Evaluating the Regulation *of* Shrinking Cosmetics and Sunscreens

to

Conference on Governance of Emerging Technologies

May 20, 2013

Professor Robin Fretwell Wilson

Class of 1958 Law Alumni Professor of Law
Washington and Lee University School of Law

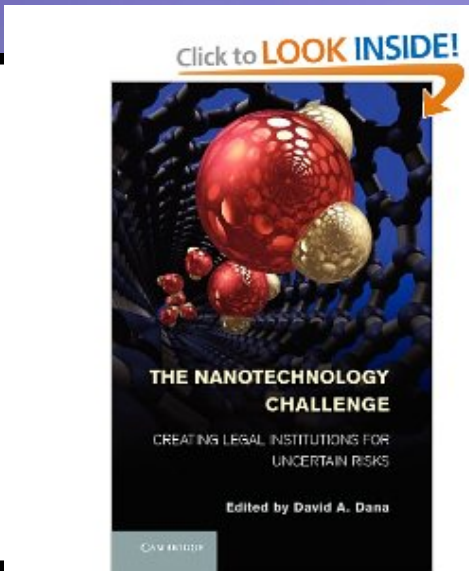
Roger and Stevie Joslin Professor of Law
University of Illinois College of Law
(as of June 15, 2013)

Most Prevalent NT Use

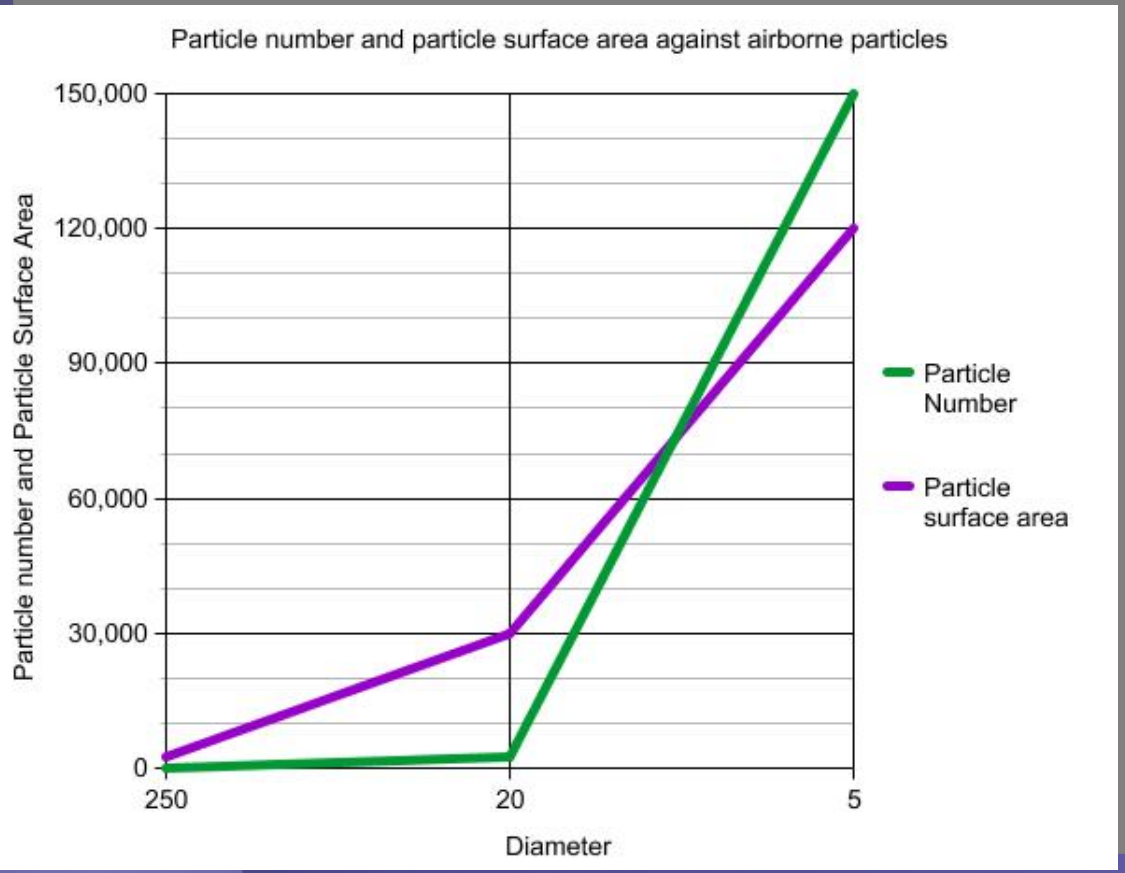
By 2006, 5% of all cosmetics contain nano-products

Cosmetics account for more than 15% of NT market

More than 300 sunscreens as of 2011



With Promise Comes *Uncertainty*



"Although impressive from a physiochemical viewpoint, these novel properties of [engineered nanomaterials] raise concerns about adverse effects on biological systems...Some studies suggest that [engineered nanomaterials] are not inherently benign and that they affect biological behaviors at the cellular, subcellular and protein levels."

--Nel et al*, Science *2006

Regulating with Incomplete Information

Ignorance
(don't know what we need to figure out)

Indeterminacy

(figure out some things, need more data)

Educated Risk Assessment

Regulators Always Act in Contexts of Greater or Lesser Inform

Existing Law is Inadequate to Respond to Risk

The FDA has "only limited authority for potentially high risk nano-products[, like] cosmetics."

Cosmetics have a "distinct regulatory pathway[] and thereby [receive] distinct FDA scrutiny."

The scope of the FDA's authority depends on the product's intended use as described by its maker. Thus, the "FDA only regulates to 'claims by a sponsor.'"

--Norris Alderson, Associate Commissioner for Science at the FDA

Health Claims

JUVENA OF SWITZERLAND

JUVENA notes that once NPs have "travel[led] deep and directly into the skin," these NPs provide a "supply depot" so that " the skin can take what it needs, whenever it needs it" by drawing the "tiny crystals directly into the cell nucleus."

Kara Vita uses NPs "small enough to easily penetrate the skin's natural surface barrier, but large enough so the body will not counterproductively absorb them prior to full effectiveness."

KARA VITA

Regulatory Vacuum

...unlike the other three regulatory silos, Cosmetics have:

- NO premarket approval
- NO proof of safety before sale
- NO ability to recall
- NO post-market safety monitoring

Regulatory Vacuum

...but Cosmetics cannot be:

- misbranded
- adulterated

Congressional Assumptions

The assumption that skin is **impermeable** shaped the regulation of cosmetics.

The FDA Thought Existing Regulation was O.K.

- ***"Currently there are no testing requirements that are specific to nanotechnology products."*** ***--Nakissa Sadrieh, PhD, Office of Pharmaceutical Sciences, CDER, FDA, 2006***

- ***FDA is "not currently aware of safety concerns" although FDA is "planning additional studies to examine the effects of select NPs on skin penetration.... Existing requirements may be adequate for most NT products that we will regulate."*** ***–FDA Nanotech FAQ, 2010***

FDA Long Thought NPs Acted like SSPs

- ***1999 Sunscreen Monograph did not classify NPs as "new ingredients."***

- ***FDA "does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of the titanium dioxide originally reviewed by the Panel"***

--Sunscreen Drug Products for Over-the-Counter Human Use; Final Monograph, 64 Fed. Reg. 27666, 27671 (May 21, 1999)

FDA Was Alone in this View

"It is clear that nanoparticles have different properties to the same chemical at a larger scale, and the implications of these different properties for long-term toxicity to the skin require rigorous investigation on a case-by-case basis."

The Royal Society, *Nanoscience and nanotechnologies: opportunities and uncertainties.*

What Do We Know About the Hazards to Humans?

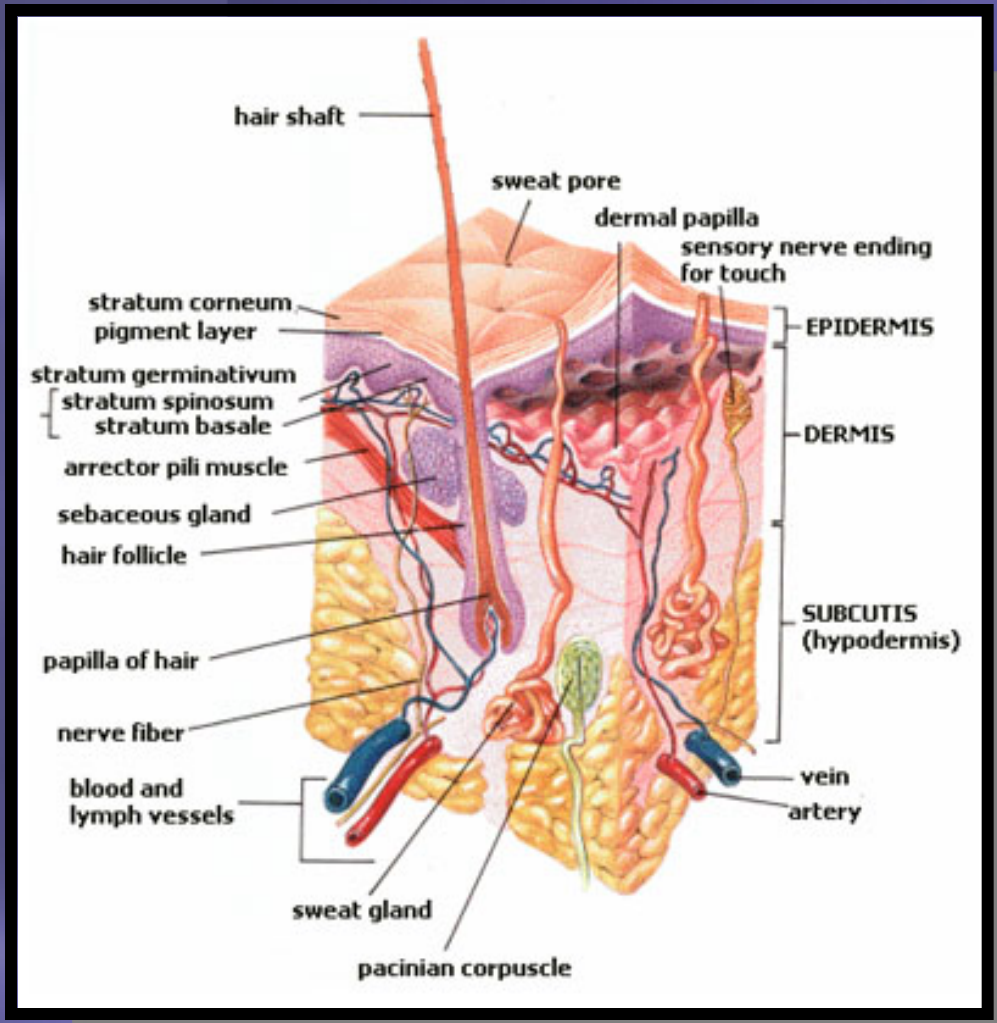
"Some nanoparticles readily travel throughout the body, deposit in target organs, penetrate cell membranes, lodge in mitochondria, and may trigger injurious responses."

--Nel et al, *Science* 2006

Three routes in:

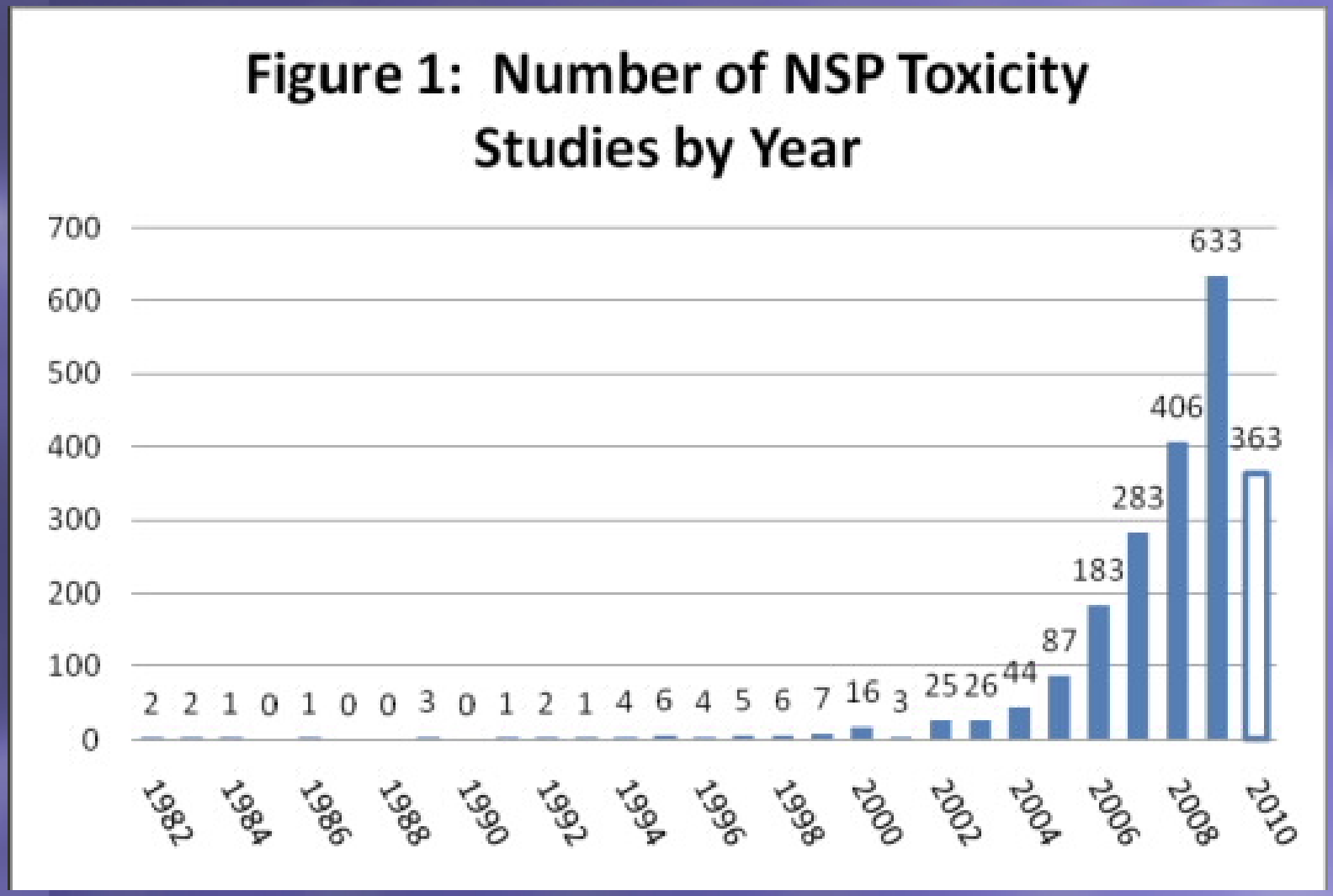
- Inhalation,
- Ingestion, and
- Dermal exposure

What Do We Know About the Hazards to Humans?

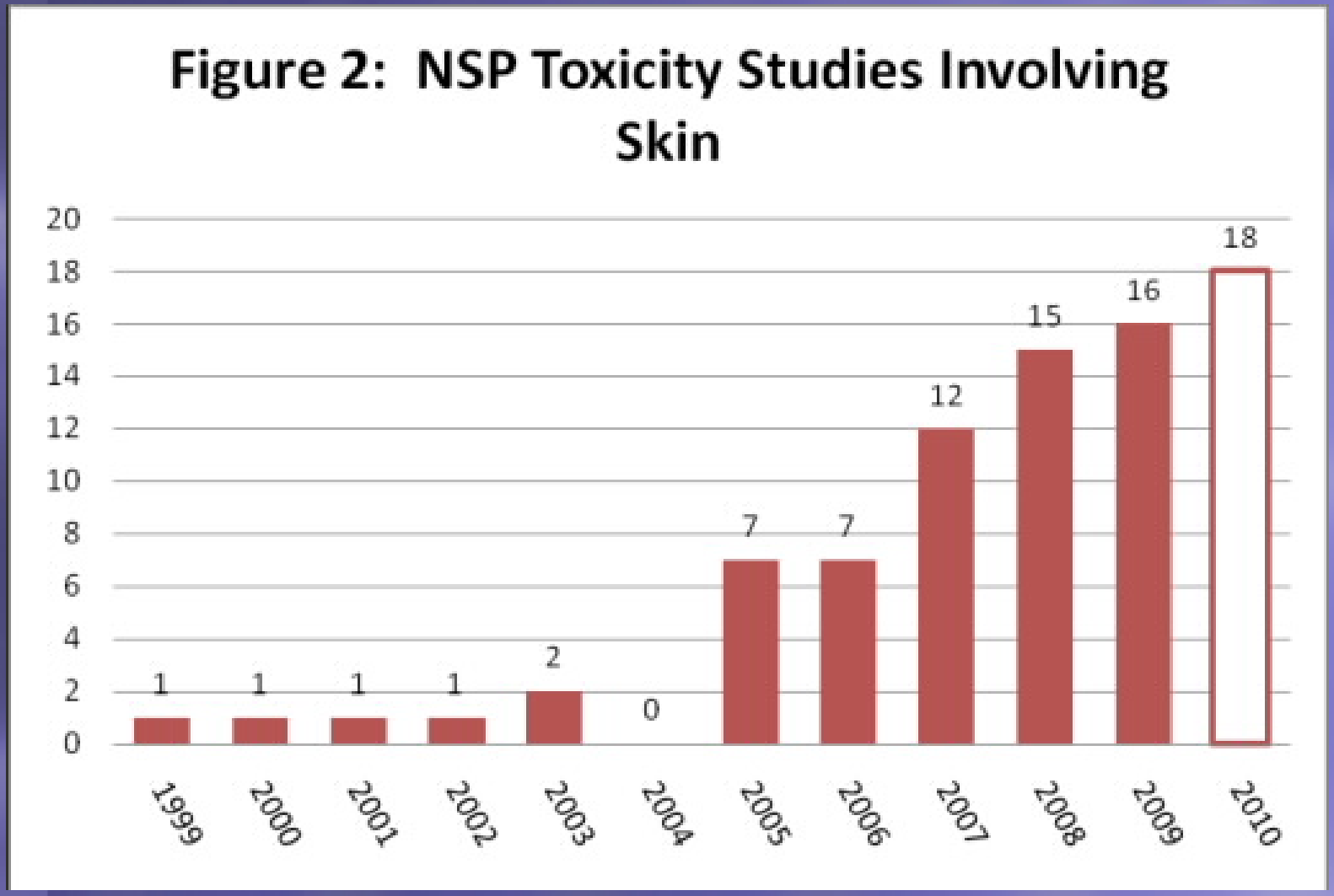


Oberdörster and colleagues worried that “NPs, once in the dermis, will localize to regional lymph nodes” and may conceivably be taken up by sensory skin nerves along which they can translocate since such “[n]euronal transport… is well established for herpes virus.”

Little Evidence in 1999…



Little Evidence in 1999…

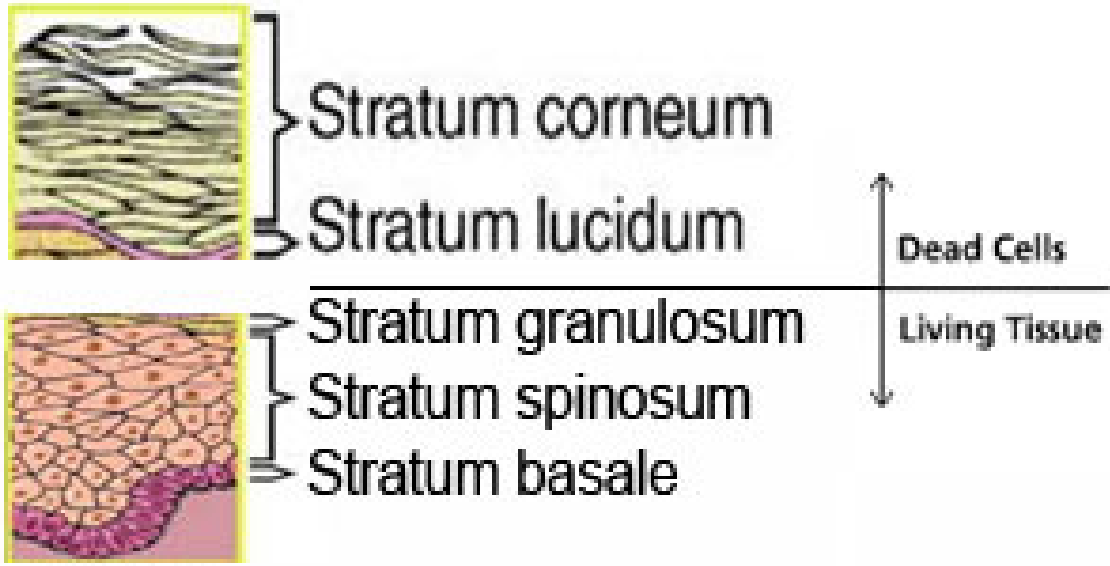


Nano-Particle Studies

Scientists have studied both NP toxicity and NP ability to penetrate healthy and damaged skin

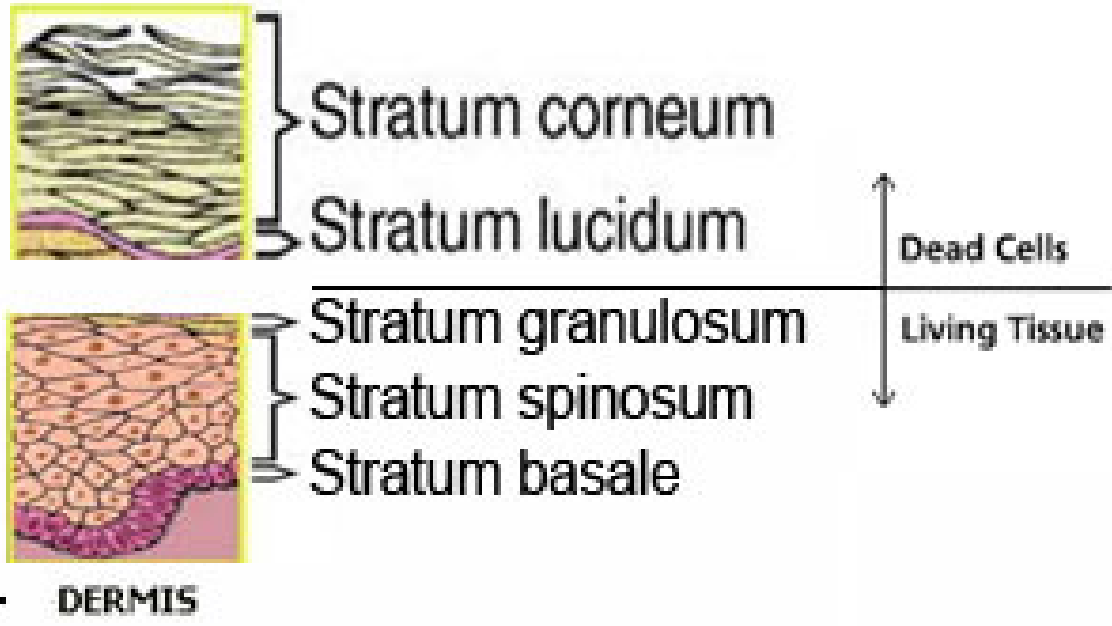
Nano-Particle Studies

Scientists have studied both NP toxicity and NP ability to penetrate healthy and damaged skin



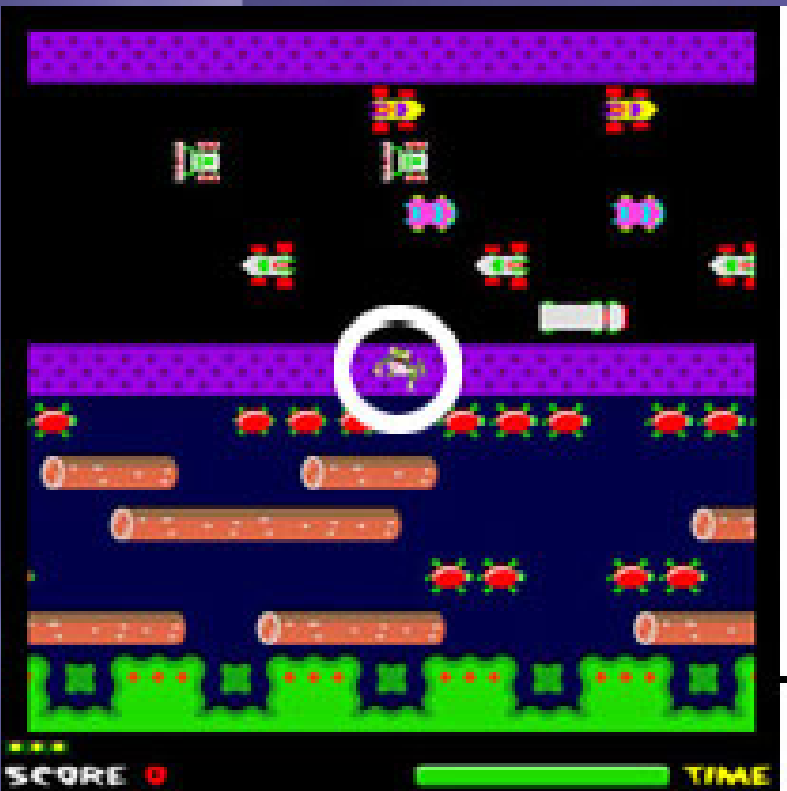
Sunscreen NPs: Human Studies

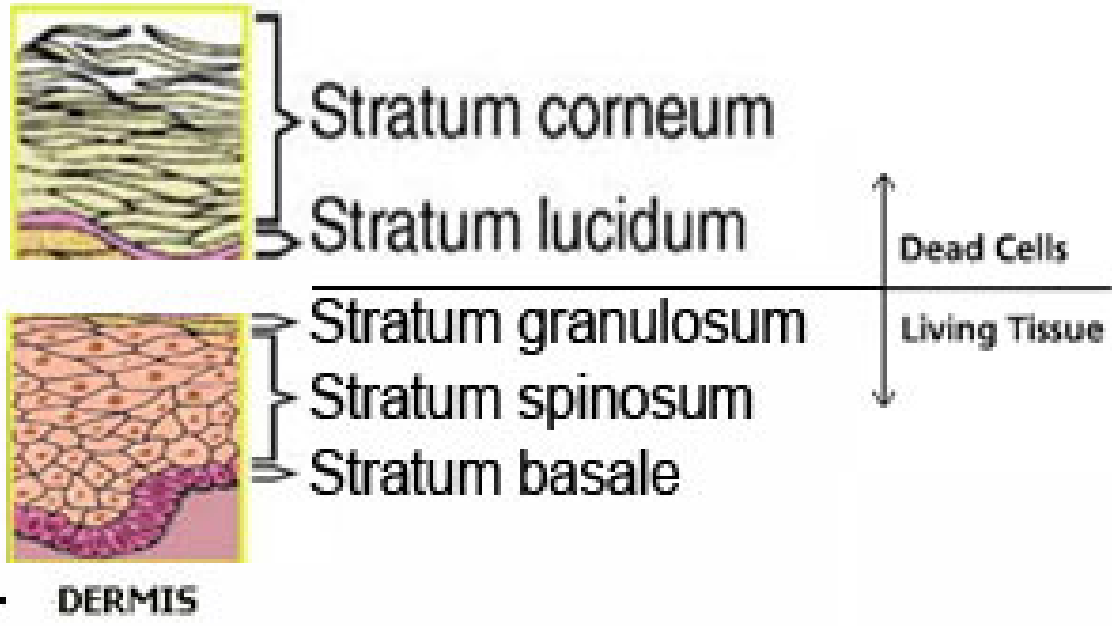
In a 1990 study by Agren et al., zinc oxide concentrations of 15 µg/g and 24 µg/g were applied to blistered skin on the lower arm of 15 volunteers to determine how far the zinc oxide would penetrate.



Sunscreen NPs: Human Studies

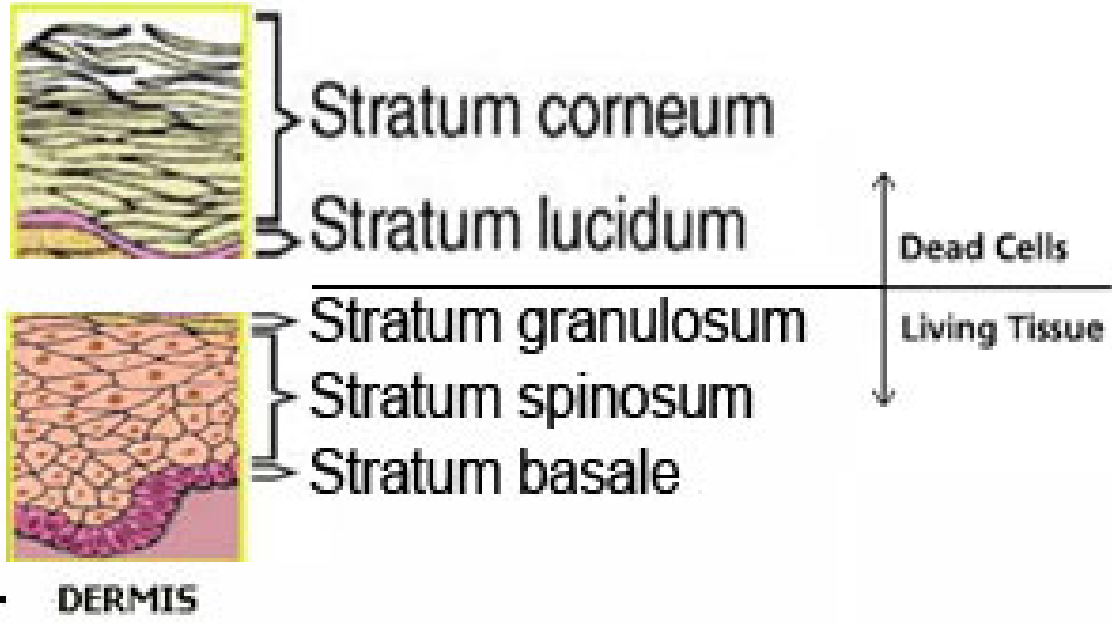
In the subjects treated with the 15 µg/g solution, zinc content was found to increase in the epidermis and in the blister fluid…





Sunscreen NPs: Human Studies

…while in the subjects treated with the 24 µg/g solution, zinc appeared to have reached the dermis.



Sunscreen NPs: Human Studies

…while in the subjects treated with the 24 µg/g solution, zinc appeared to have reached the dermis.

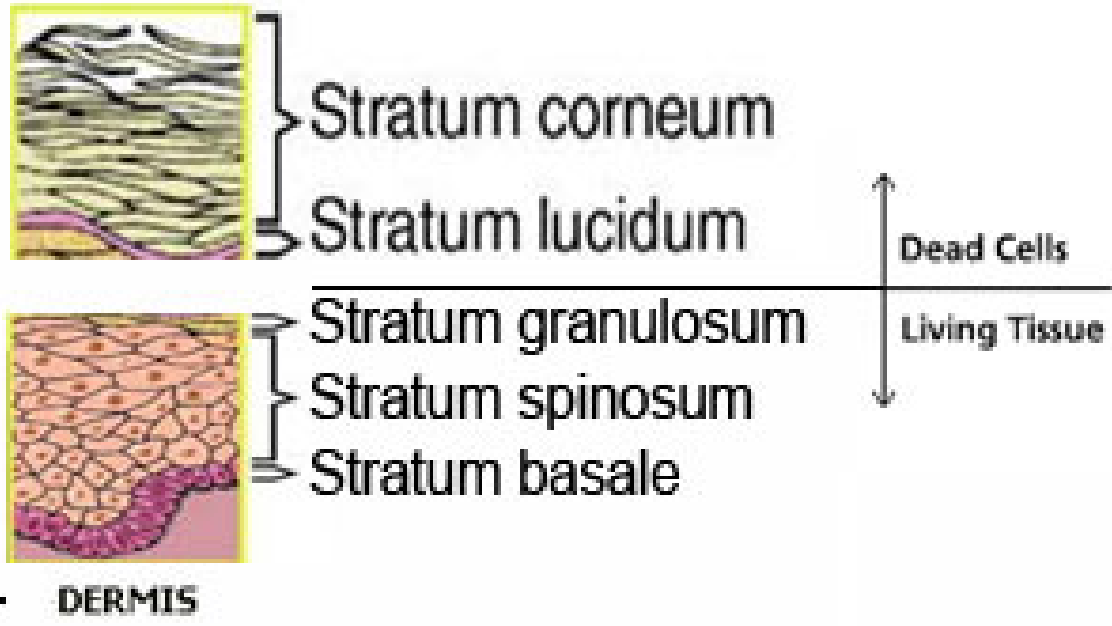
- The authors found the results problematic because “a local zinc oxide supply can influence cellular and biochemical reactions both in the epidermis and in sub-epidermal tissues.”
- N is small; studies damaged skin

Additional Penetration Studies

Unfortunately, there have not been many *in vivo* human studies, and those that have been conducted have been less than ideal, but there is still much that can be learned from *in vitro* and animal studies on the subject of NP penetration…

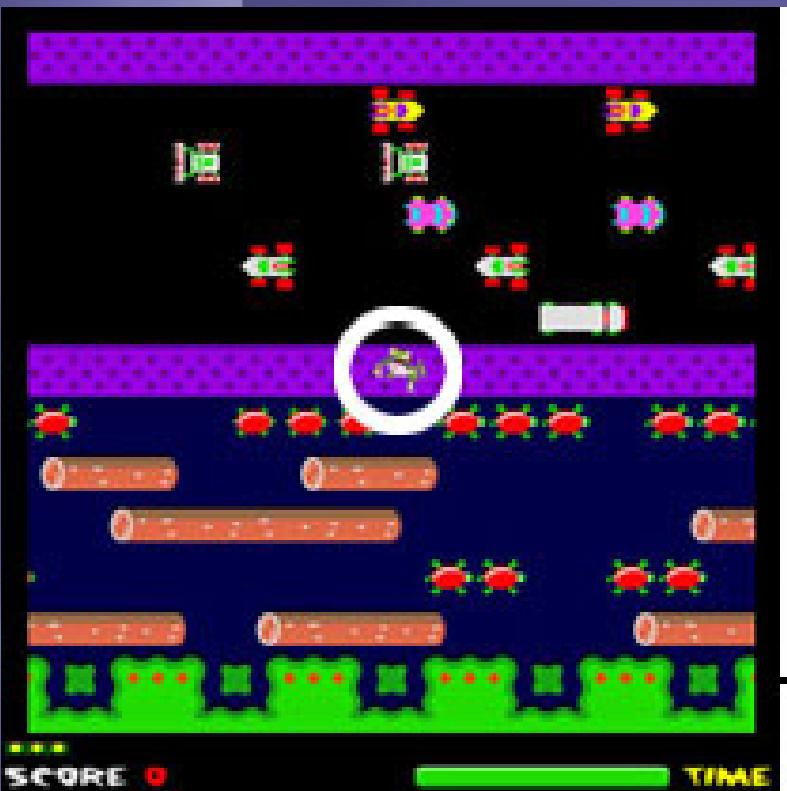
Nano-Particle Penetration Studies

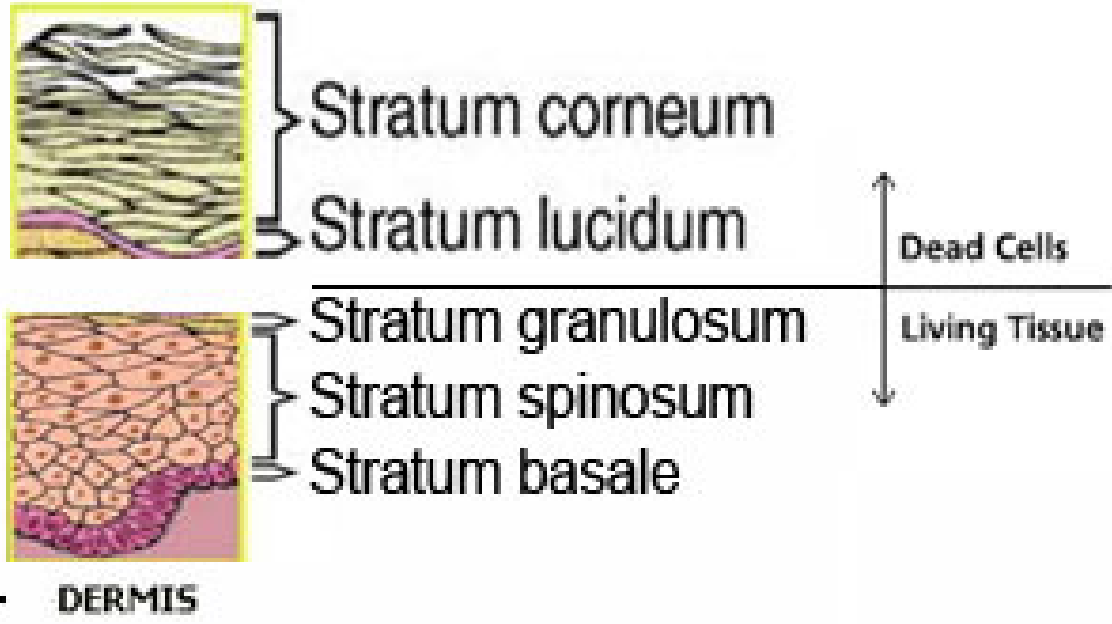
In a 2007 study by Biancamaria Baroli et al., iron oxide NPs like those used in cosmetics, ranging from 5 to 80 nm in size, were applied to full-thickness human skin samples from healthy female donors to assess penetration and permeation.



Nano-Particle Penetration Studies

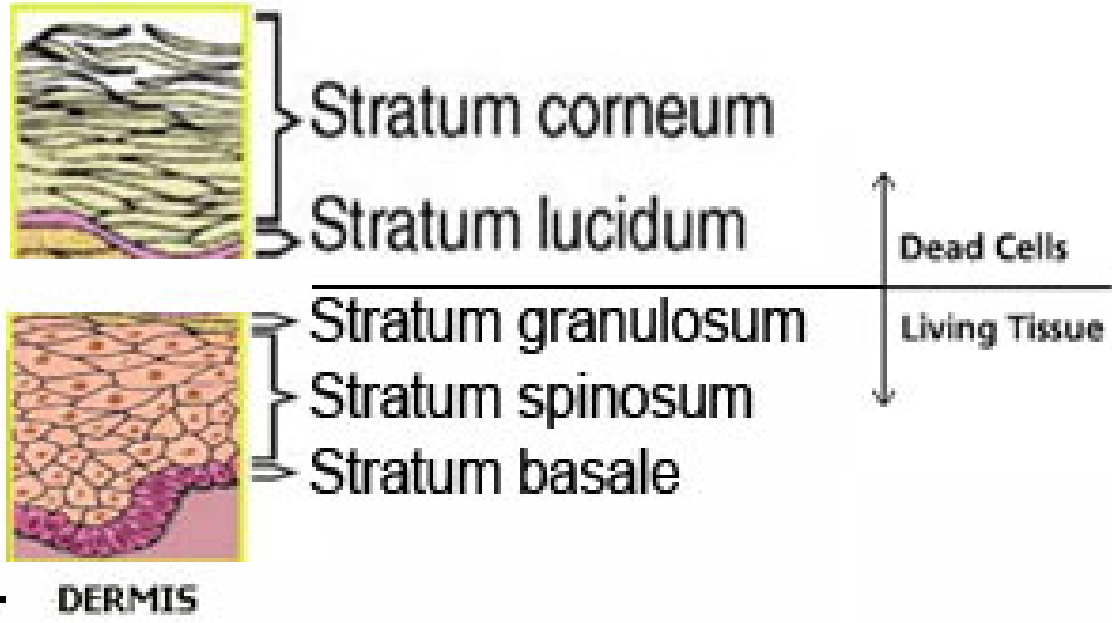
The NPs were able to penetrate the hair follicle and stratum corneum, occasionally reaching the viable epidermis…





Nano-Particle Penetration Studies

…and in rare cases appearing within the viable epidermis, but did not permeate the skin.



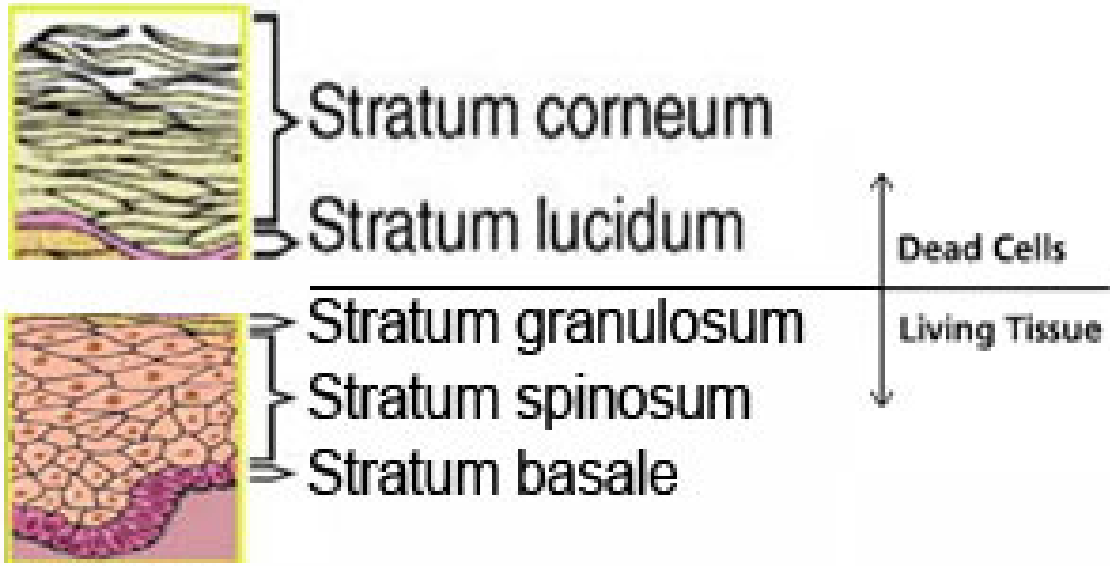
Nano-Particle Penetration Studies

…and in rare cases appearing within the viable epidermis, but did not permeate the skin.

- Authors attributed the penetration to the small dimensions of the NPs and the fact that the clusters they formed were “not rigidly fixed and may adapt to the penetration-pathway size.”
- Because of this, the authors “envisage[d] potential toxicological risks.”

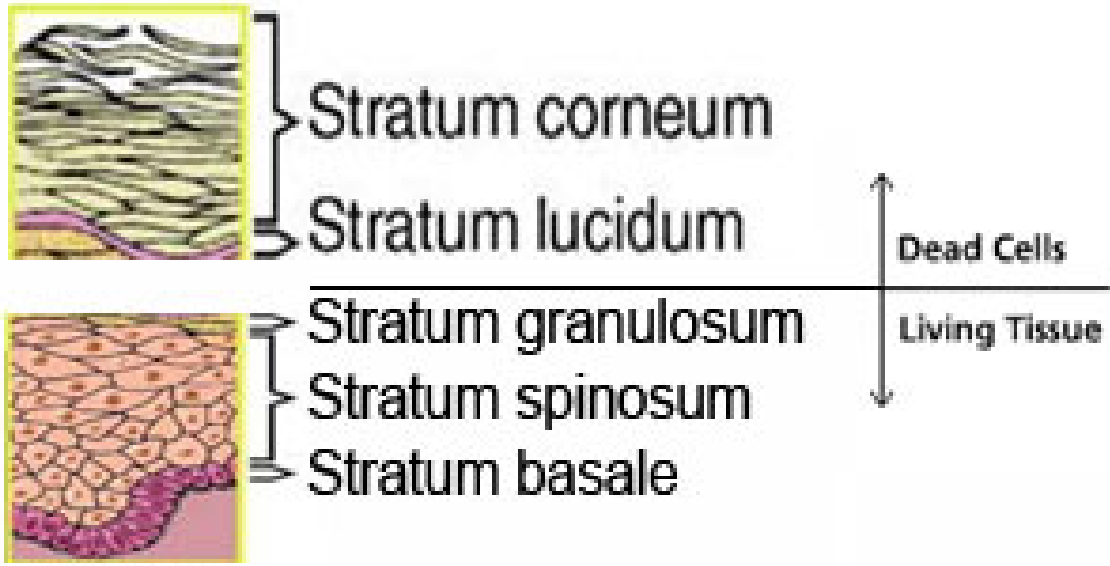
Nano-Particle Penetration Studies

In a 2007 study by Tilman Butz et al., titanium dioxide NPs, a common ingredient in sunscreens, ranging from 6 to 20 nm in size, were applied to pig skin, healthy human skin from biopsies and explants, human foreskin transplanted to mice, and psoriatic skin.



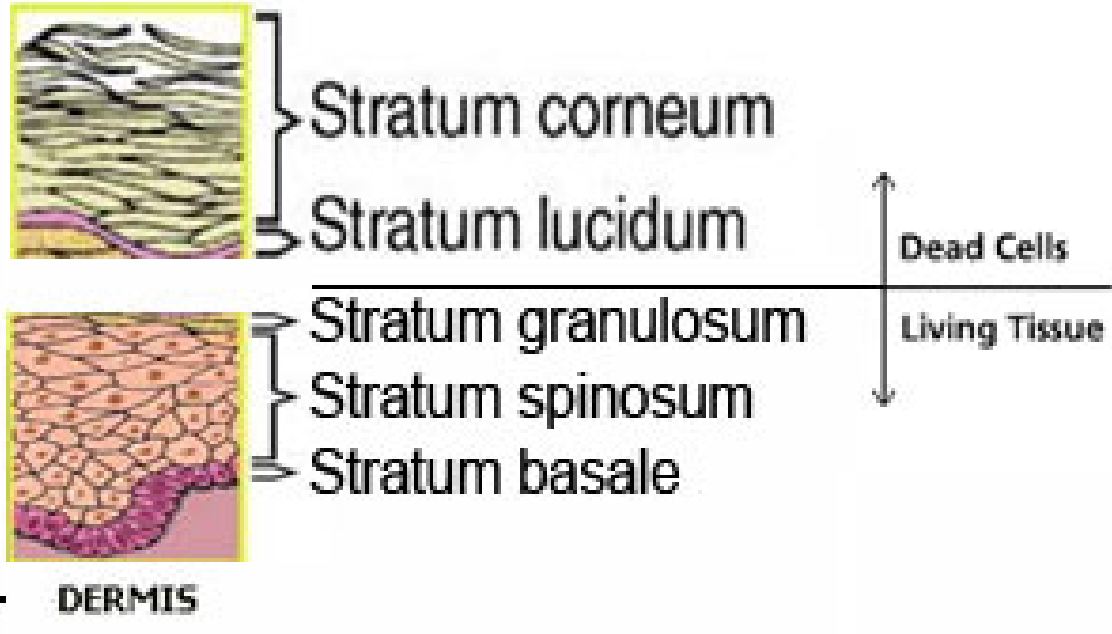
Nano-Particle Penetration Studies

In healthy skin, titanium dioxide was detected as far down as the topmost layers of the stratum corneum disjunctum and around the hair follicle at a depth of almost 0.5 mm…



Nano-Particle Penetration Studies

…but with psoriatic skin, the researchers found titanium dioxide as deep as in contact with vital keratinocytes [the predominate cell type in the epidermis].



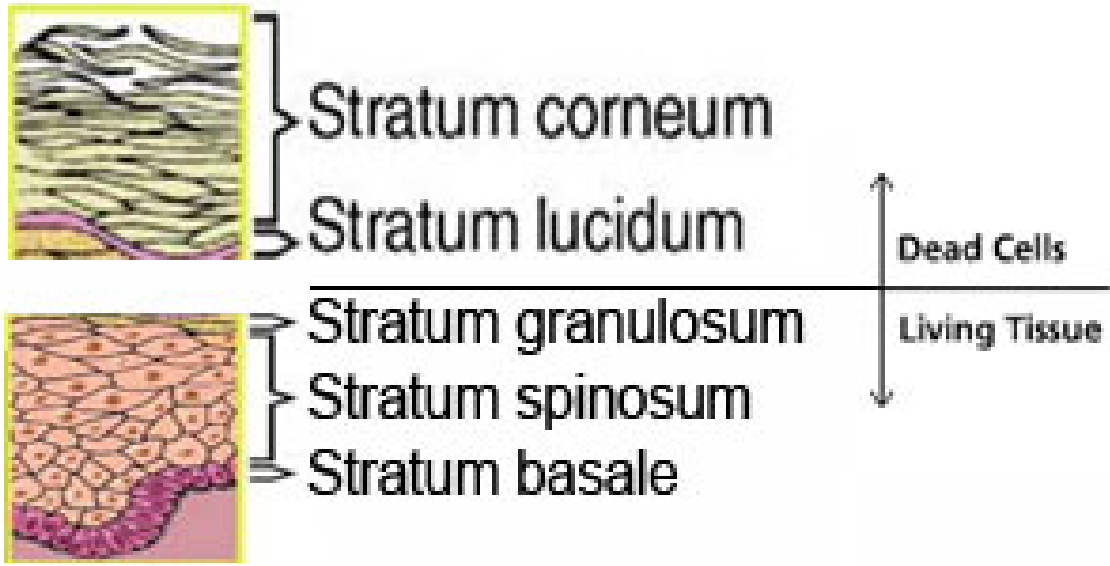
Nano-Particle Penetration Studies

…but with psoriatic skin, the researchers found titanium dioxide in contact with vital keratinocytes [the predominate cell type in the epidermis].

- Authors concluded that “for the sake of safety, direct contact of skin cells with [titanium dioxide NPs] should better be avoided.”
- e.g. application of sunscreens to damaged or compromised skin is not recommended.

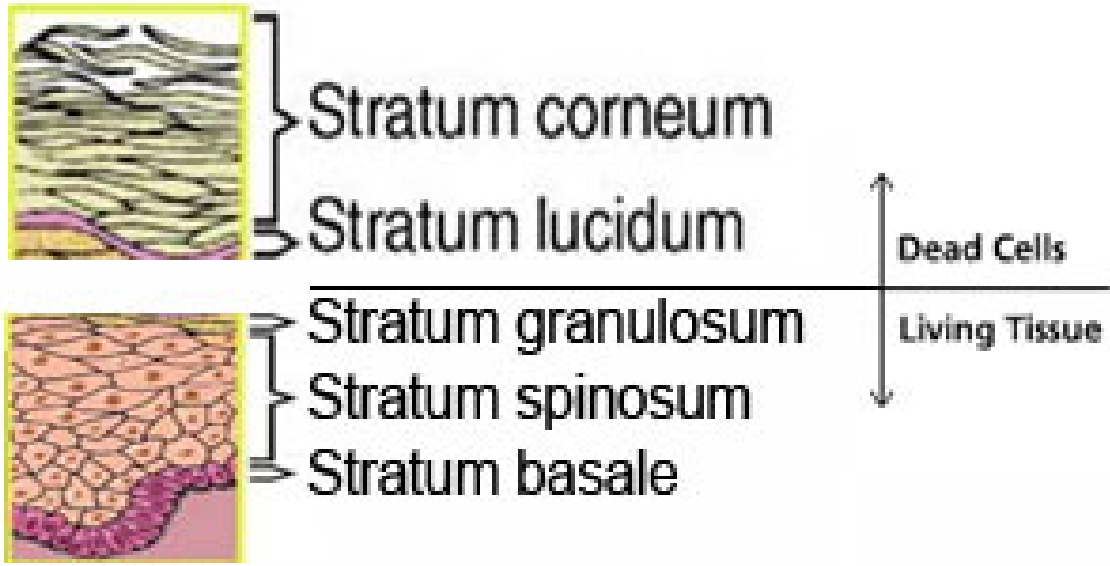
Nano-Particle Penetration Studies

In a 2007 study by Jillian G. Rouse et al., a 3.5 nm peptide sequence containing fullerene, a cosmetic ingredient, was applied to intact pig skin to see what effect mechanical flexion would have on skin penetration.



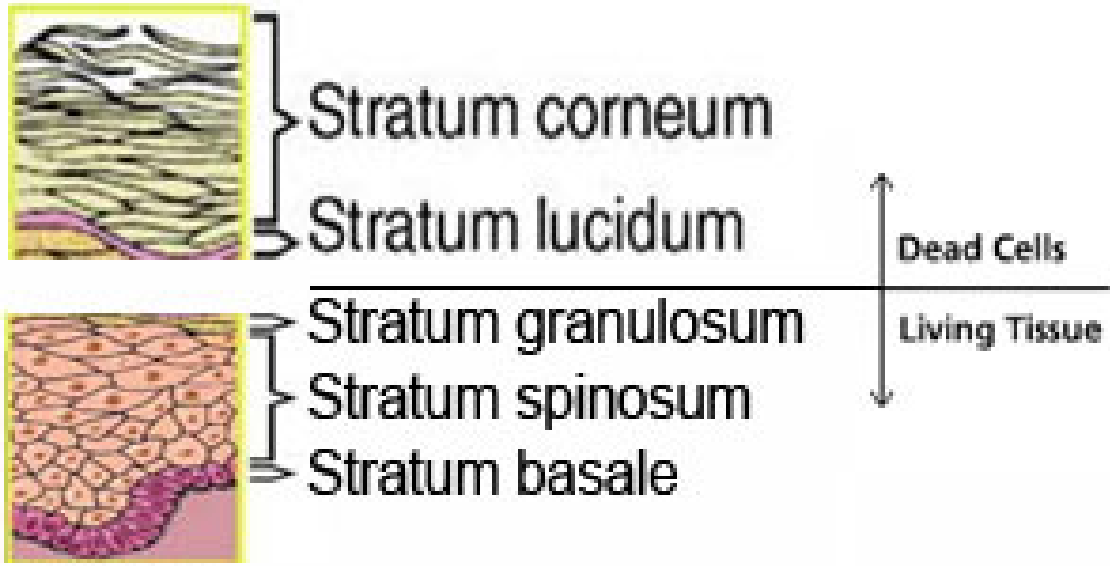
Nano-Particle Penetration Studies

- Some of the skin samples were flexed for 60 minutes or 90 minutes, with other samples left unflexed
- At 8 hours, NPs had penetrated the skin, with fullerenes localized primarily in the epidermal layers of non-flexed skin…



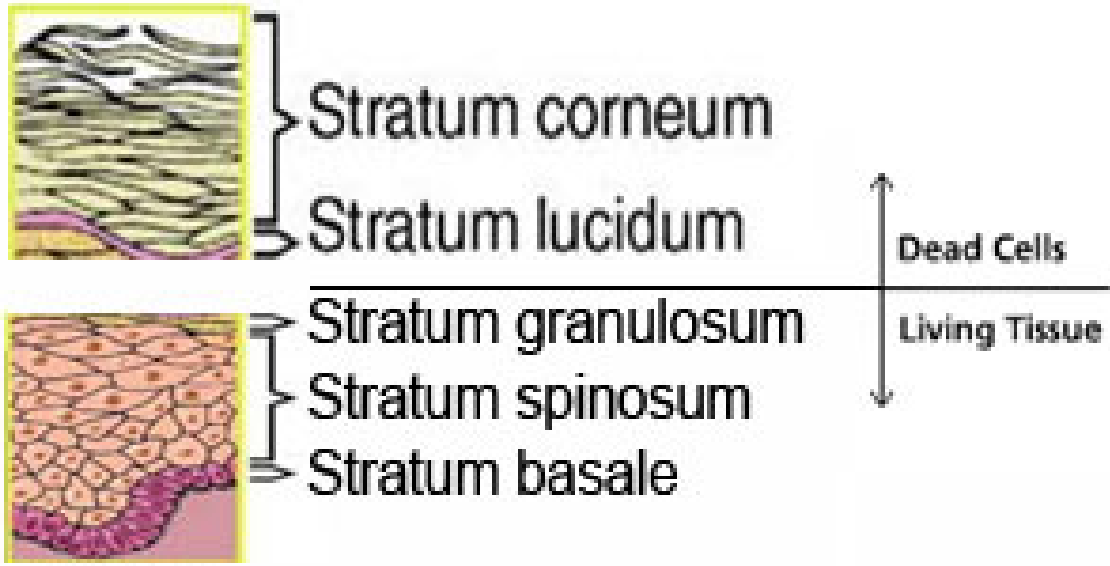
Nano-Particle Penetration Studies

…but greater epidermal penetration for samples flexed for 60 minutes…



Nano-Particle Penetration Studies

…and dermal penetration for the samples flexed for 90 minutes.



Nano-Particle Penetration Studies

…and dermal penetration for the samples flexed for 90 minutes.

- Authors predicted that NPs “could get absorbed by the capillaries… with the potential to localize elsewhere in the body.”
- This posed a “potential risk for systemic toxicity” which would have profound implications for occupational exposure and commercial use.

DERMIS

Toxicity Studies: Are NPs a Threat?

The ability to penetrate the skin would be irrelevant if the NPs are benign, teeing up the question:

“What happens when NPs reach their destination?”

Innocuous?

Toxicity Studies: Are NPs a Threat?

The ability to penetrate the skin would be irrelevant if the NPs are benign, teeing up the question:

“What happens when NPs reach their destination?”

…Harmful?

Toxicity Studies: Are NPs a Threat?

Dunford and colleagues (1997) studied 20–50 nm titanium dioxide and zinc oxide of unknown size that the researchers extracted from various sunscreens; They applied the NPs to DNA plasmids and human fibroblast cells.

Innocuous?

Toxicity Studies: Are NPs a Threat?

Dunford and colleagues (1997) studied titanium dioxide 20–50 nm in size and zinc oxide of unknown size that the researchers extracted from various sunscreens and applied the NPs to DNA plasmids and human fibroblast cells.

…Harmful?

Toxicity Studies: Are NPs a Threat?

Dunford and colleagues (1997) studied titanium dioxide 20–50 nm in size and zinc oxide of unknown size that the researchers extracted from various sunscreens and applied the NPs to DNA plasmids and human fibroblast cells.

- Researchers found that sunlight-illuminated titanium dioxide and zinc oxide NPs “catalyse[d] DNA damage both in vitro and in human cells” – causing DNA strand breaks and lesions.

Toxicity Studies: Are NPs a Threat?

Dunford and colleagues (1997) studied titanium dioxide 20–50 nm in size and zinc oxide of unknown size that the researchers extracted from various sunscreens and applied the NPs to DNA plasmids and human fibroblast cells.

- The DNA breaks, the researchers believe, were "due to direct attack by hydroxyl radicals," demonstrating that "sunscreen [titanium dioxide] and [zinc oxide] can catalyse oxidative damage to DNA in vitro and in cultured human fibroblasts."

Toxicity Studies: Are NPs a Threat?

In 2007, Reddy and colleagues evaluated the toxicity of zinc oxide NPs on human T lymphocytes, which are crucial for protecting against pathogens.

Innocuous?

Toxicity Studies: Are NPs a Threat?

In 2007, Reddy and colleagues evaluated the toxicity of zinc oxide NPs on human T lymphocytes, which are crucial for protecting against pathogens.

…Harmful?

Toxicity Studies: Are NPs a Threat?

In 2007, Reddy and colleagues evaluated the toxicity of zinc oxide NPs on human T lymphocytes, which are crucial for protecting against pathogens.

- 13-nm zinc oxide NPs "caused a significant decrease in viability" at certain concentrations.
- After exposure for 20 hours, 23% of the cells had died when exposed to five millimoles per liter (mM), and 57% died when exposed to 10 mM.

Toxicity Studies: Are NPs a Threat?

In 2007, Reddy and colleagues evaluated the toxicity of zinc oxide NPs on human T lymphocytes, which are crucial for protecting against pathogens.

- The researchers concluded that “cell cytotoxicity is limited to [zinc oxide] in the nanoscale size range as no significant effect of bulk [zinc oxide] powder was observed.”

Toxicity Studies: Are NPs a Threat?

Bai and colleagues (2010) investigated the toxicity on zebrafish embryos—“a good model vertebrate to assess the toxicity of nanoparticles”—96 hours post-fertilization.

Innocuous?

Toxicity Studies: Are NPs a Threat?

Bai and colleagues (2010) investigated the toxicity on zebrafish embryos—"a good model vertebrate to assess the toxicity of nanoparticles"—96 hours post-fertilization.

…Harmful?

Toxicity Studies: Are NPs a Threat?

Bai and colleagues (2010) investigated the toxicity on zebrafish embryos—"a good model vertebrate to assess the toxicity of nanoparticles"—96 hours post-fertilization.

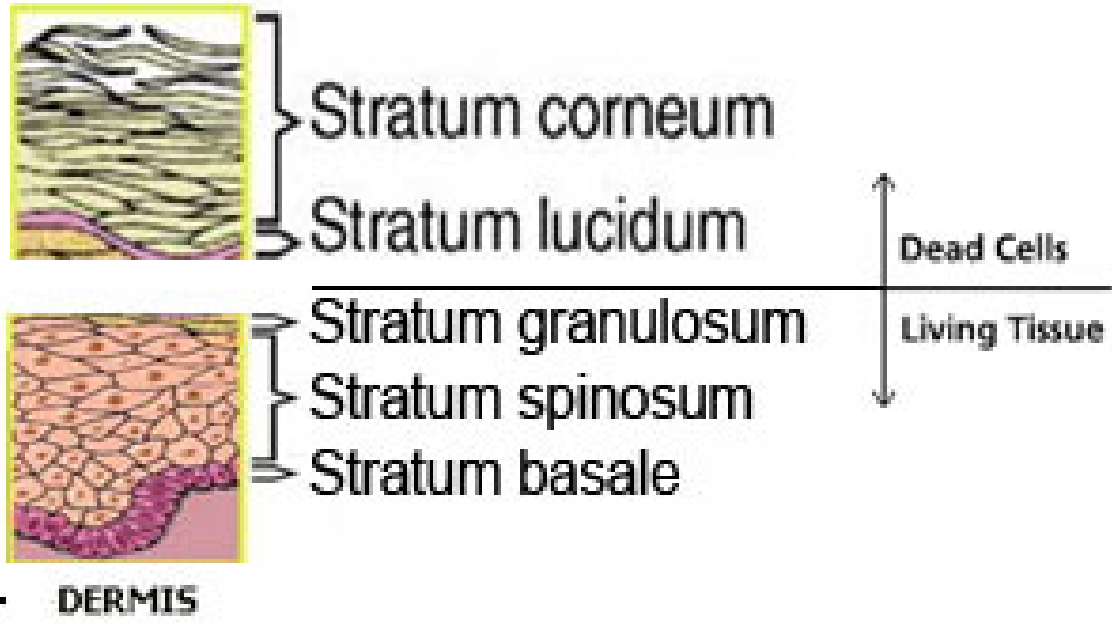
- 30-nm zinc oxide, which aggregated to as much as 1,000 nm at certain concentrations, killed the embryos, retarded the embryo hatching, reduced the body length of the larvae, and caused tail malformation.

NP Penetration and Toxicity Studies

But perhaps the most helpful study in the area of nanoparticle bioavailability is a study that investigated both skin penetration and cell toxicity…

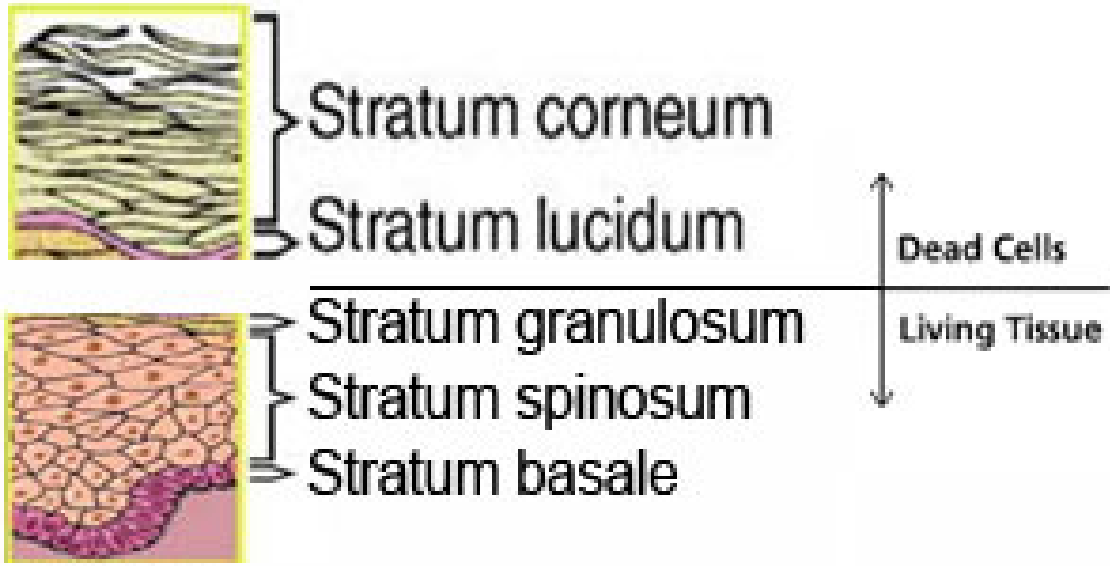
Nano-Particle Penetration and Toxicity Study

Wu and colleagues (2009) investigated the potential toxicity and penetration of three different forms of uncoated titanium dioxide NPs – 4- and 10-nm anatase; 20-, 60-, and 90-nm rutile; and 21-nm 75% anatase/25% rutile (or mixed) powder – applied *in vitro* and *in vivo* to pigs and hairless mice.



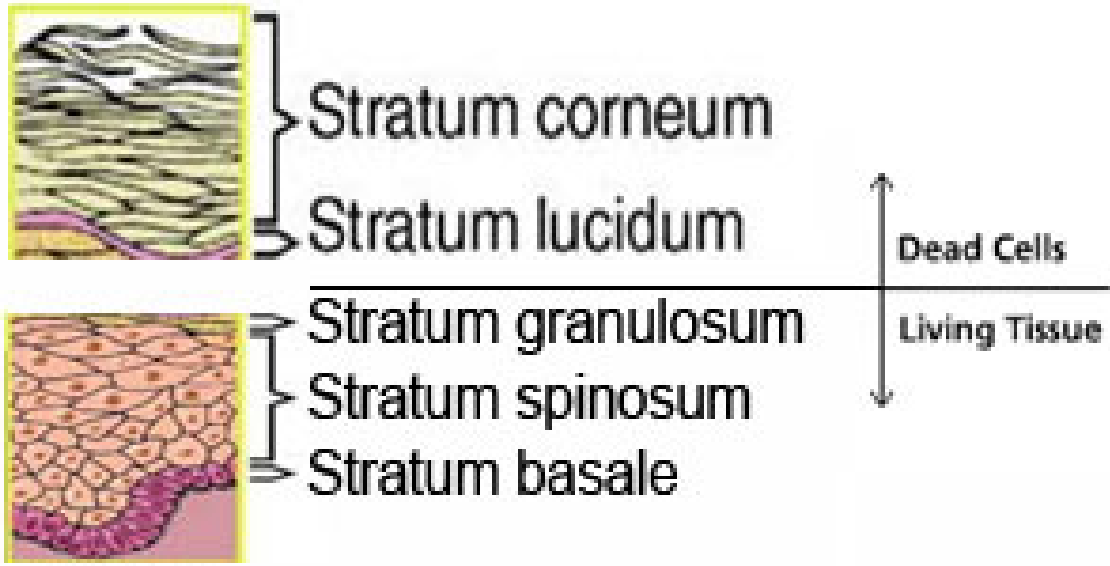
Nano-Particle Penetration and Toxicity Study

Surprisingly, in the *in vitro* studies of pig skin, Wu and colleagues found no penetration after exposure. However, the researchers saw very different results with live animals…



Nano-Particle Penetration and Toxicity Study

After topically administering a 5% titanium dioxide solution to pigs' ears for 30 days, they detected titanium dioxide NPs not only in the SC, but also in the living tissues below—the stratum granulosum, stratum spinosum (or prickle cell layer), and the deepest layer of the epidermis, the basal cell layer.



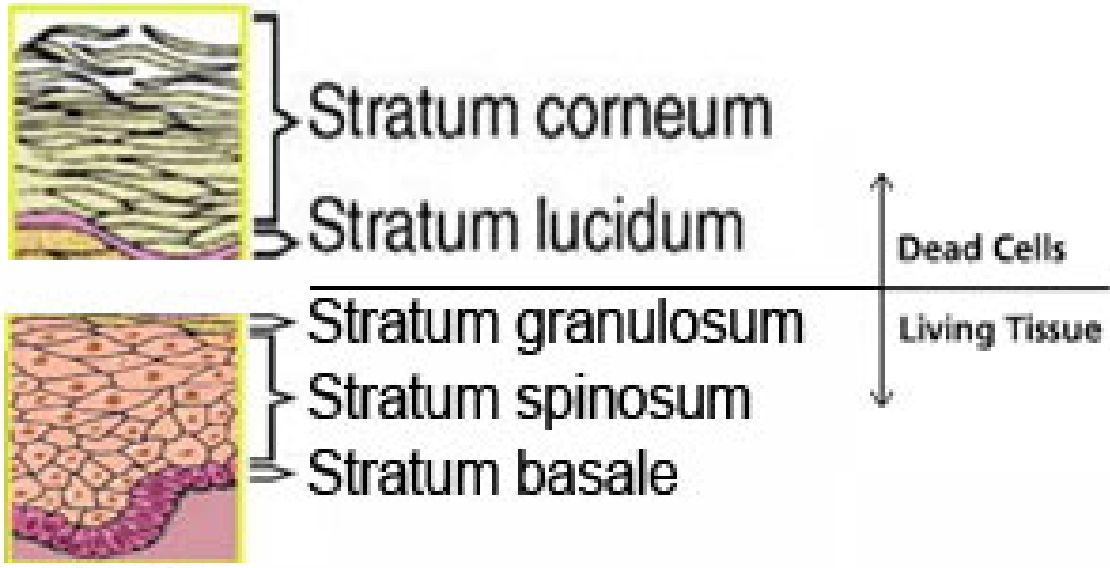
Nano-Particle Penetration and Toxicity Study

After topically administering a 5% titanium dioxide solution to pigs' ears for 30 days, they detected titanium dioxide NPs not only in the SC, but also in the living tissues below—the stratum granulosum, stratum spinosum (or prickle cell layer), and the deepest layer of the epidermis, the basal cell layer.

- Authors observed that "[p]articles of smaller size have a higher penetration capacity and can reach deeper layers of the skin, and cause more severe pathological changes in the skin structures."
- The researchers believe "that the porcine skin *in vivo* model is more suitable for penetration studies than the *in vitro* model."

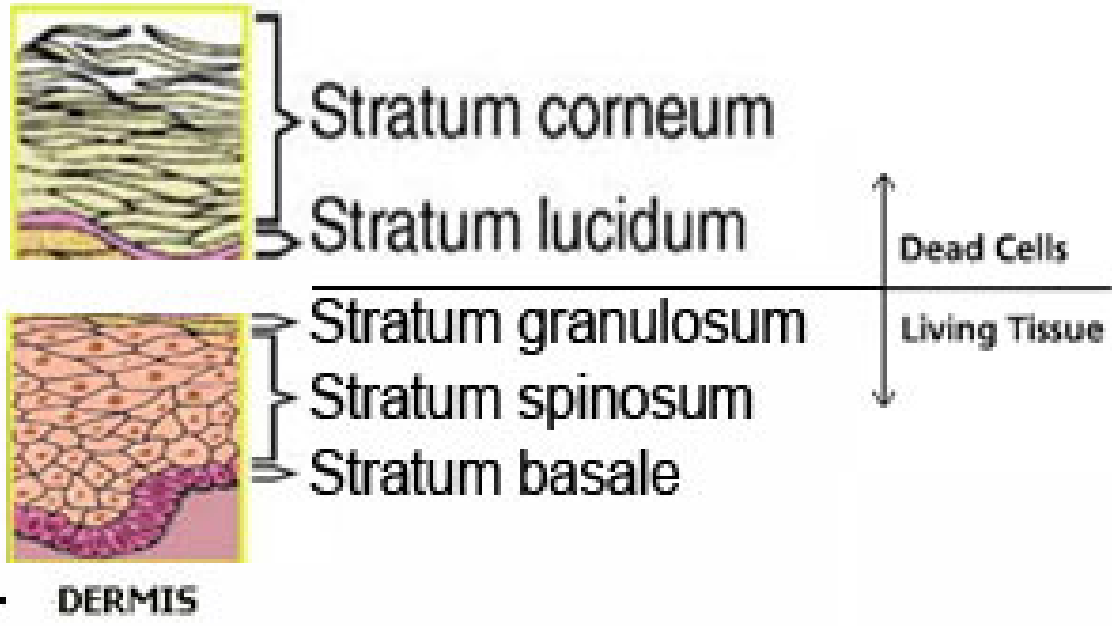
Nano-Particle Penetration and Toxicity Study

The researchers also applied 5% solutions of titanium dioxide NPs to the dorsal skin of hairless mice.



Nano-Particle Penetration and Toxicity Study

After 60 days of exposure, the titanium dioxide NPs "penetrate[d] through the skin, reach[ed] different tissues"—including "subcutaneous muscle, liver, heart, lungs and spleen."



Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

Innocuous?

Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

…Harmful?

Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

- The mice treated with 10- and 25-nm titanium dioxide and 21-nm mixed powder experienced significant decreases in body weight, as well as enlarged livers and (with the exception of the 25-nm titanium dioxide-treated mice) spleens.

Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

- In the liver, severe oxidative stress resulted from all NPs, whereas focal necrosis followed exposure to the 25-nm and 60-nm titanium dioxide and liquefaction necrosis followed exposure to the 10-nm titanium dioxide.

Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

- In the spleen and lungs, all titanium dioxide NPs induced minor lesions.
- All treated mice experienced harm to the kidney.

Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

- All NPs precipitated “excessive keratinization [in the skin], and other pathological changes such as thinner dermis and an epidermis with wrinkles,” with the 10-nm and 21-nm treated mice showing “more severe damages.”

Nano-Particle Penetration and Toxicity Study

Ultimately, the titanium dioxide NPs “accumulated in the spleen, heart, and liver” of the mice after dermal exposure, with one NP passing through the blood–brain barrier.

- The skin samples also showed “oxidative stress by increased lipid peroxidation products and reduced collagen contents.”

NP Penetration and Toxicity Studies

Not all studies, however, have found penetration or toxic effects …

- Juergen Ladermann et al., (1999)
- F. Pflucker et al. (2001)
- Kang and colleagues (2008)

NP Penetration and Toxicity Studies

What we have learned from all of these studies is that at least some nanoparticles are able to interact with viable layers of the skin, may travel throughout the body, and may have deleterious interactions with the cells, all of which suggests a need to regulate products that use this technology.

The FDA Catches Up...

FDA's Draft Guidance states:

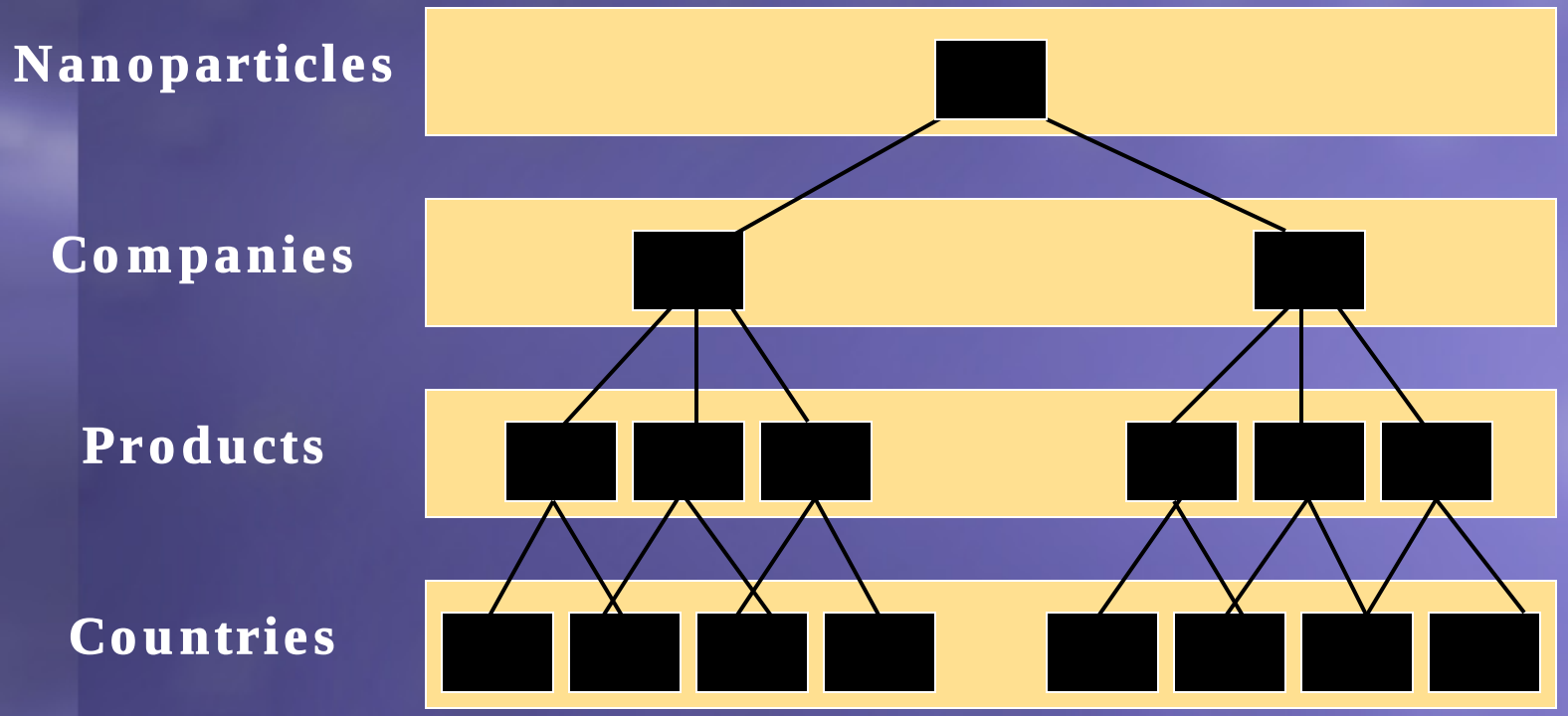
- "It is the responsibility of the manufacturer of a cosmetic product to ensure that the product is not misbranded or adulterated."
- "Nanomaterials may alter the bioavailability of the cosmetic formulation."
- "The traditional safety tests that have been used to determine the safety of cosmetic ingredients and finished products may not be fully applicable."

...But Only So Much

…but the Draft Guidance also says:

- "…does not create or confer any rights for or on any person and does not operate to bind the FDA or the public."
- "…do[es] not establish legally enforceable responsibilities."
- "…should be viewed only as recommendations."

...Is Not Going to Work



Just as Tort Will Not Suffice (The Asbestos Analogy)

Characteristic	Nanotechnology	Asbestos
Manufacturer known	√	√
Defined Substance	No	√
Worldwide dissemination	√	√
Wide range of use	√	√
Acute Toxicity	No	No
Persistent	In some cases	√
Long-term effect	Conceivable	√
Risks	Unknown	Cancer
Claims series potential	√	√
Loss accumulation potential	√	√
Agent analytically provable	√	√

Thoughts?