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Commentary

Opinion of the Scientific Committee on Consumer safety (SCCS) – Revision of the opinion on the safety of the use of titanium dioxide, nano form, in cosmetic products

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The first scientific opinion on the safe use of titanium dioxide as a UV-filter at a maximum concentration of 25% in cosmetic products was adopted 24 October 2000 by the SCCNFP (SCCNFP/0005/98).

However, a review of the substance in its nano form was deemed necessary according to the opinion on Safety of Nanomaterials in Cosmetic Products adopted on 18 December 2007 (SCCP/1147/07), where it is stated that:

> *"The SCCNFP opinion from 2000 (SCCNFP/0005/98) is on microcrystalline preparations of TiO2 and preparations of coarse particles. However, since this opinion, new scientific data on nanosized particles including, TiO_2 has become available. Therefore, the SCCP considers it necessary to review the safety of nanosized TiO_2 in the light of recent information. Also, 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".*

Supplementary information on nanosized Titanium dioxide was submitted following a meeting with stakeholders on 1 October 2008, where data requirements were agreed.

Titanium Dioxide is currently regulated – irrespective of its form – as a UV-filter in a concentration up to 25% in cosmetic products in Annex VII, entry 27 of the Cosmetics Directive.

This Opinion is based on the risk assessment of nano-sized titanium dioxide (TiO_2) for use as a UV filter in sunscreen formulations. It is important to note that risk assessment of nanomaterials in general still has certain gaps in the knowledge – for instance in relation to the behaviour of nanoparticles in a test medium, or in the animals. This has led to uncertainties over whether the nanoparticles are able to reach and interact with various moieties and biological target sites, and whether, on dermal application, they may penetrate through (damaged) skin, or during repeated or long term applications. There are also uncertainties over the validity of the currently available tests used for nanomaterials. However, a positive toxic response in these tests is still considered valid for risk assessment as it would indicate a hazard potential.

On the basis of physicochemical considerations discussed in the Opinion, the conclusions only apply to the TiO_2 nanomaterials presented in this submission. In addition, the Opinion may also be applicable to other TiO_2 nanomaterials that are similar to the nanomaterials covered in this Opinion in terms of physicochemical parameters listed in Tables 1–3, and the specific provisions laid out in the overall conclusions.

It needs to be stressed that the main consideration in the current assessment is the apparent lack of penetration of TiO_2 nanoparticles through skin, which is supported by a body of evidence both in the form of studies provided by the Applicant and other studies reported in open literature. In the absence of a systemic exposure, a margin of safety (MoS) could not be calculated for TiO_2 nanomaterials in this assessment. From the limited relevant information provided in the submission, and the information from open literature, the SCCS considers that TiO_2 nanomaterials in a sunscreen formulation are unlikely to lead to:

- systemic exposure to nanoparticles through human skin to reach viable cells of the epidermis, dermis, or other organs;
- acute toxicity via dermal application or incidental oral ingestion. This, however, does not apply to sprayable applications that may

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lead to inhalation exposure of TiO_2 nanomaterials, which may result in lung inflammation;
- skin irritation, eye irritation, or skin sensitisation when (repeatedly) applied on healthy skin (except possible photoxicity of insufficiently coated nanomaterials);
- reproductive effects when applied on healthy skin.

Some TiO_2 nanoparticles have been shown to be able to damage DNA and should be considered genotoxic. However as negative results have also been reported, the current evidence in relation to potential genotoxicity of TiO_2 nanomaterials is not conclusive. TiO_2 particles have also shown to lead to carcinogenic effects after inhalation. These manifestations are a major hazard concern. However, no penetration was found through the stratum corneum of reconstructed human full thickness skin models and no DNA damage was detected by the Comet assay in these cells in contrast to epidermal cell line. Considering the absence of a systemic exposure, the SCCS considers that the use of nano TiO_2 in dermally applied cosmetic products should not pose any significant risk to the consumer.

Evidence on acute and sub-chronic inhalation toxicity does not support the overall safety of use of TiO_2 nanomaterial formulations for spray applications. In addition, tumour promoter activity of nano (non-coated) TiO_2 has been shown after intra-pulmonary spraying. Therefore the SCCS does not recommend the use of nano TiO_2 in sprayable applications. This may be reconsidered if further evidence is provided to rule out the possibility that the nanoparticles can reach the lower respiratory tract during spray applications.

Although there is no conclusive evidence at present to indicate penetration of TiO_2 nanoparticles through the skin to viable cells of the epidermis, a number of studies have shown that they can penetrate into the outer layers of the stratum corneum, and can also enter hair follicles and sweat glands. It is therefore recommended not to use TiO_2 with substantially high photocatalytic activity in sunscreen formulations. Other TiO_2 nanomaterials that have a relatively lower but still significant level of photocatalytic activity may be used, but further investigations over longer post-application periods taking into account the potential photocatalytic activity post-application, whilst allowing for appropriate lag-time and using realistic application scenarios may be necessary to ascertain that they do not pose a risk due to photocatalytic activity.

On the basis of the available evidence, the SCCS has concluded that the use of TiO_2 nanomaterials with the characteristics as indicated below, at a concentration up to 25% as a UV-filter in sunscreens, can be considered to not pose any risk of adverse effects in humans after application on healthy, intact or sunburnt skin. This, however, does not apply to applications that might lead to inhalation exposure to TiO_2 nanoparticles (such as powders or sprayable products). Furthermore, this assessment applies to the TiO_2 nanoparticles presented in the submission, but may also be applicable to other TiO_2 nanomaterials that are similar to the parameters in Tables 1–3 of this Opinion, i.e. TiO_2 nanomaterials that:

- have TiO_2 purity of $\geq$99%, or in case of a lesser purity, the impurities are demonstrated to be safe for use in cosmetic formulations;
- are composed of mainly the rutile form, or rutile with up to 5% anatase, with crystalline structure and physical appearance as described in the current submission, i.e. clusters of spherical, needle, or lanceolate shapes;
- have a median particle size based on number size distribution of 30–100 nm (measured by different methods) as submitted in the dossier, or larger. Thus whilst primary particle size may be smaller (around 10 nm), the median particle size of TiO_2 nanomaterials in a cosmetic formulation must not be smaller than 30 nm in terms of number based size distribution;
- have an aspect ratio from 1.0 and up to 4.5, and volume specific surface area up to 460 m^2/cm^3;
- are coated with one of the coating materials described in Table 1, and the coatings are stable in the final formulation and during use. Other cosmetic ingredients applied as stable coatings on TiO_2 nanomaterials can also be used, provided that they can be demonstrated to the SCCS to be safe and the coatings do not affect the particle properties related to behaviour and/or effects, compared to the nanomaterials covered in this Opinion;
- are photostable in the final formulation;
- do not have photocatalytic activity. However, the SCCS considers up to 10% photocatalytic activity compared to corresponding non-coated or non-doped reference as acceptable.

It is also worth highlighting again that this Opinion is based on the currently available scientific evidence which shows an overall lack of dermal absorption of TiO_2 nanoparticles. If any new evidence emerges in the future to show that the TiO_2 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. At the moment, testing of nanomaterials and the present assessment, are both based on the methodologies developed for substances in non-nano form, and the currently available knowledge on properties, behaviour and effects of nanomaterials. This assessment is, therefore, not intended to provide a blue-print for future assessments of other nanomaterials, where depending on the developments in methodological risk assessment approaches and nano-specific testing requirements, additional/different data may be required and/or requested on a case-by-case basis.

It is also important to note that the potential ecotoxicological impacts of nano TiO_2 when released into the environment have not been considered in this Opinion.

A detailed SCCS guidance on risk assessment of nanomaterials in cosmetics has been published (SCCS/1484/12). The guidance provides a detailed account of the important nano-related parameters that should be considered in relation to physicochemical characterisation, hazard identification, exposure assessment and risk assessment of nanomaterials.

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