014**, *5*, 3796. [CrossRef] [PubMed]

a Skin surface application

b Mouse tail-vein injection

De Matteis, V. Immune response, biodistribution and in vitro/in vivo toxicity evaluation. *Toxics* 5, 29; 2017.

No conclusions

Nondecisional remarks with discussion

Questions?