Titanium dioxide and zinc oxide nanoparticles in sunscreen formulations: A study of the post production particle size distribution of particles in a range of commercial emulsion variants.

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Introduction:

In June 2003 the UK Government commissioned the Royal Society and the Royal Academy of Engineering to carry out an independent study into current and future developments in nanoscience, nanotechnologies and their impacts. The remit of the study was wide ranging and included:

- defining what is meant by nanoscience and nanotechnologies, and
- identifying what health and safety, environmental, ethical and societal implications or uncertainties may arise from the use of the technologies, both current and future.

In July 2004 the the Royal Society and the Royal Academy of Engineering published a report[1] in which they speculated that if nanoparticles penetrate the skin they might facilitate the production of reactive molecules that could lead to cell damage. The report noted however, while there was no evidence to show that nanoparticles of titanium dioxide do penetrate normal skin, there was no information relating to sun damaged or diseased skin. At the time of the report there was insufficient information about whether other nanoparticles used in cosmetics (e.g. zinc oxide) penetrate the skin and the report suggested there was a need for more research[1].

The key concern is therefore that nanoparticles may penetrate beyond the dead cells of the stratum corneum into the living cells of the dermis causing cellular damage, or accumulation in organs remote from the application site. If the nanoparticles do not penetrate the skin then there are no detrimental health implications from topical application of sunscreen containing these particles. Additionally as the particles are effectively trapped in an emulsion structure they cannot be inhaled.

Since the 2004 report the Therapeutic Goods Administration (TGA) has reviewed the scientific literature and concluded[2] "There is evidence from isolated cell experiments that zinc oxide and titanium dioxide can induce free radical formation in the presence of light and that this may damage these cells (photo-mutagenicity with zinc oxide). However, this would only be of concern in people using sunscreens if the zinc oxide and titanium dioxide penetrated into viable skin cells. **The weight of current evidence is that they remain on the surface of the skin and in the outer dead layer (stratum corneum) of the skin**."

More recent publications provide further evidence that titanium dioxide[3] and zinc oxide[4] nanoparticles do not penetrate the stratum corneum.

Particles size of Titanium Dioxide and Zinc Oxide used in sunscreens:

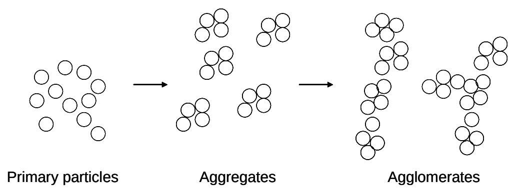
The 2004 report[1] defined the size of a nanoparticle as "typically from 100nm down to the atomic level" (approximately 0.2 nm), because it is in this range (particularly at the lower end) that materials can have different or enhanced properties compared with the same materials at a larger size.

Nanoparticles of titanium dioxide and zinc oxide, as reported by the manufacturers, have a particle size which has been termed the "primary particle size". These primary particles however have a tendency to form very tightly bound "aggregates", due to van Der Waals forces, electrostatic forces, hydrogen bonding and water molecules bridging between the particles[5]. The aggregates in turn cluster further to form less strongly bound "agglomerates". Once formed, the aggregates require large amounts of energy to disrupt, much more than the particles are exposed to during manufacture of the sunscreen emulsion used by the consumer. These aggregates and agglomerates have a particle size much larger than the primary particle size, examples of which are shown in Table 1.

The question therefore arises what is the true particle size of titanium dioxide and zinc oxide in a particular sunscreen emulsion, and are the particles in a particular sunscreen nanoparticles or not?

Measurement of particle size of nanoparticles using Dynamic Light Scattering:

One technique that can be used to measure sub-micron particle sizes is Dynamic Light Scattering (DSL). DSL measures Brownian motion and relates this to the size of the particles. The larger the particle, the slower the Brownian movement will be. Small particles are "kicked" further than larger particles by molecules of the solvent used to suspend the particles and hence move more rapidly. The velocity of Brownian motion is defined by a property known as translational diffusion coefficient (D) and the size of a particle is calculated from (D) using the Stokes – Einstein equation. The diameter that is obtained by this technique is the diameter of a sphere that has the same translational diffusion coefficient as the particle and is termed the hydrodynamic diameter d(H).



Product	TiO_2 / ZnO	Particle Coating	Primary Particle Size*
Family SPF 30+ Lotion	TiO_2	Aluminium hydroxide	30-50 nm
Family SPF 30+ Cream	TiO_2	Aluminium hydroxide	30-50 nm
Everyday Face	TiO_2	Aluminium oxide / Stearic acid	14 nm
	ZnO	Triethoxycaprylylsilane	<200 nm
Toddler	TiO_2	Aluminium stearate / Aluminium hydroxide	15 nm
Sensitive	TiO_2	Aluminium stearate / Aluminium hydroxide	15 nm
	ZnO	Triethoxycaprylylsilane	<200 nm
Quadlbock	TiO_2	Aluminium stearate / Aluminium hydroxide	15 nm

*Claimed by the pigment manufacturer

Table 1: Summary of inorganic UV filters used in Hamilton Sunscreen range.

$$d(H) = \frac{kT}{3\pi\eta D}$$

Where
- d(H) = Hydrodynamic diameter
- D = Translational diffusion coefficient
- K = Boltzmann's constant
- T = Absolute temperature
- η = Viscosity

Objective:

To examine the post production particle size of six different Hamilton Laboratories sunscreen formulations containing titanium dioxide and/or zinc oxide, which by the definition of the 2004 report and the suppliers specification, are primary nanoparticles (i.e. <100 nm).

Method:**

Particle size analysis of six Hamilton Laboratories sunscreen formulations was performed using a Malvern Zetasizer nano ZS dynamic light scattering instrument, covering the range of 0.6 nm to 6 µm.

In order to obtain a concentration suitable for analysis, a small volume of sample (approx 10 µl) was added to approx 2 ml of cyclohexane, agitated and then sonicated for 5 min using a 'Soniclean 120T' sonicator unit, which has a maximum power of 60W and multiple frequencies of ultrasound. Three measurements of each sample were made.

Results:

Hamilton Sunscreen	Peak 1		Peak 2		Peak 3	
	D_{mean} (nm)	% Area	D_{mean} (nm)	% Area	D_{mean} (nm)	% Area
Family SPF 30+ Lotion	1871	40.5	404.6	8.4	5425	50.7
Family SPF 30+ Cream	746.1	58.7	126.8	1.9	5534	39.4
Everyday Face	1833	55.8	207.6	2.1	5570	42.2
Toddler	553.7	62.8	4778	37.2	-	-
Sensitive	815.7	100	-	-	-	-
Quadblock	4114	100	-	-	-	-

Table 2: Summary of Particle Size Results at 25°C

** Measurements were conducted by the Ian Wark Research Institute, University of South Australia.

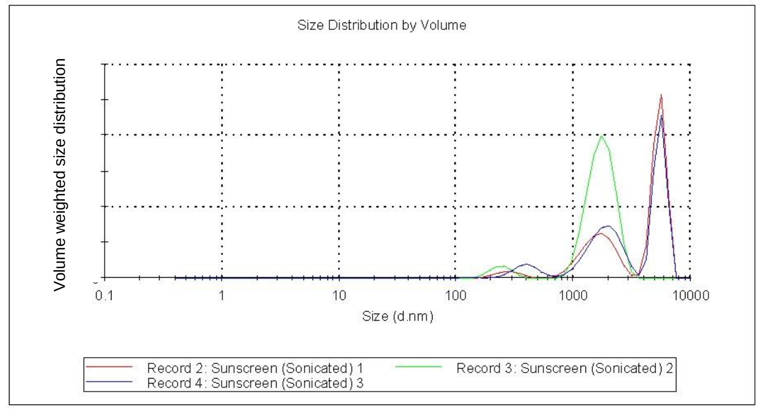


Figure 1: Integration of Particle Size Distribution by volume of Family SPF 30+ Lotion.

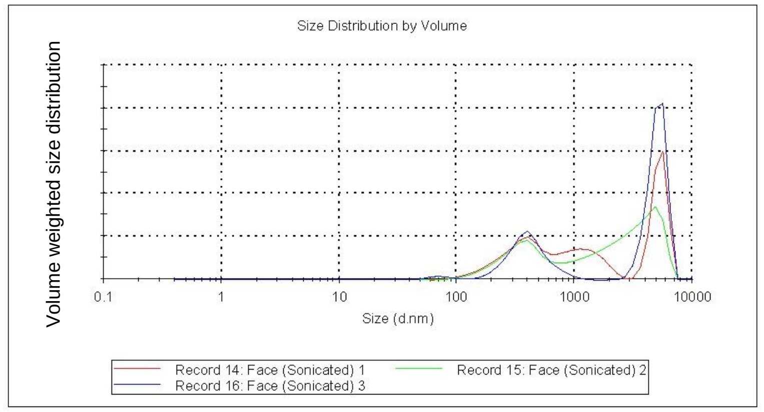


Figure 2: Integration of Particle Size Distribution by volume of Hamilton Everyday Face.

Discussion:

Analysis shows some variability in results between measurements, however despite this variability, there is little evidence of particles of diameters smaller than 100 nm.

The formulation with the smallest particle size, Toddler, showed 62.8% of the particles with a mean diameter of 553 nm and 37.2% with a mean diameter of 4778 nm. Three of the six formulations, Family SPF 30+ Lotion, Quadblock and Everyday Face, had greater than 40% of their particles with a mean diameter of greater than 4000 nm.

None of the formulations had any significant number of particles less than 100 nm under the test conditions, and therefore would not be classified as nanoparticles by the Royal Society definition.

Conclusions:

Although the primary particle size of the titanium dioxide and zinc oxide claimed by manufacturers of these pigments are by the Royal Society definition nanoparticles, processing of the particles during manufacture of the sunscreen formulations tested has shown that aggregation occurs leading to a particle size distribution of greater than 100 nm and therefore the particles are no longer considered as nanoparticles.

References:

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4. Cross, S.E., Innes, B., Roberts M., Tsuzuki, T., Robertson, T.A. and McCormick, P., 2007, Skin Pharmacol Physiol, 20:148-154
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