Submission regarding SCCS Opinion on Titanium dioxide (nano form)

September 2013

Introduction

In 2004 the United Kingdom's Royal Society and Royal Academy of Engineering recommended that nanomaterials be treated as new chemicals and that nano-ingredients in products be required to pass rigorous safety assessment before commercial use be permitted. Friends of the Earth Australia (FoEA) believes that adopting a precautionary approach to assessing the risks posed by nanomaterials is the best way to protect human health and the environment.

FoEA shares the SCCS's conclusion that nano titanium dioxide (TiO_2) with high photocatalytic activity – specifically anatase TiO_2 - should not be used in dermal formulations.[1] Given the evidence of carcinogenic effects and acute and chronic toxicity after inhalation, FoEA also share the SCCS's concerns regarding the use of nano TiO_2 in sprayable applications.[2]

However, FoEA does not agree with the SCCS's conclusion that there is sufficient evidence to conclude that the other forms of nano TiO_2 outlined in the document are safe for use in sunscreens. This conclusion is based on the assumption that skin penetration is unlikely to occur.

FoEA believes there is insufficient evidence to make such an assumption and are concerned about:

1. **The SCCS's reliance on unrealistic TiO_2 skin penetration research data provided by industry groups with a vested interest in negating such concerns.** The majority of the skin penetration studies evaluated by the SCCS are short term, *in vitro* and don't consider the role of flexing, skin condition and the widespread use of penetration enhancers in cosmetics. The SCCP's 2007 opinion on Safety of Nanomaterials in Cosmetics Products stated that "a safety assessment of nanosized TiO_2, taking into account abnormal skin conditions and the possible impact of mechanical effects on skin penetration needs to be undertaken". FoEA believes that this work still needs to be completed before a conclusion of safety can be reached regarding nano TiO_2.

2. **The high degree of uncertainty regarding the extent of skin penetration by nano TiO_2.** There are still no long-term human *in vivo* studies looking at the extent of penetration into the basal skin layer. The SCCS acknowledges that "it is not clear whether TiO_2 nanoparticles will be able to penetrate through cuts and bruises, or over repeated or long term applications of a sunscreen formulation."[3] We therefore believe that the SCCS's assumption that nanoparticles do not penetrate the skin is premature. In formulating its opinion we believe the SCCS failed to adequately consider evidence of skin penetration by other nanomaterials. The SCCS also appears to have failed to consider the strong affinity nanoparticles have with proteins and how this might impact the extent of skin penetration.

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[1] SCCS (2013) Opinion on Titanium Dioxide, nano form, July 2013, p.95.
[2] *Ibid.* p. 100-101.
[3] *Ibid.* p.97.

3. The numerous data gaps regarding certain aspects of the toxicity and fate of nano TiO_2. The SCCS noted "the relevance and usefulness of the data provided for this evaluation is poor and patchy."[4] There are numerous data gaps regarding certain aspects of the toxicity and fate of nano TiO_2 including its possible cellular uptake, mutagenicity and reproductive toxicity.[5]

4. **The high demonstrated levels of toxicity of nano TiO_2.** Various aspects of nano-TiO_2 toxicity are clearly demonstrated and acknowledged in the SCCS Opinion. These included genotoxicity, inhalation toxicity, photocatalytic activity and possible carcinogenicity.[6]

5. **Methodological problems in the existing research which prevent reliable conclusions from being drawn** Many of the studies cited by the SCCS have methodological flaws which limit their value in assessing the extent of toxicity and skin penetration.

6. **Lack of evidence that coatings are stable.** The SCCS states that nanomaterials with high photocatalytic activity "can only be recommended after appropriate coating/doping has been applied to quench their photocatalytic activity down to acceptable levels."[7] However the SCCS also raises concerns about the stability of coatings in final formulations.[8]

More detailed comments on specific sections follow.

1.3 Chemical and Physical Specifications

1.3.2 Physical form

The Applicant claims that in sunscreen products TiO_2 is not present in the form of primary nanoparticles but as aggregates formed during the manufacturing process. It appears no evidence was submitted to back up this assertion. Furthermore, it cannot necessarily be assumed that any aggregates formed are stable. For example, Bennett *et al* 2012[9] found that when some liquid mixtures of nanoparticles are exposed to natural sunlight, small nanoparticles can separate from the larger cluster of nanoparticles. Given this phenomenon, the authors investigated whether photo-induced disaggregation could assist nanoparticles to move across a skin barrier. They found that when titanium dioxide nanoparticles were applied topically to pig skin in the presence of sunlight they could penetrate the skin. These findings, say the authors, "are in stark contrast to much of the literature and may have important health consequences."

1.3.12 Homogeneity and stability

The submission refers to three studies which suggest that the coatings applied to nanoparticle surfaces are stable. However Virkutyte *et al* 2012[10] found that chlorine in

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[4] *Ibid.* p.94.
[5] *Ibid.* p.98-99.
[6] *Ibid.* p.95-98.
[7] *Ibid.* p. 95.
[8] *Ibid.*
[9] Bennett SW, Zhou D, Mielke R, Keller AA (2012) Photoinduced Disaggregation of TiO_2 Nanoparticles Enables Transdermal Penetration. *PLoS ONE* **7(11):** e48719. doi:10.1371/journal.pone.0048719
[10] J. Virkutyte et al. (2012) Depletion of the protective aluminum hydroxide coating in TiO2-based sunscreens by swimming pool water ingredients, *Chemical Engineering Journal* **191**: 95–103.

swimming pools could potentially strip the coating off titanium dioxide nanoparticles in sunscreens that protect against UV radiation, leaving them able to react with water to form free radicals.

1.5 Toxicological Evaluation

1.5.1 Acute Toxicity

The Opinion notes that only limited data was available and that the only studies submitted referred to one particular type of coated nano TiO_2.[11]

1.5.1.2 Acute dermal toxicity

Only two studies were submitted which were considerd "of no value to the current assessment of nano forms of TiO_2."[12]

1.5.1.3 Acute inhalation toxicity

No study was provided on acute inhalation toxicity. However the Opinion notes from the open literature that alveolar deposition has been noted for particles with a size of 200-300nm down to 2-3nm and that clearing of particles from this region may take weeks to years. The Opinion notes that a small fraction of the inhaled particles can reach the systemic circulation and the brain and that "exposure to ultrafine particles has been linked to inflammatory and neurodegenerative changes in the olfactory mucosa, olfactory bulb and cortical and subcortical brain structures." It also notes that "there exists a vast epidemiological literature which clearly indicates exposures to urban ambient aerosols containing nano-sized particles at high number concentrations are associated with cardiovascular morbidity and mortality."[13]

The Opinion concludes that "studies (including open literature) on acute and sub-chronic inhalation exposure to TiO_2 nanomaterials have indicated substantial inflammatory responses, and histologically clear indications of epithelial hypertrophy and hyperplasia at high exposure doses."[14] FoEA therefore agrees with the SCCS's decision not to recommend the use of nano TiO_2 in applications that would lead to any significant inhalation exposure such as in powder or sprayable products.

1.5.2.1 Skin irritation

The Opinion notes that only two of the skin irritation studies submitted were relevant and that these related to one specific type of coated nano TiO_2, with the other studies deemed "of little value."[15]

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[11] *Ibid.* pp. 18-20
[12] *Ibid.* p. 22.
[13] *Ibid.*
[14] *Ibid.* p. 25.
[15] *Ibid.*

1.5.3 Skin sensitisation

FoEA believes that there is insufficient evidence for the SCCS to conclude that nano TiO_2 does not penetrate the skin for the reasons outlined below.

1.5.4 Dermal/percutaneous absorption

The majority of the skin penetration studies evaluated by the SCCS are short term, *in vitro*, and don't consider the role of flexing, skin condition and the widespread use of penetration enhancers in cosmetics. The SCCP's 2007 opinion on Safety of Nanomaterials in Cosmetics Products stated that:

> *"a safety assessment of nanosized TiO_2, taking into account abnormal skin conditions and the possible impact of mechanical effects on skin penetration needs to be undertaken".*

FoEA believes that this work still needs to be completed before it can be concluded that nano TiO_2 does not penetrate the skin.

Furthermore, most of the dermal penetration studies used assays that were developed for traditional chemicals/molecules, not nanomaterials. An objective of the OECD Sponsorship Programme was to review the existing OECD Test Guidelines developed for chemicals to determine their suitability to assess nanomaterials. The OECD's preliminary conclusion in 2009 was that most Test Guidelines are applicable, but this conclusion was made well before most testing in the Sponsorship Program had started. In fact, the OECD is now holding a series of Expert Workshops to review OECD Test Guidelines for their suitability for nanomaterials, or the need for modification or development of new Test Guidelines.[16]

Two of the studies cited in the Opinion – Sadrieh *et al* 2010[17] and Monteiro-Riviere *et al* 2011[18] suggest that a small percentage of TiO_2 nanoparticles applied to the skin may be able to reach the viable dermis. Furthermore, Sadrieh *et al* conclude that:

> *"since some studies have shown that compromised skin allows particle penetration through the skin…we cannot at this time rule out the possibility that damaged skin could be a risk factor for TiO_2 penetration."*[19]

The Opinion acknowledges the potential for photocatalytic nano TiO_2 in sunscreen to lead to generation of reactive oxygen species (ROS) on exposure to UV light.[20] It also acknowledges that there are:

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[16] OECD (2010) Guidance manual for the testing of manufactured nanomaterials: OECD's sponsorship programme; first revision, p. 48, http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282009%2920/rev&doclanguage=en

[17] Sadrieh, N. *et al.* (2010) Lack of Significant Dermal Penetration of Titanium Dioxide from Sunscreen Formulations Containing Nano- and Submicron-Size TiO2 Particles, *Toxicological Sciences*, **115(1)**, 156–166.

[18] Monteiro-Riviere, N. A. *et al.* (2011) Safety Evaluation of Sunscreen Formulations Containing Titanium Dioxide and Zinc Oxide Nanoparticles in UVB Sunburned Skin: An In Vitro and In Vivo Study, *Toxicological Sciences,* **123(1):** 264–280

[19] *Ibid.*

[20] SCCS (2013) Opinion on Titanium Dioxide, nano form, July 2013, p.59.

> *"certain knowledge gaps in relation to the possible dermal penetration of nano TiO_2 on repeated or long term use of cosmetic products, which may not only be used on flexed healthy skin but also on skin that may have lesions or cuts."*[21]

The Opinion also acknowledges that "information on flexed or damaged skin is currently not available."[22]

Monteiro-Riviere *et al*[23] found nano TiO_2 penetrated deeper in sunburnt skin. FoEA therefore believes that there is insufficient evidence to conclude that nanoparticles do not penetrate sunburnt skin, particularly when used repeatedly over a long-term period.

1.5.6 Mutagenicity/Genotoxicity

The Opinion concludes that "the potential to cause DNA damage has been clearly demonstrated for some TiO_2 nanomaterials.[24] Given this, and the data gaps relating to skin penetration FoEA believes it is premature to conclude that the use of nano TiO_2 in sunscreen is safe.

1.5.7 Carcinogenicity

The Opinion concludes that

> *"Since TiO_2 particles have shown carcinogenic activity and since nc[non-coated] TiO_2 also showed promoter activity after intra-pulmonary spraying, the use of nano TiO_2 in sprayable applications needs specific considerations."*[25]

FoEA therefore supports the SCCS's recommendation that nano TiO_2 not be used in applications that might lead to inhalation exposure (such as powders or sprayable products).[26] FoEA also believes that, given the data gaps relating to skin penetration a precautionary approach should be applied to the use of nano TiO_2 in all dermal formulations.

1.5.9 Reproductive toxicity

The Opinion concluded that no relevant study on reproductive toxicity was provided and that "overall data on this endpoint is as yet patchy and inconclusive."[27]

1.5.10 Toxicokinetics

The Opinion concludes that "the limited evidence suggests that if TiO_2 nanoparticles become systemically available, they may accumulate mainly in liver with very slow clearance."

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21 *Ibid.*
22 *Ibid.*
23 Monteiro-Riviere, N. A. *et al.* (2011)
24 SCCS (2013) Opinion on Titanium Dioxide, nano form, July 2013, p.77.
25 *Ibid.* p. 85.
26 *Ibid.* p. 94.
27 *Ibid.* p. 87.

1.5.15 Discussion

Photocatalytic activity

The Opinion notes that "uncoated and non-doped TiO_2 nanoparticles are photocatalytic when exposed to UV light" and that "the anatase from has been shown to be more photoreactive than rutile or anatase-rutile mixtures".[28] The Opinion also notes that "anatase from of TiO_2 has been reported to be 100 times more cytotoxic under UV than rutile of a similar size".[29]

FoEA shares the SCCS's concerns regarding the stability of some of the coatings used and the photocatalytic activity of some nano TiO_2 products.
The Opinion notes that:

> *"A number of studies have indicated that TiO2 nanoparticle can enter the hair follicles and sweat glands, and that they may remain there for a number of days. This is a scenario in which TiO2 nanoparticles are likely to get and remain in a close proximity to the living cells for a length of time. A photocatalytic nanoparticle in such a situation may cause generation of reactive oxyradical species (ROS) and potential harmful effects when exposed to sunlight. As mentioned before, more data would be needed to justify the use of those TiO2 nanoparticles in skin applications that have a considerable level of photocatalytic activity."*[30]

The Opinion states that generally nanomaterials with high photocatalytic potential are "uncoated, partially coated, or have not been quenched by other means (e.g. doping) to adequately reduce photoreactivity."[31] However, it is clear from the Opinion that the photocatalytic activity of Aeroxide T8 05 (S75-F) is high, even though these particles are coated.[32] Likewise, three coated forms of rutile TiO_2 (Tioveil 50 Fin, Solveil CT-100 and Solaveil CT-10W) still exhibit moderate photocatalytic activity.

The SCCS states that it considers up to 10% photocatalytic activity of a coated or doped nanomaterial acceptable. However, no evidence has been provided to justify this assessment.[33]

FoEA supports the SCCS's recommendation that the nano anatase TiO_2 products under assessment not be used in dermal formulations. However, a number of the rutile products under assessment are also moderate photocatalysts. Furthermore, the SCCS has raised concerns about the stability of the coatings. FoEA therefore believes that it is unwise to allow the use of these products in dermal formulations.

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[28] *Ibid.* p. 16.
[29] *Ibid.*
[30] *Ibid.* p. 97.
[31] *Ibid.*
[32] *Ibid.* pp. 9, 12 & 17.
[33] SCCS (2013) Opinion on Titanium Dioxide, nano form, July 2013, p.12.

2. Conclusions

The Opinion concludes that:

> *"If any new evidence emerges in the future to show that the TiO2 nanoparticles used in a sunscreen formulation can penetrate skin (healthy, compromised, or damaged skin) to reach viable cells, then the SCCS may consider revising this assessment.*
>
> *It should also be noted that the risk assessment of nanomaterials is currently evolving. In particular, the toxicokinetics aspects have not yet been fully explored in the context of nanoparticles (e.g. the size dependency). Also, long term stability of the coatings remains unclear."*[34]

Elsewhere in the Opinion it states:

> *"the relevance and usefulness of the data provided for this evaluation is poor and patchy. It is difficult (in some cases impossible) to relate the studies to the types of nanomaterials under evaluation."*[35]

Nano TiO_2 has been shown to damage DNA, to lead to carcinogenic effects after inhalation, and is often photocatalytic. The SCCS has stated that quality of the data provided by industry was poor and that there are data gaps regarding the extent of skin penetration and the stability of coatings. FoEA therefore believes there is insufficient evidence to conclude that the use of nano TiO_2 as a UV filter is safe.

[34] *Ibid.* p. 102.
[35] *Ibid.* p. 94.