Scientific Committee on Consumer Safety

SCCS

OPINION

for clarification of the meaning of the term "sprayable applications/products" for the nano forms of Carbon Black CI 77266, Titanium Oxide and Zinc Oxide

The SCCS adopted this opinion at its 7th plenary meeting
on 23 September 2014

First revision on 16 December 2014

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This opinion has been subject to a commenting period of minimum four weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged. Revised opinions carry the date of revision.

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1. BACKGROUND

At the last Standing Committee and Working Party on Cosmetic Products of the 26th of June, the Commission has presented legislative proposals for the nano forms of Carbon Black CI 77266[1], Titanium Oxide[2] and Zinc Oxide[3] based on the recent SCCS opinions. For these ingredients, the scientific conclusions clearly indicated that although these ingredients are considered safe for use, sprayable applications are of concern because of possible risks due to inhalation:

"*SCCS is of the opinion that the animal cancer data are relevant to humans and that the use of nano carbon black in sprayable applications is not recommended.*"[1]

"*Therefore the SCCS does not recommend the use of nano TiO2 in sprayable applications*"[2]

"*…the use of ZnO nanoparticles with the characteristics as indicated below, at a concentration up to 25% as a UV-filter in sunscreens, can be considered not to pose a risk of adverse effects in humans after dermal application. This does not apply to other applications that might lead to inhalation exposure to ZnO nanoparticles (such as sprayable products)*"[3]

Member States asked a clarification by the SCCS for the meaning of the term "*sprayable applications/products*" in the conclusions of the safety assessments for Carbon Black CI 77266, Titanium Oxide and Zinc Oxide.

Generally speaking, the term spray is broad and includes:

a) aerosol dispensers, for which there is the definition contained in Directive 75/324: "*non-reusable containers made of metal, glass or plastic and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state*";

b) spray bottles containing a pump that draws a liquid up from the bottom and forces it through a nozzle generating a stream or a mist.

In addition, according to literature "*aerosol*" indicates a suspension of solid or liquid particles in a gas (usually air) with particle size 2 nm to more than 100 µm while "*spray*" indicates a droplet aerosol formed by the mechanical breakup of a liquid with particles larger than a few micrometers.[4]

Many cosmetic products present on the market are dispensed through a mechanical pump that, instead of aerosol/nebulisation, produces a single dose of cream. Therefore, there is a need to clarify whether "sprayable applications/products" of the nano forms of Carbon Black CI 77266, Titanium Oxide and Zinc Oxide would also include these pump dispensers for creams.

For clarity of the next scientific opinions, a harmonised terminology could be adopted meaning with the term "spray" the production of aerosols and/or nebulisation and with "pump dispensers" the dispensing devices for single-dose cream.

[1] SCCS/1515/13
[2] SCCS/1516/13
[3] SCCS/1489/12
[4] Hinds, William C. (1999). Aerosol Technology (2nd ed.). Wiley - Interscience. ISBN 978-0-471-19410-1.

2. TERMS OF REFERENCE

(1) In light of the different definitions of spray, could the SCCS clarify the product types included in the term "sprayable applications/products" used in the conclusions of the safety assessments for the nano forms of Carbon Black CI 77266, Titanium Oxide and Zinc Oxide?

(2) For clarity of the future safety assessment, could the SCCS adopt a harmonised terminology that will allow a distinction between aerosol (with propellant), spray (spray bottles) and pump dispensers (single-dose cream)?

3. OPINION

General concerns over the safety of inhaled insoluble nanoparticles have been expressed in numerous scientific publications (e.g. Oberdorster et al., 2005, Kreyling et al., 2006, Wjjnhofen et al., 2009). These concerns originate from the already well-known relationship between inhalation exposure to airborne particles (e.g. combustion derived particles in the urban environment) and incidents of respiratory problems and hospitalisations (e.g. see www.epa.gov/airscience/air-particulatematter.htm). These concerns are further exacerbated in relation to respiratory exposure to nanoparticles due to the potential ability of the particles to cross the lung barrier and to reach other parts of the body due to their nano-scale dimensions. In addition, the available evidence on the few nano forms of UV filters that have gone through SCCS assessment has not ruled out their potential genotoxicity. For these reasons, the SCCS opinions on nanomaterials (ETH50, TiO_2, ZnO, Carbon Black) have not recommended the use of the nanoparticles in sprayable formulations.

3.1 Considerations for deposition and clearance of particles in the respiratory tract

According to the European Standard CEN 481(1993), airborne particulate matter and droplets can be divided into the following three main fractions:

- inhalable fraction - the mass fraction of particles/droplets which can be inhaled by nose or mouth); only applies to particles with an aerodynamic diameter d_{ae} of ≤100 µm, since there are no experimental data on the inhalable fraction of particles with an aerodynamic diameter of > 100 µm
- thoracic fraction (the mass fraction of particles/droplets that passes the larynx); the median value of the particle size is 11.64 µm with a geometric standard deviation (GSD) of 1.5 µm. It has been shown that 50 % of the particles in air with an aerodynamic diameter of 10 µm (PM10) belong to the thoracic fraction,
- respirable fraction (the mass fraction of particles/droplets that reaches the alveoli); the median value is 4.25 µm with a GSD of 1.5 µm. It has been shown that 50 % of the particles with an aerodynamic diameter of 4 µm belong to the respirable fraction[5]

Nanoparticles fall into an even smaller-sized category within the respirable fraction, which is referred to as ultrafine particles (PM0.1), i.e. with an aerodynamic diameter d_{ae} of ≤0.1 µm.

Deposition of airborne particles and droplets in the lung depends on the size (and shape) of the particles, structure of the lung, and the breathing pattern (Sarangapani and Wexler, 2000). In general, particles/droplets >10 µm deposit in the extrathoracic region. Nanoparticles also mainly deposit in the extrathoracic region, but alveolar deposition has also been noted for particles/droplets with a size of 300-200 nm down to 3-2 nm (ICRP, 1994; Cassee et al., 2002; Oberdorster, 2005). Similarly, in the SCCS Notes of Guidance (SCCS, 2012) a distinction is made between particles >10 µm, which cannot reach the deeper lungs, and particles < 10 µm, which can reach the deeper lungs.

Any particles getting into the respiratory system are generally cleared by different mechanisms depending on the region where they are deposited (Bakand et al., 2012; Kreyling et al., 2013). Particles in the extrathoracic region are generally removed by

[5] Text adapted according to draft of EUR 20268 EN (2002), EC, JRC, Institute for Health and Consumer Protection Unit: Toxicology and Chemical Substances European Chemicals Bureau: Guidance document on the determination of particle size distribution, fibre length and diameter distribution of chemical substances

coughing followed by swallowing into the gastrointestinal tract. Particles deposited into the tracheo-bronchial region are in contact with the mucus layer covering the ciliated cells and are generally cleared via the 'mucociliary escalator', which moves the mucus (and the particles) towards the epiglottis where they are also subsequently swallowed and cleared via the gastrointestinal tract. Large insoluble particles are cleared mechanically or by adsorption to the mucous layer, whereas those that dissolve in the lung are removed via absorption.

It is important to note that, contrary to clearance from the tracheo-bronchial region, clearing of particles from the alveolar region is much slower and may take weeks to years (Möller et al., 2008). A small fraction of the inhaled particles can reach the systemic circulation by passing the pulmonary epithelial barrier. The most important clearing pathway in the alveolar region involves macrophages. These phagocytic cells reside on the alveolar epithelium, and phagocytise the particles. The particle-laden macrophages can be removed via the mucociliary escalator, or can translocate to the interstitial tissue – together with free particles (Kreyling et al., 2013). These clearance mechanisms are similar in humans and most mammals, although clearance rates can significantly differ between species. Moreover, when the lungs are continuously or repeatedly exposed to (high concentrations of) particles, the high particle burden in the macrophages can hinder phagocytosis of other particles.

Taken together, during chronic and/or cumulative exposure, nanoparticles in the alveoli can potentially accumulate in the tissue of the entire lung.

The particles in the interstitium - both free particles and those in macrophages - may enter the lymphatic system and/or traverse the alveolar-capillary endothelium and subsequently enter the blood. The passage through the endothelial cell layer has been shown for particles of different chemical identity but seems to be restricted to "small" nanoparticles (Geiser and Kreyling, 2010; Kreyling et al., 2013).

The translocation of nanoparticles from the lungs into the systemic circulation has been reported in humans (Nemmar et al., 2001) and animals (Kreyling, 2002; Nemmar et al., 2002; Rothen-Rutishauser, 2007), although these findings are still controversial.

3.2 Specific concerns relating to nanomaterials in sprayable products

As mentioned above, a decrease in the size of airborne particles or droplets increases the possibility of particles reaching deeper parts of the respiratory system. Therefore the use of delivery systems that can generate aerosolised nanoparticles, or spray droplets containing nanoparticles, raises a concern in relation to the potential respiratory exposure of the user. Because of their very small size, inhaled nanoparticles may not only reach deeper parts of the lung, but also the systemic circulation by passing the pulmonary epithelial barrier. It is reported that a small fraction of the inhaled particles in the nose can reach the brain directly via the olfactory bulb (Kao et al., 2012).

As highlighted in the SCCS Nano Guidance (SCCS/1484/12), the estimation of exposure to nanomaterial containing aerosols is likely to be quite challenging. This relates to the complex architecture of the respiratory system and the exposure/uptake depending on the breathing mode, and further on aerosols as a complex system of different substances in at least two different aggregation states: Liquid or gaseous propellants coexist with vapours of the formulated product that contains the nanoparticles. Moreover, continuous evaporation/condensation and coalescence/agglomeration modify the concentrations in the aerosol as well as the size distribution of the liquid and solid parts, which in turn affect their deposition and uptake in the different compartments of the respiratory tract.

A model commonly used for exposure assessment to solvents and aerosols generated after the use of spray applications is the ConsExpo model (www.consexpo.nl). This tool comprises two modules for inhalation: 1) exposure to vapour and 2) exposure to aerosol from sprays. The spray module calculates the exposure based on the inhalable fraction of the generated

aerosols. For conventional substances it is assumed that these are homogeneously distributed over the generated aerosols, on a mass basis. For that reason, in the experiments carried out for the calibration of the model, aerosols with a size <1 μm are not taken into account. It should be noted that the mass of aerosol droplets <1μm is negligible compared to the aerosols present in the inhalable fraction of 1-20 μm, while the surface area among other parameters can be dominant for fractions of the aerosol with smaller dimensions. Since ConsExpo has not been calibrated for aerosol droplets whose size is less than 1 μm and is based on mass, rather than on particle number and size distribution (to capture e.g. surface effects), it does not capture the critical features of nanoparticles. Hence, in the current form it is not applicable for nanoparticle containing sprays. Furthermore, for spray application of products with nanomaterial, a careful characterisation is needed of the droplet size and the nanomaterial distribution in the droplets. These spray characteristics depend critically on the engineering and type of the dispenser and the rheological properties of the used formulation. The size of the droplets or particles in the aerosol determines whether the droplet/particle is inhaled and where it deposits in the respiratory tract. Toxicity, in turn, depends on the size of the particles that are released from the aerosol when inside the lung, leading to local effects (on the lung) and/or systemic effects after uptake via the lung. Therefore, both the size of the inhaled aerosol and the size of the released nanoparticles in the lung influence toxicity. A complicating factor is that after spraying, the size of the nanoparticle containing droplets may quickly decrease due to evaporation of the solvent, and either primary particles or agglomerates remain. Hence, the size distribution changes with time.

Models for exposure assessment of nanoparticles in sprays are evolving (Schneider et al., 2011). A model for consumer exposure assessment to nanoparticles in sprays has been proposed e.g. by Lorenz et al., 2011. This model is based on particle/droplet size distributions determined in a spray experiment. The experimental data is combined with the ICRP deposition model (ICRP, 1994) and consumer exposure can be calculated for different parts of the respiratory tract. For qualitative estimates the control banding tool Nano-Stoffenmanager (https://nano.stoffenmanager.nl/) can be used.

In this context, the SCCS recommendation in relation to the use of nanomaterials in sprayable products relates to those means of delivering nanoparticle-containing formulations that can lead to the generation of airborne particles as such, or particle-containing spray droplets. This includes sprays resulting from aerosol dispensers (as defined in Directive 75/324[6]), or a spray bottle that pumps a liquid through a nozzle generating a spray stream or a mist. In the latter case, depending on the engineering and size of the nozzle, the generated spray droplets may be too large to be respirable. Indeed it has been hypothesised that droplets from pump sprays (i.e. liquids in a pump dispenser with spraying nozzle) are too big to be inhaled and therefore do not pose a risk (Lorenz et al., 2011). More recent work (Quadros & Marr, 2011, Losert et al., 2014, in preparation) has shown that pump sprays can also release particles/droplets in the nano range, which may potentially be inhaled. However, as highlighted in the SCCS Nano Guidance (SCCS/1484/12), the airborne particles or spray droplets containing particles may rapidly reduce in size due to evaporation of the solvents/ formulants before settling out and thus may become inhalable/ respirable. It was therefore recommended that the safety assessment of the dispensing methods that generate airborne sprays should take into account not only the size distribution of the generated aerosol droplets but also the size distribution of the dried residual particles (SCCS/1484/12).

[6] "non-reusable containers made of metal, glass or plastic and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state"

4. CONCLUSION

In view of the foregoing, the SCCS view is that dispensing devices for single-dose cream that do not generate airborne particles or droplets that are either respirable as such, or that dry off while airborne to become small enough to be respirable, should be excluded from the term 'spray' or 'sprayable'. However, the proposed term "pump dispenser" is too inclusive, since not only the type of dispenser, but also the formulation that is dispensed together with the nozzle size, determine the droplet size after dispensing. To reflect this, and for the purpose of clarity, the SCCS will use the following harmonised terminology in the existing and future opinions when describing various dispensing methods as follows:

- The term 'spray' or 'sprayable' will mean that a formulation is either dispensed by the use of propellant gas as defined in Directive 75/324 (propellant spray), or by a spray bottle with a pump dispenser that forces a liquid through a nozzle generating a spray stream or a mist of a liquid (pump spray). Where this term is used in an SCCS opinion, further clarification will be added. For example, instead of [the use of nano…. in sprayable applications is not recommended.] the recommendation will state [the use of nano…. in sprayable applications that could lead to exposure of the consumer's lungs to nano…. by inhalation is not recommended.]
- The term 'dispenser without spray nozzle' denotes a device by which a formulation is dispensed in the form of a single dose or a foam, where the process does not generate a significant quantity of airborne particles or droplets that are either respirable as such, or become respirable as a result of drying while airborne. Typical formulations that are dispensed with such a device are liquid soap, cream, shaving foam and other formulations that are more viscous than water.

This clarification should prevent any confusion, misinterpretation or unnecessary queries on the issue, and the SCCS suggests replacing the following text in the current opinions on nano-forms of Carbon black, Titanium dioxide and Zinc oxide.

The SCCS proposes to incorporate the following changes to the existing Opinions:

4.1 Opinion SCCS/1515/13 on nano Carbon black

Existing text on page 95 (part of Discussion):

"SCCS is of the opinion that the animal cancer data are relevant to humans and that the use of nano carbon black in sprayable applications is not recommended."

New text:

"SCCS is of the opinion that the animal cancer data are relevant to humans and that the use of nano carbon black in sprayable applications that could lead to exposure of the consumer's lungs to nano carbon black by inhalation is not recommended."

Existing text on page 97 (part of Conclusion):

"This opinion does not apply to applications that might lead to inhalation exposure to carbon black nanoparticles, where the preparation might lead to inhalable particles."

New text:
"This opinion does not apply to applications that might lead to exposure of the consumer's lungs to carbon black nanoparticles by inhalation."

4.2 Opinion SCCS/1516/13 on nano Titanium dioxide

Existing text on page 99:

"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."

New text:

"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 titanium dioxide in spray applications that could lead to exposure of the consumer's lungs to nano titanium dioxide by inhalation. 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."

Existing text on page 100 (part of overall conclusion):

"….. 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 not to pose a 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). …"

New text:

"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 not to pose a risk of adverse effects in humans after application on healthy, intact or sunburnt skin. This, however, does not apply to spray applications that might lead to exposure of the consumer's lungs to TiO_2 nanoparticles by inhalation."

4.3 Opinion SCCS/1489/12 on nano Zinc oxide

Existing text on page 96: *Inhalation exposure*

"Upon inhalation of ZnO nanoparticles, serious local effects in the lung were observed. Even if this may be due to the solubilized Zn+2 ions, the effects are a direct result of the exposure to the ZnO nanoparticles. Therefore, the SCCS is of the opinion that, on the basis of available information, the use of ZnO nanoparticles in spray products cannot be considered safe."

New text: *Inhalation exposure*

"Upon inhalation of ZnO nanoparticles, serious local effects in the lung were observed. Even if this may be due to the solubilized Zn ions, the effects are a direct result of the exposure to the ZnO nanoparticles. Therefore, the SCCS is of the opinion that, on the basis of available information, the use of ZnO nanoparticles in spray products that could lead to exposure of the consumer's lungs to nano ZnO by inhalation cannot be considered safe."

Existing text on page 97:

"In summary, it is concluded on the basis of available evidence that the use of ZnO nanoparticles with the characteristics as indicated below, at a concentration up to 25% as a UV-filter in sunscreens, can be considered not to pose a risk of adverse effects in humans after dermal application. This does not apply to other applications that might lead to inhalation exposure to ZnO nanoparticles (such as sprayable products)."

New text:

"In summary, it is concluded on the basis of available evidence that the use of ZnO nanoparticles with the characteristics as indicated below, at a concentration up to 25% as a UV-filter in sunscreens, can be considered not to pose a risk of adverse effects in humans after dermal application. This does not apply to spray applications that might lead to exposure of the consumer's lungs to ZnO nanoparticles by inhalation."

Existing text on page 98:

"In view of the lung inflammation induced by ZnO particles after inhalation exposure, the use of ZnO in cosmetic products which may result in inhalation is of concern."

New text:

"In view of the lung inflammation induced by ZnO particles after inhalation, the use of ZnO in cosmetic products that may result in exposure of the consumer's lungs by inhalation is of concern."

5. MINORITY OPINION

None

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