

Beauty industry backs high risk small particles: Controversial nano-ingredients found in big name brands



Summary:

Scientific testing commissioned by Friends of the Earth Australia and carried out by the Australian Microscopy and Microanalysis Research Facility¹ has found:

- Concealers, foundations and mineral foundations sold by 8 leading brands contained particles measuring less than 100nm in size (Clinique, Clarins, L'Oréal, Revlon, The Body Shop, Max Factor, Lancôme Paris and By Terry)
- A further 2 products contained particles that measured 100nm (Yves Saint Laurent and Christian Dior)

Furthermore, Friends of the Earth has found:

- 7 of the cosmetics tested contained ingredients known to act as 'penetration enhancers', making it more likely that nanoparticles will be taken up into the skin
- The 3 cosmetics that did not contain penetration enhancers were mineral foundations, which pose greater inhalation risks due to their powdered form
- Only one of the brands surveyed (Christian Dior) indicated the use of nano-ingredients on the product label. Failing to label nano-ingredients denies consumers the capacity to make an informed choice

For a summary of the testing methodology and limitations of the study see Appendix.

Nanoparticles are extremely small particles manufactured using nanotechnology.

Nanoparticles are generally defined as measuring around 1-100 nanometres (nm) in one or more dimensions (70 times smaller than a red blood cell). Nanoparticles are now used in Australian cosmetics, sunscreens, 'health' supplements, clothing, appliances and more².

The long-term health risks of nanoparticles remain poorly understood. The likely exposure in 'real life' conditions is also unknown. But early studies have suggested that if exposure is high enough, nanoparticles now used by the cosmetics industry could cause lung damage³, cell toxicity⁴, damage DNA⁵, and possibly even harm unborn children⁶.

Production of free radicals by nanoparticles used in sunscreens and cosmetics is greater when exposed to UV light⁷. Last year, in relation to nano-sunscreens, the director of CSIRO's Nanosafety research program warned The 7.30 Report that: "the worst case scenario, I suspect, could be development of cancer. But we don't know. That's what we're trying to find out"⁸. Dr McCall cautioned that CSIRO's research will take another two years.

In 2004, the United Kingdom's Royal Society, the world's oldest scientific institution, recommended that given the evidence of serious nanotoxicity risks, nanoparticles should be treated as new chemicals⁹ and subject to new safety assessments before being allowed in consumer products¹⁰. It also recommended that nano-ingredients in products should be labelled, to give people the chance to make an informed choice.

Europe has passed new laws that will require most nano-ingredients in sunscreens cosmetics to face new safety testing and mandatory labelling. Yet where substances have been approved for use as larger particles, Australian laws do not make companies test for safety before using these substances as nanoparticles, nor to label nano-ingredients¹¹.

Results of cosmetics testing for nanoparticle content – commissioned by Friends of the Earth Australia, carried out by the Australian Microscopy and Microanalysis Research Facility (penetration enhancers identified by Friends of the Earth)

For notes on methodology and limitations see Appendix

Brand	Type of cosmetic	Product	Nanoparticle content	Probable chemical composition	Penetration enhancers (ingredients listed on product labels known to act as penetration enhancers)
By Terry	Mineral Foundation	Light-expert compact	50-100nm	Aluminium iron, titanium dioxide	No penetration enhancers identified
Christian Dior	Foundation	DiorSkin Forever Extreme Wear Flawless Makeup SPF 25	100-200nm spheroids 200-600nm rods (length)	Titanium dioxide Iron oxide	Octinoxate, tetrasodium EDTA, phenoxyethanol
Clarins	Foundation	Truly Matte Foundation Light Reflecting SPF 15	100nm rods (length), 100-200nm plates (length)	Alumino-silicate oxides	Disodium EDTA, phenoxyethanol
Clinique	Concealer	Line smoothing concealer	50-300nm spheroids 80-400nm rods (length)	Titanium and aluminium oxides, some copper and silicon Iron oxide	Disodium EDTA, hexylene glycol
Lancôme Paris	Concealer	Long lasting softening concealer SPF 12	20-80nm spheroids	Aluminium oxide	Propylene glycol, urea, disodium EDTA
L'Oréal	Foundation	Visible lift lifting anti-wrinkle foundation SPF 15	80nm spheroids 400nm to 1µm rods (length)	Titanium oxide Aluminium/ iron oxide	Glyceryl isostearate, octinoxate, denatured alcohol (ethanol), phenoxyethanol
Max Factor	Mineral Foundation	Natural Minerals Foundation	80nm spheroids 200nm-450nm rods (length)	Aluminium oxide with high phosphor content Iron oxide rods	Ingredients not listed
Revlon	Concealer	Revlon Age Defying Spa Concealer	50-80nm spheroids 300-500nm rods (length)	Titanium oxides Aluminium/ iron oxide	Tribehenin, tetrasodium EDTA, phenoxyethanol
The Body Shop	Mineral Foundation	Nature's Minerals Foundation SPF 25	30-100nm spheroids 80-600nm rods (length)	Titanium Iron oxide	No penetration enhancers identified
Yves Saint Laurent	Concealer	Anti-cernes multi-action concealer	100-500nm spheroids	Aluminium oxide or silicon oxide – test inconclusive	Lecithin, ricinus communis (castor seed oil), citric acid

Nanoparticles are used in Australian cosmetics for their novel properties

The cosmetics sector is interested in using extremely small nanoparticles for their novel properties. Nano-aluminium oxide is used in concealers, foundations and mineral foundations because it diffuses light, giving a ‘soft focus’ effect that disguises wrinkles. Nano-titanium dioxide is used in many cosmetics to give sun protection. As a larger particle, titanium dioxide is white and opaque. But when it is ground down to nano size, titanium dioxide becomes transparent. Nanoparticles of iron oxide are used as pigments.

Early studies suggest that nanoparticles in cosmetics could pose health risks

If nanoparticles are accidentally inhaled (eg from mineral foundation), eaten (eg from foundation or lipstick applied to lips) or absorbed through skin, they could cause skin damage, lung damage, organ toxicity or even harm unborn children¹². Because they are so extremely small, once they gain access to our bodies, some types of nanoparticles can readily travel throughout the body, deposit in our organs, penetrate cell membranes including the blood-brain barrier, and even lodge in nuclei – the control centre of cells¹³.

Nanoparticles of titanium dioxide were found in 6 of the cosmetics tested. Scientific studies have shown that nanoparticles of titanium dioxide can produce free radicals¹⁴, damage DNA¹⁵ and cause cell toxicity¹⁶ in test tube studies, especially when exposed to UV light¹⁷. Animal studies have shown that after inhalation¹⁸ or injection¹⁹ into the blood stream of pregnant mice, titanium dioxide nanoparticles can cross the placenta and enter developing embryos. This has altered gene expression associated with brain function in the mice offspring²⁰, affected their behaviour²¹ and damaged the brains and reproductive systems of baby mice²². Mice studies have also found that inhalation of nanoparticles of titanium dioxide caused inflammation to the lungs of test animals²³. Furthermore, inhaled titanium dioxide nanoparticles can be transported to the brain²⁴, raising concerns of potential neurotoxicity.

Nanoparticles of iron and aluminium were each found in 7 of the cosmetics tested. In a test tube study, US researchers found that nanoparticles of aluminium oxide and iron oxide were almost as toxic to cells as chrysotile asbestos²⁵. Other US test tube studies found that aluminium oxide nanoparticles produced free radicals and demonstrated a potential carcinogenic effect²⁶, caused dose-dependent stem cell toxicity²⁷, caused inflammation that could lead to diseases such as atherosclerosis²⁸, disrupted the blood-brain barrier and were directly toxic to brain blood vessel cells²⁹. The potential for nanoparticles to increase the risk of neuro-degenerative diseases such as Alzheimer’s and Parkinson’s is a big concern. Test tube study has also found that magnetic iron oxide nanoparticles can be toxic to nerve cells and interfere with the formation of their signal-transmitting extensions³⁰.

We still don’t know whether nanoparticles penetrate intact human skin, although it seems likely they will penetrate damaged skin

It is still unknown whether or not nanoparticles used in cosmetics will penetrate the dead outer layers of our skin and pose risks to living cells. Several studies have shown that titanium dioxide and zinc nanoparticles used in sunscreens and cosmetics do not penetrate intact, healthy adult skin³¹. However Friends of the Earth is concerned that

many factors that are relevant to real life conditions have not been included in these studies. Skin flexing, skin condition, and the presence of 'penetration enhancing' ingredients in cosmetics could all promote greater skin uptake of nanoparticles used in cosmetics, but these factors have not been adequately studied.

Scientific studies have shown that nanoparticles can penetrate skin³², especially if skin is flexed³³ (as during exercise). Incredibly, one study found that even particles up to 1,000nm in size can be taken up through intact skin to reach living cells, when skin is flexed³⁴. The same study found that particles 1,000nm clustered in the living layers of the skin underneath a tear in the skin³⁵, suggesting that skin penetration by nanoparticles is likely in people with eczema or acne. A preliminary study found that nanoparticle penetration was deeper in skin affected by psoriasis than in unaffected skin³⁶, although the nanoparticles still did not reach the skin's living cells. Another preliminary study found that particle uptake is also more likely in sunburnt skin³⁷. The influence of sunburn or UV exposure is not addressed in most skin penetration studies.

7/10 cosmetics we surveyed contain skin 'penetration enhancers'

Perhaps the most significant variable that could promote skin uptake of nanoparticles from cosmetics in 'real life' conditions is the presence in many cosmetics of chemicals that act as penetration enhancers. 'Penetration enhancers' are chemicals that alter skin structure, allowing other chemicals to penetrate deeper into the skin, and increasing the amounts of chemicals that reach the bloodstream³⁸. Some chemicals that act as penetration enhancers are included in products to increase skin uptake of moisturisers or other active ingredients, whereas for other chemicals their ability to promote skin penetration is incidental. US researchers have found that penetration enhancers "greatly enhance" the uptake of carbon fullerene nanoparticles through skin³⁹. However to our knowledge the influence of penetration enhancers hasn't been explored in relation to the vast majority of nano-ingredients now used in cosmetics.

Friends of the Earth identified penetration enhancers in 7 of the 10 cosmetics we surveyed. The 3 cosmetics in which we did not identify penetration enhancers are mineral foundations which pose greater risks of inhalation, due to their powder form.

European regulators are acting to manage nano-risks, Australia lags behind

This year the European Parliament passed new laws that will require most nanoparticles in sunscreens and cosmetics to go through nano-specific safety testing before they can be sold, and to be listed on product labels. These laws will probably take effect in 2012.

There has been little action from Australian regulators. Where chemicals have been approved for use in larger particle form, companies are legally allowed to use them in nanoparticle form without conducting any new safety testing, or even notifying the relevant regulator (the National Industrial Chemicals Notification and Assessment Scheme NICNAS) has responsibility for cosmetics; the Therapeutic Goods Administration (TGA) has responsibility for cosmetics that have an SPF rating of more than 15; the Australian Competition and Consumer Commission (ACCC) has responsibility for labels).

NICNAS has recently released a discussion paper regarding possible future regulation of

nanoparticles in cosmetics. The TGA has resisted calls to introduce any new regulation of nano-products. The ACCC has not stated any intention of labelling nano-cosmetics. Meanwhile, millions of Australian women face daily exposure to cosmetics that contain nanoparticles about which safety concerns exist. The absence of mandatory labelling denies the public the chance to make an informed purchasing choice.

Earlier this year, after a state Parliamentary Inquiry, the NSW Minister for Science and Medical Research Ms Jodi McKay said the NSW Government would raise the possibility of labelling nanoparticles in cosmetics and sunscreens with the Federal Government⁴⁰. However, Minister McKay said NSW would recommend a health impact assessment of nanoparticles before any changes, as she claimed labelling could deter people from using sunscreens.

Friends of the Earth is calling for a moratorium

Friends of the Earth Australia believes that Australian women shouldn't be used as guinea pigs by the big cosmetics companies. We are calling for a halt to all sales of cosmetics that contain nano-ingredients, until the safety science catches up, new laws are introduced to make companies demonstrate the safety of their products and until nano-ingredients face mandatory labelling. We are also calling for public involvement in decision making about nanotechnology funding, policy development and regulation.

Appendix: Notes on the testing methodology and limitations of this study

For a full description of the test methodology see the original AMMRF report at:
<http://ift.ucc.usyd.edu.au/ift-download.cgi?id=4ddf3aa7e05c1b0e9499be74>

A general note on the study's limitations:

This study was conducted with a limited budget and should be considered to be preliminary, rather than comprehensive. Only a small number of observations of each sample were made. Correct sizing of particulates at this scale, a full analysis of particle types and matching to the listed ingredients requires significantly more extensive analyses, such as TEM or X-ray diffraction studies to identify crystal structures.

Particle sizes listed here are only those observed. Therefore, whilst observation in this study of certain particle sizes does indicate that they were present in the cosmetics sampled, observations may not be statistically representative of the full sample. There may also be nanoparticles or other particles present in the samples that were not identified here.

The limited number of observations and analysis of the samples precludes any assessment as to whether the particles observed were primary particles (single particles) or agglomerates or aggregates (clumps of multiple particles). Larger particles observed here may in fact clumps of smaller nanoparticles.

The high content of waxes in some samples made it difficult to prepare them for observation. This reduced the ability to observe and identify nanoparticle content of these samples.

X-ray analysis enables identification of the chemical composition of nanoparticles observed, but there are limitations to its accuracy (see below). The quoted chemical composition of nanoparticles observed therefore requires confirmation.

Sample preparation

The samples were prepared by dilution in order to dissolve vacuum unstable ingredients, such as oils or other ethanol soluble organic components, or ingredients that may dissolve the support film. Additionally this also dispersed particulates to a sufficiently dilute level to permit observation, as well as minimising particle aggregation. Dissolution of organics is dependant upon properties such as solubility of the chemical in ethanol, and some samples may still have fine-scale residues present.

A small quantity (0.1-0.4 g, dependant upon sample) of each sample was weighed and diluted with 15mL of ethanol. This was then placed in an ultrasonic bath (Bruker ultrasonic), for a period of five minutes to ensure adequate dispersion. Thereafter, 1.5 ml of each sample was then dispersed into a second container, the solution was diluted further to a total of 15 ml using ethanol and the ultrasonic treatment repeated. This was subsequently repeated for a third dilution. One drop from each solution was then dispersed onto copper mesh grids with a Formvar support film. Samples were then coated with a 600 ms single pulse carbon-arc deposition to deposit a conductive layer of carbon to provide charge dissipation.

The following analysis techniques were used in the testing

- Field Emission Scanning Electron Microscopy (FESEM)
 - Secondary Electron Imaging
 - Scanning Electron Microscopy - Scanning Transmission Electron Microscopy (SEM-STEM)
 - Energy Dispersive X-ray Spectroscopy (EDS)

Scanning Electron Microscopy (SEM) was used to give a snapshot of particle sizes and shapes. SEM illuminates each specimen with a fine electron 'probe' generated from an electron source. The electrons are focussed to a spot at the surface of the sample, whereby the electrons penetrate into a small volume at the sample surface. Electrons are then emitted from the sample surface, which are then collected by a nearby detector, providing surface sensitive imaging, with contrast indicative of specimen topography.

X-ray Spectroscopy was used to identify the chemical composition of particles identified by SEM. X-ray Spectroscopy counts X-rays ejected from the sample when illuminated by the electron beam. The energy of these X-rays is dependant upon the type of atom that composes the sample, and independent of the sample structure. Elements with those higher in the periodic table than carbon produce sufficiently energetic X-rays to allow for detection. By examining the relative proportions of the different X-ray energies, an approximate atomic composition can be calculated, using a method known as the ZAF method. By synchronising the beam raster rate with X-ray data acquisition, images can be constructed that estimate the position of the emitted X-rays. These images are known as X-ray maps, and provide information on the spatial distribution of selected elements in the illuminated region.

Limitations of SEM and X-ray analysis

Analysis of particulates via SEM is a highly specific method, allowing only small sampling of large particulate populations. Hence the particulates shown are those observed via SEM and may not be representative of the average particle in the analysis. Such statistical analyses are time consuming to perform via SEM in terms of instrument time, and furthermore require human assisted particle identification to ensure correct results.

The information extracted by X-ray analysis is limited to the atomic composition of specific regions of the sample, which is unable to distinguish between compounds of differing chemical structure, but similar composition. Furthermore for light elements, specifically elements with an atomic number equal to or less than that of carbon, the extraction of the composition of these elements via the ZAF method is highly inaccurate and may significantly differ from the true value. For higher atomic number elements, such as the metal oxides observed in this study, the composition may be estimated to as accurately as several percent. Additionally as the SEM illuminates an approximately circular region of a radius on the order of one nanometre, and electron scattering within the sample may increase this region by several more nanometres, the X-ray may be generated from anywhere within this larger region. Therefore the detected X-rays are from anywhere within this region, which can cause an averaging effect if compositional variation is occurring at a scale below this radius. Finally the sample is placed upon a stage, which is a mechanical device to maintain the position of the sample relative to the microscope beam. The stage may have a slight drift rate that can be as high as the 10 nm/minute. This drift can cause a blurring of X-ray data owing to the combination of stage drift, and long scanning times required for X-ray acquisition, which is visible as streaking in the image.

References

- 1 To download the test report visit: <http://ift.ucc.usyd.edu.au/ift-download.cgi?id=4ddf3aa7e05c1b0e9499be74>
- 2 For a sample list of Australian products see <http://nano.foe.org.au/node/242>
- 3 Grassian V, Adamcakova-Dodd A, Pettibone J, O'Shaughnessy P, Thorne P. 2007. Inflammatory response of mice to manufactured titanium dioxide nanoparticles: Comparison of size effects through different exposure routes. *Nanotoxicology*, 1(3): 211-226
- 4 Chen L, Yokel R, Hennig B, Toborek M. (2008). Manufactured Aluminum Oxide Nanoparticles Decrease Expression of Tight Junction Proteins in Brain Vasculature. *J Neuroimmune Pharmacol* (2008) 3:286–295; Long T, Saleh N, Tilton R, Lowry G, Veronesi B. 2006. Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): Implications for nanoparticle neurotoxicity. *Environ Sci Technol* 40(14):4346-4352; Sayes C, Wahi R, Kurian P, Liu Y, West J, Ausman K, Warheit D, Colvin V. 2006. Correlating nanoscale titania structure with toxicity: A cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. *Toxicol Sci* 92(1):174–185; Soto K, Carrasco A, Powell T, Garza K, Murr L (2005). Comparative in vitro cytotoxicity assessment of some manufactured nanoparticulate materials characterized by transmission electron microscopy. *Journal of Nanoparticle Research* 7: 145–169
- 5 Donaldson K, Beswick P, Gilmour P. 1996. Free radical activity associated with the surface of particles: a unifying factor in determining biological activity? *Toxicol Lett* 88:293-298., Dunford R, Salinaro A, Cai L, Serpone N, Horikoshi S, Hidaka H, Knowland J. 1997. Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients. *FEBS Lett* 418:87-90
- 6 Hougaard K, Jackson P, Jensen K, Vogel U, Wallin H (2009). Nano-sized titanium dioxide: Effects of gestational exposure. *Reproductive Toxicology* 28, p122; Shimizu M, Tainaka H, Oba T, Mizuo K, Umezawa M, Takeda K. 2009. Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to brain development in the mouse. *Particle and Fibre Toxicology* 2009, 6:20; Takeda K, Suzuki K, Ishihara A, Kubo-Irie M, Fujimoto R, Tabata M, Oshio S, Nihei Y, Ihara T, Sugamata M. 2009. Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems. *J Health Sci* 55(1):95-102
- 7 Dunford R, Salinaro A, Cai L, Serpone N, Horikoshi S, Hidaka H, Knowland J. 1997. Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients. *FEBS Lett* 418:87-90
- 8 ABC (2008). Safety concerns over high-tech sunscreens. The 7.30 Report 17 December 2008. Available at: <http://www.abc.net.au/7.30/content/2008/s2449409.htm>
- 9 P85 Recommendation 10, The Royal Society and The Royal Academy of Engineering, UK (2004). Nanoscience and nanotechnologies. Available at <http://www.royalsoc.ac.uk/>
- 10 P86 Recommendation 12 (i), The Royal Society and The Royal Academy of Engineering, UK (2004). Nanoscience and nanotechnologies. Available at <http://www.royalsoc.ac.uk/>
- 11 Ludlow K, Bowman D, Hodge G. (2007). A Review of Possible Impacts of Nanotechnology on Australia's Regulatory Framework. Final Report. September 2007. Available at: <http://www.industry.gov.au/Section/Innovation/Pages/AustralianOfficeofNanotechnology.aspx>
- 12 Hougaard K, Jackson P, Jensen K, Vogel U, Wallin H (2009). Nano-sized titanium dioxide: Effects of gestational exposure. *Reproductive Toxicology* 28, p122; Shimizu M, Tainaka H, Oba T, Mizuo K, Umezawa M, Takeda K. 2009. Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to brain development in the mouse. *Particle and Fibre Toxicology* 2009, 6:20; Takeda K, Suzuki K, Ishihara A, Kubo-Irie M, Fujimoto R, Tabata M, Oshio S, Nihei Y, Ihara T, Sugamata M. 2009. Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems. *J Health Sci* 55(1):95-102
- 13 Chen M, von Mikecz A. 2005. Formation of nucleoplasmic protein aggregates impairs nuclear function in response to SiO₂ nanoparticles. *Experiment Cell Res* 305:51-62; Porter A, Gass M, Muller K, Skepper J, Midgley P, Wellandt M (2007). Visualizing the Uptake of C60 to the Cytoplasm and Nucleus of Human Monocyte-Derived Macrophage Cells Using Energy-Filtered Transmission Electron Microscopy and Electron Tomography. *Environ. Sci. Technol* 41(8):3012–3017
- 14 Nel A, Xia T, Li N. 2006. "Toxic potential of materials at the nanolevel". *Science* Vol 311:622-627
- 15 Donaldson K, Beswick P, Gilmour P. 1996. Free radical activity associated with the surface of particles: a unifying factor in determining biological activity? *Toxicol Lett* 88:293-298.
- 16 Long T, Saleh N, Tilton R, Lowry G, Veronesi B. 2006. Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): Implications for nanoparticle neurotoxicity. *Environ Sci Technol* 40(14):4346-4352; Sayes C, Wahi R, Kurian P, Liu Y, West J, Ausman K, Warheit D, Colvin V. 2006. Correlating nanoscale titania structure with toxicity: A cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. *Toxicol Sci* 92(1):174–185.
- 17 Dunford R, Salinaro A, Cai L, Serpone N, Horikoshi S, Hidaka H, Knowland J. 1997. Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients. *FEBS Lett* 418:87-90
- 18 Hougaard K, Jackson P, Jensen K, Vogel U, Wallin H (2009). Nano-sized titanium dioxide: Effects of gestational exposure. *Reproductive Toxicology* 28, p122
- 19 Shimizu M, Tainaka H, Oba T, Mizuo K, Umezawa M, Takeda K. 2009. Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to brain development in the mouse. *Particle and Fibre Toxicology* 2009, 6:20; Takeda K, Suzuki K, Ishihara A, Kubo-Irie M, Fujimoto R, Tabata M, Oshio S, Nihei Y, Ihara T, Sugamata M. 2009. Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems. *J Health Sci* 55(1):95-102

-
- 20 Shimizu M, Tainaka H, Oba T, Mizuo K, Umezawa M, Takeda K. 2009. Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to brain development in the mouse. *Particle and Fibre Toxicology* 2009, 6:20
- 21 Hougaard K, Jackson P, Jensen K, Vogel U, Wallin H (2009). Nano-sized titanium dioxide: Effects of gestational exposure. *Reproductive Toxicology* 28, p122
- 22 Takeda K, Suzuki K, Ishihara A, Kubo-Irie M, Fujimoto R, Tabata M, Oshio S, Nihei Y, Ihara T, Sugamata M. 2009. Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems. *J Health Sci* 55(1):95-102
- 23 Grassian V, Adamcakova-Dodd A, Pettibone J, O'Shaughnessy P, Thorne P. 2007. Inflammatory response of mice to manufactured titanium dioxide nanoparticles: Comparison of size effects through different exposure routes. *Nanotoxicology*, 1(3): 211-226
- 24 Wang J, Chen C, Yu H, Sun J, Li B, Li Y, Gao Y, He W, Huang Y, Chai Z, Zhao Y, Deng X, Sun H. 2007. Distribution of TiO₂ particles in the olfactory bulb of mice after nasal inhalation using microbeam SRXRF mapping techniques. *Journal of Radioanalytical and Nuclear Chemistry*, 272 (3): 527–531
- 25 Soto K, Carrasco A, Powell T, Garza K, Murr L (2005). Comparative in vitro cytotoxicity assessment of some manufactured nanoparticulate materials characterized by transmission electron microscopy. *Journal of Nanoparticle Research* 7: 145–169
- 26 Dey S, Bakthavatchalu V, Tseng M, Wu P, Florence R, Grulke E, Yokel R, Kumar Dhar S, Yang H-S, Chen Y, St Clair D (2008). Interactions between SIRT1 and AP-1 reveal a mechanistic insight into the growth promoting properties of alumina (Al₂O₃) nanoparticles in mouse epithelial cells. *Carcinogenesis* 29(10):1920-1929
- 27 Braydich-Stolle L, Hussain S, Schlager J, Hofmann M-C (2005). In Vitro Cytotoxicity of Nanoparticles in Mammalian Germline Stem Cells. *Toxicological Sciences* 88(2): 412–419
- 28 Oesterling E, Chopra N, Gavalas V, Arzuaga X, Jin Lim E, Sultana R, Butterfield D, Bachas L, Hennig B (2008). Alumina nanoparticles induce expression of endothelial cell adhesion molecules. *Toxicology Letters* 178 3(30):160-166
- 29 Chen L, Yokel R, Hennig B, Toborek M. (2008). Manufactured Aluminum Oxide Nanoparticles Decrease Expression of Tight Junction Proteins in Brain Vasculature. *J Neuroimmune Pharmacol* (2008) 3:286–295
- 30 Pisanic II T, Blackwell J, Shubayev V, Fiñones R, Jin S (2007). Nanotoxicity of iron oxide nanoparticle internalization in growing neurons. *Biomaterials* 28(16):2572-258
- 31 Lademann J, Weigmann H, Rickmeyer C, Bathelmes H, Schaefer H, Mueller G and Sterry W (1999). "Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice". *Skin Pharmacol Appl Skin Physiol* 12:247-256; Pflücker P, Wendel V, Hohenberg H, Gärtner E, Will T, Pfeiffer S, Wepf R and Gers-Barslag H (2001). "The Human Stratum corneum Layer: An Effective Barrier against Dermal Uptake of Topically Applied Titanium Dioxide". *Skin Pharmacology and Applied Skin Physiology* 14 (Suppl 1): 92-97; Shulz J, Hohenberg H, Pflucker F, Gartner E, Will T, Pfeiffer S, Wepf R, Wendel V, Gers-Barlag H, Wittern K-P (2002). "Distribution of sunscreens on skin". *Advanced Drug Delivery Reviews* 54 Supplement 1:S157-S163; Zvyagin A, Zhao X, Gierden A, Sanchez W, Ross J, Roberts M. 2008. Imaging of zinc oxide nanoparticle penetration in human skin in vitro and in vivo. *Journal of Biomedical Optics* 13(6).
- 32 Ryman-Rasmussen J, Riviere J, Monteiro-Riviere N. 2006. Penetration of intact skin by quantum dots with diverse physicochemical properties. *Toxicol Sci* 91(1):159-165.
- 33 Rouse J, Yang J, Ryman-Rasmussen J, Barron A, Monteiro-Riviere N. 2007. Effects of mechanical flexion on the penetration of fullerene amino acid derivatized peptide nanoparticles through skin. *Nano Lett* 7(1):155-160.
- 34 Tinkle S, Antonini J, Roberts J, Salmen R, DePree K, Adkins E. 2003. Skin as a route of exposure and sensitisation in chronic beryllium disease, *Environ Health Perspect* 111:1202-1208.
- 35 Tinkle S, Antonini J, Roberts J, Salmen R, DePree K, Adkins E. 2003. Skin as a route of exposure and sensitisation in chronic beryllium disease, *Environ Health Perspect* 111:1202-1208.
- 36 Pinheiro T, Pallon J, Ives L, Veríssimo A, Filipe P, Silva J, Silva R (2007). The influence of corneocyte structure on the interpretation of permeation profiles of nanoparticles across skin. *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, 260 (1):119-123
- 37 Mortensen L, Oberdörster G, Pentland A, DeLouise L. 2008. In Vivo Skin Penetration of Quantum Dot Nanoparticles in the Murine Model: The Effect of UVR. *Nano Lett* 8(9):2779-2787
- 38 Eg Pont AR, Charron AR, Brand RM. 2004. Active ingredients in sunscreens act as topical penetration enhancers for the herbicide 2,4-dichlorophenoxyacetic acid. *Toxicol Appl Pharmacol* 195(3): 348-354.
- 39 Monteiro-Riviere N, Yang J, Inman A, Ryman-Rasmussen J, Barron A, Riviere J. 2006. Skin penetration of fullerene substituted amino acids and their interactions with human epidermal keratinocytes. *Toxicol* 168 (#827).
- 40 SMH (2009). NSW pushes for nano risk labels. *Sydney Morning Herald* 05.05.09. Available at: <http://www.smh.com.au/national/nsw-pushes-for-nano-risk-labels-20090504-asmk.html>