Scientific Committee on Consumer Safety

SCCS

OPINION ON

solubility of Synthetic Amorphous Silica (SAS)

The SCCS adopted this Opinion
at the Plenary meeting on 20-21 June 2019

ACKNOWLEDGMENTS

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http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

This Opinion has been subject to a commenting period of 9 weeks after its initial publication (from 15 March until 17 May 2018). Editorial comments received during this time were considered by the SCCS.

1. ABSTRACT

The SCCS concludes the following:

1. Does the SCCS consider that Synthetic Amorphous Silica (SAS) are soluble (100 mg/L or higher) or degradable/non-persistent in biological systems, in light of the nanomaterial definition of the Cosmetic Regulation?

Having considered the data provided in this dossier and that available in published literature, the SCCS concludes that:

i) the solubility values for hydrophilic SAS materials have been reported to range from 22 mg/L to 225 mg/L for the solubility tests performed in aqueous media, or following the enhanced OECD TG 105 (0.5% ethanol). The latter protocol has been noted to increase the solubility by a factor of 10 for some hydrophilic SAS materials.

ii) the solubility values of hydrophobic surface-treated SAS materials have been reported to range from 0.4 to 180 mg/L for solubility tests performed in aqueous media, or following a modified enhanced OECD TG 105 protocol (i.e. using 10% ethanol). The latter protocol has been noted to strongly increase the solubility of some hydrophobic SAS materials (by a factor up to 173).

The hydrophilic and hydrophobic SAS materials can therefore be regarded as “insoluble” (i.e. below 100 mg/L) to “very slightly soluble” (i.e. 100 mg/L to 1000 mg/L) by the SCCS based upon the terminology used in USP38 and USP 38 NF33 (Table 1 corrected by the SCCS).

In regard to the nanomaterial definition in the Cosmetic Regulation, none of the SAS materials (hydrophilic or hydrophobic) included in the dossier can be regarded as soluble. In fact, the Applicant had mistakenly interpreted the SAS materials as soluble on the basis of the solubility of some of the materials being 100 mg/L or higher. The threshold for regarding a material 'soluble' is 33.3 g/L under the USP38 and USP 38 NF33 categorisation (not 100 mg/L as claimed by the Applicant).

No data were provided to help establish whether the SAS materials could be regarded degradable/non-persistent in biological systems.

2. Can the SCCS indicate to which kind of Silica this solubility applies?

The solubility values reported in the dossier are applicable when SAS materials are subject to the following conditions:

- hydrophilic SAS: Silica and hydrated silica when solubilised in aqueous media containing up to 0.5% ethanol,
- hydrophobic surface treated SAS: when solubilised in aqueous media containing up to 10% ethanol,
- at temperatures between 19.5 to 20.5°C,
- with a pH level of between 3 and 8,
- over a period between 3 days (hydrophilic SAS) up to 49 days (hydrophobic SAS).

3. Does the SCCS have any further scientific concerns with regard to solubility of Synthetic Amorphous Silica (SAS)?

- The solubility values considered by the SCCS in this Opinion may not be valid in situations where the SAS materials are formulated/used under conditions that are different from those used in the solubility tests - e.g. when used in a less/non aqueous formulation, or at a different temperature.

- In the context of the definition of nanomaterial under the Cosmetics Regulation, which relates to insoluble materials in conjunction with other size/particle related parameters, the question of solubility of a nano-structured material needs to be seen in perspective for use in cosmetics. For nano-structured materials, with the exception of the materials that are completely soluble, it is important to establish whether a proportion of these materials would still exist in undissolved form comprising nanoparticles, at the given use level in a cosmetic formulation.

- The SCC has noted that the protocols used for solubility tests have a strong influence on the solubility of SAS materials.

Keywords: SCCS, scientific opinion, Synthetic Amorphous Silica (SAS), solubility, nanomaterials, Regulation 1223/2009

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on solubility of Synthetic Amorphous Silica (SAS), 20-21 June 2019, SCCS/1606/2019

About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of scientists appointed in their personal capacity.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Article 2(1)(k) of Regulation (EC) No 1223/2009 (Cosmetics Regulation) establishes that "nanomaterial" means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.

That definition covers only materials in the nano-scale that are intentionally made and are insoluble/partially-soluble or biopersistent (e.g. metals, metal oxides, carbon materials, etc.). It does not cover those that are soluble or degradable/non-persistent in biological systems (e.g. liposomes, emulsions, etc.). Article 16 of the Cosmetics Regulation requires cosmetic products containing nanomaterials other than colorants, preservatives and UV-filters and not otherwise restricted by the Cosmetics Regulation to be notified to the Commission six months prior to being placed on the market. Article 19 of this Regulation requires nano-scale ingredients to be labelled (name of the ingredient, followed by 'nano' in brackets). If there are concerns over the safety of a notified nanomaterial, the Commission shall refer it to the Scientific Committee on Consumer Safety (SCCS) for a full risk assessment.

The Commission received several notifications under Article 16 of the Cosmetics Regulation on four types of nano silica and consequently requested the SCCS to provide a safety assessment on Silica, Hydrated Silica, and Silica Surface Modified with Alkyl Silylates (nano form).

The SCCS adopted an Opinion (SCCS/1545/15) in September 2015 with the following conclusion:

> *After detailed evaluation of the current submission, the SCCS has concluded that the evidence, both provided in the submission and that available in scientific literature, is inadequate and insufficient to allow drawing any firm conclusion either for or against the safety of any of the individual SAS material, or any of the SAS categories, that are intended for use in cosmetic products.*

In January 2018, the Association of Synthetic Amorphous Silica Producers (ASASP), a Cefic Sector Group, submitted a dossier with the purpose of demonstrating that SAS does not fall under the nanomaterial definition of the Cosmetic Regulation. Therefore, according to the applicant, no further actions required for nanomaterials as defined in the Cosmetics Regulation would apply to SAS.

Terms of reference

(1) Does the SCCS consider that Synthetic Amorphous Silica (SAS) are soluble (100 mg/L or higher) or degradable/non-persistent in biological systems, in light of the nanomaterial definition of the Cosmetic Regulation?

(2) Can the SCCS indicate to which kind of Silica this solubility applies?

(3) Does the SCCS have any further scientific concerns with regard to solubility of Synthetic Amorphous Silica (SAS)?

3. OPINION

Preamble:

According to the definition provided under Article 2(1)(k) of Regulation (EC) No 1223/2009 (Cosmetics Regulation) "nanomaterial" means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm. The current mandated questions relate to assessment of the claims made in the submitted dossier that, on the basis of solubility (being ≥100 mg/L), synthetic amorphous silica (SAS) is a soluble material and therefore does not fall under the nanomaterial definition of the Cosmetic Regulation. No toxicological or exposure data were provided as part of the dossier, and therefore this Opinion has not considered either toxicological hazard, exposure, or risk to the consumer. As such, this Opinion is only focused on the physicochemical aspects related to the solubility of SAS materials in the context of whether or not they can be regarded as nanomaterials in light of the nanomaterial definition provided in the Cosmetic Regulation. In this context, this Opinion has also considered the dissolution rate of SAS materials in relevant media with a view to their potential solubility when used in cosmetic products.

It is important to highlight that a clear distinction is needed between 'solubility' and 'dispersion' of the materials that are composed of small particles because boundaries between the two may become blurred at the nano-scale. As described in the SCCS Guidance on Nanomaterials (SCCS/1484/12), the SCCS regards 'solubility' as disintegration of a nanomaterial in an aqueous medium or biological environment into molecular (or ionic) components with the loss of nano-scale features. The ECHA Guidance on Information Requirements Chapter 7a (Appendix R7-1 for nanomaterials applicable to Chapter R7a (Endpoint specific guidance) Version 2.0 – May 2017) has also highlighted this aspect as follows:
'The behaviour of particles in liquid media presents some additional important aspects and challenges to recognise. In particular, it can be difficult to distinguish between when a nanomaterial is dispersed and when it is dissolved due to its small particle size. It is important to recognise that solubility and dispersibility are two distinct phenomena. Solubility is the degree to which a material (the solute) can be dissolved in another material (the solvent) such that a single, homogeneous, stable phase results, and is relevant to solids, liquids and gases. Dispersibility is the degree to which a particulate material can be uniformly distributed in another material (the dispersing medium or continuous phase). Historically, the term "dissolved" meant the component of a liquid sample that had passed through a 0.45 μm (or similar) filter. However, as (colloidal) dispersions of nanoparticles might also pass through such filters, it is recommended that use of the term "dissolved" should be restricted to the formation of true solutions, and where both liquid and particulates are present the term "dispersed" should be used.'

In view of the above considerations, this Opinion has evaluated the data and information provided in the submission, as well as that obtained from the available scientific literature, to ascertain that the data provided on solubility of synthetic amorphous silica (SAS) materials unambiguously relate to solubility and not dispersion.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

Silicon dioxide (IUPAC)
(from SCCS/1545/15 - Revision of 29 September 2015)

3.1.1.1 Primary name and/or INCI name

Hydrophilic SAS:
  Silica
  Hydrated silica

Hydrophobic SAS:
  Silica dimethyl silylate
  Silica silylate
  Silica dimethicone silylate[1]
  Silica caprylyl silylate[1]
  Silica cetyl silylate[1]

[1] INCI only available in USA (PCPC, personal care products council)

3.1.1.2 Chemical names

Name	Description
Silica	Pyrogenic silica
Hydrated silica	Precipitated silica, Silica gel, Colloidal silica
Silica dimethyl silylate	Hydrophobic silica/ silica surface-treated with dichlorodimethylsilane
Silica silylate	Hydrophobic silica/ silica surface-treated with hexamethyldisilazane
Silica dimethicone silylate	Hydrophobic silica/ silica surface-treated with polydimethylsiloxane
Silica caprylyl silylate	Hydrophobic silica/ silica surface-treated with organosilane
Silica cetyl silylate	Hydrophobic silica/ silica surface-treated with hexadecylsilane

SCCS comment :
As shown in the Table above, the submitted information in the dossier refers to pure silica materials, as well as treated silica materials - i.e. with a surface treatment that rendered the material hydrophobic.

3.1.1.3 Trade names and abbreviations

ACEMATT®, AEROSIL®, AEROSIL® specific R-types, AEROPERL® CAB-O-SIL®, CAB-O-SIL® specific TS-types, Elfadent®, HDK®, HDK® specific H-types, Ibersil®, Ludox®, Perkasil®, RxCIPIENTS®, Silica VP, SIDENT®, SIPERNAT®, Sorbosil®, Syloblanc®, Sylodent®, Syloid®, Tixosil®, ZEODENT®, ZEOFREE®, ZEOTHIX®, ZEOPHARM®

3.1.1.4 CAS / EC number

CAS (generic): 7631-86-9
CAS (specific): 112945-52-5, 112926-00-8[2], 68611-44-9, 60842-32-2, 67762-90-7, 1158846-14-0, 68909-20-6, 102262-30-6, 126877-03-0, 211811-62-0, 67762-90-7, 92797-60-9, 199876-45-4

[2] CAS 112926-00-8 is for silica gel, precipitated; crystalline free; other names: amorphous synthetic silica gel; cryst.-free silica gel; pptd. crystalline-free silica sol; pptd. synthetic amorphous silica; silica sol, pptd., crystalline-free; synthetic amorphous silica, pptd.; synthetic crystalline free silica gel; pptd.: precipitated

SCCS comment:
The following discrepancies were found in the information provided in the dossier relating to CAS numbers. These need correcting or explaining as some CAS numbers do not match with description of the SAS materials referred to in the dossier:

- The CAS numbers 1158846-14-0 and 211811-62-0 do not seem to be associated with SAS materials.
- Four different CAS numbers (68611-44-9, 60842-32-2, 67762-90-7, 1158846-14-0) have been quoted for one material 'Silane, dichlorodimethyl-, reaction products with silica'. Another four CAS numbers (68909-20-6, 102262-30-6, 126877-03-0, 211811-62-0) have been quoted for one material 'Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl), hydrolysis products with silica'. These should be clarified to keep only the relevant ones.
- The following CAS numbers have been found to be associated with materials that are different from those quoted in the dossier (source: EchemPortal/ChemicalBook). These discrepancies should be clarified/addressed:

CAS NUMBER (as in the dossier)	SILICA DESCRIPTION
CAS: 112926-00-8, quoted in the dossier as "Synthetic amorphous silica, pptd.; cryst.-free"	• Silica gel, pptd., cryst.-free (Echemportal) • Silica Gel and Metals scavenging agent, Mercaptopropyl modified silica (BASF MSA-FC Si-3) (ChemicalBook)
CAS: 60842-32-2, quoted in the dossier as "Silane, dichlorodimethyl-, reaction products with silica	• Aerosil 972 (EchemPortal and ChemicalBook) • Hydrophobic fumed silica
CAS: 67762-90-7, quoted in the dossier as "Silane, dichlorodimethyl-, reaction products with silica"	• Siloxanes and Silicones, di-Me, reaction products with silica" (EchemPortal) • Reaction products of dimethyl siloxanes and silicones with silica" (EPA Registry)
CAS: 102262-30-6, quoted in the dossier as "Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica"	• Aerogel powder, hydrophobic (SiO_2) (ChemicalBook)
CAS: 126877-03-0, quoted in the dossier as "Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica"	• Silica gel, trimethylsilylated" (Echemportal)

3.1.1.5 Structural formula

Silica (unmodified)

$(O{=}Si{=}O)_n$

3.1.1.6 Empirical formula

SiO_2 (unmodified)

SCCS comment:
Exact chemical formulae should be provided for all the moieties used for surface modification of the SAS materials included in the dossier.

3.1.2 Physical form

/

3.1.3 Molecular weight

No information is provided in the Dossier.

SCCS comment:
Molecular weight of SiO_2 (unmodified): 60.08 g/mol

3.1.4 Purity, composition and substance codes

Information on purity has been provided upon request by the SCCS.

According to the Applicant, SAS is a material of high purity, containing only minor impurities. This allows it to be used in many sensitive applications such as pharmaceuticals, food, and cosmetics. As the minor impurities do not contribute to solubility, only impurities exceeding 0.1 % are listed in Annexes I and II in the dossier.

SCCS comment:
The provided information has been noted by the SCCS.

3.1.5 Impurities / accompanying contaminants

Information on impurities and accompanying contaminants has been provided upon request by the SCCS.

According to the Applicant, wet production route SAS materials, such as gels or precipitates, contain only sodium sulfate as a relevant impurity above 0.1 %, while pyrogenic SAS materials typically do not contain any impurities above 0.1 %.
According to Iler (1979), the solubility of SAS is influenced by temperature, pH above 8.5 and particle size. At lower temperatures, impurities such as sodium sulfate do not influence either the solubility, or rate of dissolution of SAS (Chen and Marshall (1982)). This is supported by Greenberg and Price (1957), who found that an up to 0.1 mol/L Na_2SO_4 concentration had no effect on the solubility of a pure silica powder. Bai *et al.* (2009) reported that the dissolution rate of amorphous silica is enhanced by sulfate ions starting at a 0.1 molar solution of Na_2SO_4 at 25°C. This is still far above the concentration which can be achieved if all Na_2SO_4 contained as impurity (typical average maximum value 2.5 % corresponding to 0.0088 mol Na_2SO_4) was dissolved.

SCCS comment:
The information provided on the impurities has been noted by the SCCS.

3.1.6 Solubility

A/ Solubility scale

The following definitions for solubility terms were provided by the Applicant:

Term	Parts of Solvent Required for 1 Part of Solute	Solubility defined in mg/L
Very soluble	Less than 1 part	> 1000
Freely soluble	1 to 10 parts	100 – 1000
Soluble	10 to 30 parts	33 – 100
Sparingly soluble	30 to 100 parts	10 – 33
Slightly soluble	100 to 1000 parts	1 – 10
Very slightly soluble	1000 to 10000 parts	0.1 – 1
Insoluble	> 10000 parts	< 0.1

Table 1: Definitions for solubility terms provided by the Applicant based on documents USP38 and USP 38 NF33

SCCS's comments on Table 1:
The values quoted in 1st and 2nd column of the above Table are the same as in USP38/ USP38–NF33, whereas values in the 3rd column are deduced by the Applicant. Upon request for clarification by the SCCS, the Applicant agreed that the values for solubility ranges (3rd column) had been reported erroneously. These should have been 'Solubility defined in g/L', and not 'Solubility defined in mg/L' as reported in the dossier. The Table 1 has therefore been corrected and reproduced by the SCCS as below:

Term	Parts of Solvent Required for 1 Part of Solute	Solubility defined in g/L
Very soluble	Less than 1 part	>1000
Freely soluble	1 to 10 parts	100-1000
Soluble	10 to 30 parts	33.3-100
Sparingly soluble	30 to 100 parts	10-33.3
Slightly soluble	100 to 1000 parts	1-10
Very slightly soluble	1000 to 10000 parts	0.1-1
Insoluble	>10000 parts	<0.1

Table 1 corrected by the SCCS: Definition of solubility terms

The following further information on solubility has been provided by the Applicant: The solubility of silica (synthetic amorphous silica gel) has already been reviewed by Struckmann in 1855 [Struckmann (1855)] and Lenher and coworkers [Lenher and Merril (1917)] in 1917.

Struckmann [Struckmann (1855)] concluded that amorphous silica dissolved in water at ordinary temperature to the extent of 100 to 150 mg/L.

Lenher and Merril (1917) concluded that silica is soluble and that the solubility in water, hydrochloric acid and sulfuric acid is definite and depends on the temperature and concentration.

Alexander *et al.* [Alexander *et al.* (1954)] found that the solubility of silica (amorphous) is relatively constant at about 120 to 140 mg/L SiO_2 in the pH range 5 to 8. At a pH of 2.1 to 2.7, the solubility is lower, approx. 100 mg/L SiO_2.

Otterstedt and Brandreth [Otterstedt and Brandreth (1998)] concluded in their review that the solubility of SAS is a function of temperature, pressure, structure, particle size (primary particle size) and pH. The solubility of SAS at 20 °C and within a pH range from 4 to 8 is in the range of 100 to 150 mg/L and increases with temperature.

Goto, Okura and Kayama [Okamoto *et al.* (1957)] showed that the solubility is a constant from pH 2 to 8, then increasing rapidly at higher pH. The dissolution of SAS is a hydration reaction forming monomeric silicic acid.

The dissolution of the SAS surface requires the alkaline hydroxyl ion (OH-) as a catalyst, forming monomeric silicic acid. It has been noticed that the reaction is completely reversible and that silica is deposited on the surface by the same reaction. Actually, the dissolution in water is a hydrolytic de-polymerization and the solubility of silica is the concentration of silicic acid monomer or dimer reached at a steady state in the de-polymerization-polymerization equilibrium.

Figure 1 shows that the hydroxyl ion is chemisorbed on the surface and increases the coordination number of the silicon atom to more than four, hence weakening the silicon oxygen bonds in the surface. After the adsorption of the OH- ion, a silicon atom dissolves as a silicic ion, $Si(OH)_4$ and OH-. Below pH 3 the rate is very slow because the concentration of OH-, acting as a catalyst, is very low. Between pH 3 and 6 the rate is proportional to the hydroxyl ion concentration.

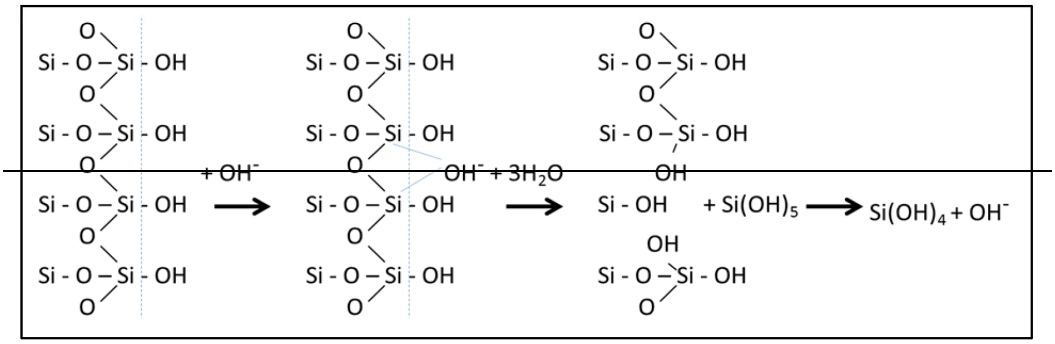

Figure 1: *Proposed mechanism of dissolution of SAS in water in the presence of hydroxyl ions.*

SCCS comment:
Referring to the solubility terms in Table 1 corrected by the SCCS, the SCCS acknowledges that conventional chemical substances with solubility in the range of 100-1000 mg/L are generally regarded as 'very slightly soluble', and those with solubility less than 100 mg/L as 'insoluble'. Although such values have not yet been established for nanomaterials, the SCCS can accept the same for nanomaterials in consideration that solubility is an inherent property of a material.

B/ Solubility Tests

According to the Applicant, the solubility of hydrophilic SAS was tested by an 'enhanced OECD TG 105' method. All solubility data on hydrophilic SAS was measured according to this enhanced OECD 105 protocol, in the same GLP certified lab, under standardized conditions. Surface treated, hydrophobic grades, were examined using a modified procedure owing to poor solubility.

According to the Applicant (Solubility test protocol: Modified enhanced OECD 105 protocol)
Following the NanoGenotox approach, pre-wetting with ethanol was chosen to improve reproducibility. Moreover, ethanol is included in many cosmetic formulations, so the conditions used lead to a more realistic picture.

The 10% ethanol medium was not used to simulate any biological or environmental conditions. It simply serves as a vehicle to measure the solubility of hydrophobic grades. To date there is no established protocol to determine the solubility of hydrophobic powders. Applying either the standard, or enhanced, OECD 105 methods show a high scatter of results or no real result.

Roelofs and Vogelsberger (2004) determined the solubility of pyrogenic, precipitated and gel forms of SAS, including surface treated forms in simulated biological medium. The study showed that at 37 °C and pH values near 7, solubility for the different forms was between 138 to 162 mg/L, and close to the solubility in water reported in the Dossier (reference ASASP1059b dated 26 January 2018). The authors confirmed that SAS has a tendency to supersaturate meaning dissolution rate is more rapid than the precipitation rate. Hence, the different forms of SAS dissolve both in water and in simulated biological systems beyond the equilibrium concentration.

Total dissolution can be expected in biological systems where dissolved SAS is quickly removed, Roelofs and Vogelsberger (2004). In principle, the OECD 105 enhanced method could be used for such tests. However, this would require additional work on the calibration of the Tyndall system and the UV-VIS (molybdate method), as dissolved SAS in form of mono or dimeric orthosilicic acid, will likely already be present in such biological fluids and may influence the solubility, or cause a high false result.

10% ethanol was chosen to provide comparable conditions for all surface modified grades. Pre-tests at different ethanol concentrations had demonstrated that 0,5 % ethanol, as applied in the original NanoGenotox protocol, is not sufficient to wet all surface modified grades.

10 mL ethanol was added to 5.0 g of the test item and the mixture shaken overnight. 65 mL of water p.a. was subsequently added (75 mL final volume) and the solution homogenized via ULTRA-TURRAX at 20,000 rpm for 30 seconds. The dispersing device was rinsed with 25 mL water (100 mL final volume in the flask). The homogenized mixture was then mixed at 250 rpm. All subsequent steps were similar to the procedure in water.

In addition, two samples of hydrophilic SAS, one gel and one precipitated grade were tested in pure ethanol following the OECD 105 enhanced method to evaluate the solubility in a non-polar solvent. In agreement with literature, Iler (1979) and others, the solubility was low; approx. 1 mg SiO_2/L, due to the absence of OH- ions in the solvent, which catalyse dissolution of SAS.

Further information on the performed solubility tests according to the Applicant's dossier:

pH of the test solutions

For solubility in water all tests were run with “Water p.a., Roth” - deionized water with total organic carbon (TOC) < 1 ppm, Si free (SiO_2 content < 0,000001 %) and conductivity below 0.3 µS/cm. As synthetic amorphous silica (SAS) is known to have buffering properties (pKs 6.6 for $(OSiO)_3$ SiOH [Iler (1979)]), the pH of the solvent was not measured, but the pH of the slurry was monitored during the test. Only minor changes occurred over the duration of the test. Data is reported in Annexes I and II of the Applicant's Dossier. Annex I contains data on a wide range of untreated grades. Annex II contains company confidential information on untreated and surface-treated silica grades[1] ([1]=Surface treated are designated hydrophobic in the original dossier). The influence of pH on amorphous silica solubility is reported in the literature. All tests were carried out in the pH range between 3.5 and 7.7. Iler (1979) demonstrated that there is no influence on overall solubility in the pH range 2 to 8.5. In comparison to Iler (1979), all tests were investigated in this range (see also Alexander (1954)).

Temperature at which each solubility test was performed.

All tests were run in a temperature window of 19 to 21 °C, with variation of not more than ± 0.5 °C as shown in Annexes I and II of the Applicant's Dossier. Based on the theoretical work of Iler (1979) and many others, the 2 °C variation can be neglected. It is well known, that silica solubility increases with temperature [Alexander (1954), Iler (1979), Otterstedt and Brandreth (1998), Otterstedt and Brandreth (2010)]. Hence at higher temperatures such as the human body temperature of 37 °C, the 100 mg/L threshold will be further exceeded.

Duration of each of the solubility tests.

The test duration shown in Annexes I and II of the Applicant's Dossier corresponds to the total test duration. In many cases, the solubility reaches a plateau after 24 hours. To detect deviations greater than 15%, according to OECD 105 test requirements, the tests were continued for an additional 2 to 6 days. Tests were complete when the OECD 105 criterion of less than 15% variation in solubility was met.

Separation and checking of any remaining particulate SiO_2 from test solution

- Centrifugation, using an ultra-centrifuge (Ultracentrifuge Himac CP 65, Hitachi) at approximately 40,000 rpm was used to produce a clear eluate for colloidal, and in some cases for silica gel, samples.

- Filtration was made using membrane filters Roth KY64.1 (0,45 µm) Nylon. Effectiveness of filtration in removing particulates was confirmed using the Tyndall method.

- In order to exclude false SiO_2 readings caused by particular nanoscaled SiO_2, SiO_2 content in the filtrate was determined by two independent methods: ICP-OES and UV-VIS (molybdate method). While the ICP-OES method determines “total SiO_2” including any particulate SiO_2 accidently passing the filter, the UV-VIS (molybdate) method exclusively detects monomeric and dimeric orthosilicic acid; that is, the completely dissolved species [Alexander *et al.* (1954), Iler (1979), Coradin *et al.* (2004), Greenberg *et al.* (1985)]. Comparison of the ICP-OES and UV-VIS results can serve as an indicator to the presence of any particulate material.

In the case of a discrepancy between UV-VIS and ICP-OES results, precedence is given to UV-VIS, as this responds only to dissolved silica, that is the silicic acid/silicate form. ICP-

OES determines silica in all forms, as the plasma (> 7000 °C) can decompose all of the silica molecules present.
Additional proof of the absence of particulates is provided by a high sensitivity Tyndall device [SAS Detection Device, Serial number P13072/02-002; Manufacturer: Fraunhofer ICT – IMM, Mainz, located at Laus GmbH] to test for any nanoscaled particles in the filtrate. Sensitivity of the device is 2 – 4 mg SiO_2/L with a detection limit of 5 nm [Frese *et al.* (2016), Annex IV of the Applicant's Dossier]. This detection limit is far below typical SAS aggregate diameters and is below typical primary particle sizes of SAS used in cosmetics.
Results from UV-VIS for all (uncoated) sample sets report solubility levels above 100 mg/L. Results were validated by there being no detection of particulates in the test solution by the Tyndall device.

Electron microscopy investigations
Electron microscope investigations of the test solutions from two representative grades with low primary particle size have been performed. There is no validated protocol for this procedure and drying of the filtrate on the grid results in a re-precipitation of dissolved silica, with morphologies comparable to precipitated silica itself. Quantification of "undissolved" versus "re-precipitated" particles therefore is not possible with this method.
A small number of aggregate fragments, but no isolated primary particles were detected on the sample grid. A rough geometrical estimation indicates that the amount of aggregates detected on the grid does not exceed 1 mg SiO_2/L, which is well below the sensitivity of the Tyndall device.
A summary of the investigation is given in Annex III of the Applicant's Dossier.

C/ Solubility results

The following solubility results were provided by the Applicant:

Hydrophilic SAS

Three companies tested more than 20 different pyrogenic SAS products using the Enhanced OECD 105 Test Guideline to evaluate the solubility of SAS produced by the thermal process. The BET was also used as leading parameter to cover the variety of products placed on the market (see Figure 2).

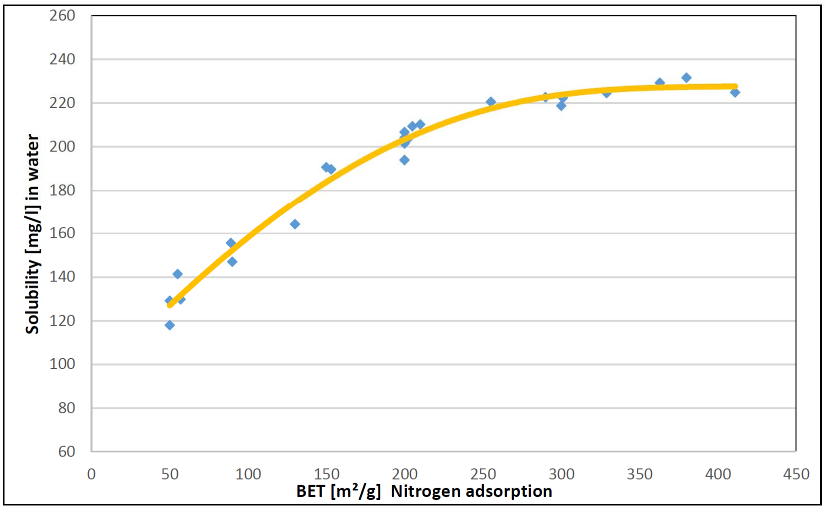

Figure 2: *Water solubility of pyrogenic SAS (Thermal route manufacturing process). The yellow curve is a calculated trend line, based on the individual measured data to illustrate that the measured data of individual products are correlated to the surface area. If required, additional statistics information can be provided.*

Four companies tested more than 50 different precipitated SAS and Silica Gels using the Enhanced OECD 105 Test Guideline to evaluate the solubility of SAS produced by the wet process (see Figure 3). The BET (Brunauer–Emmett–Teller)-theory aims to explain the physical adsorption of gas molecules on a solid surface and serves as the basis for an important analysis technique for the measurement of the specific surface area of materials. It was used as leading parameter to cover the variety of products placed on the market.

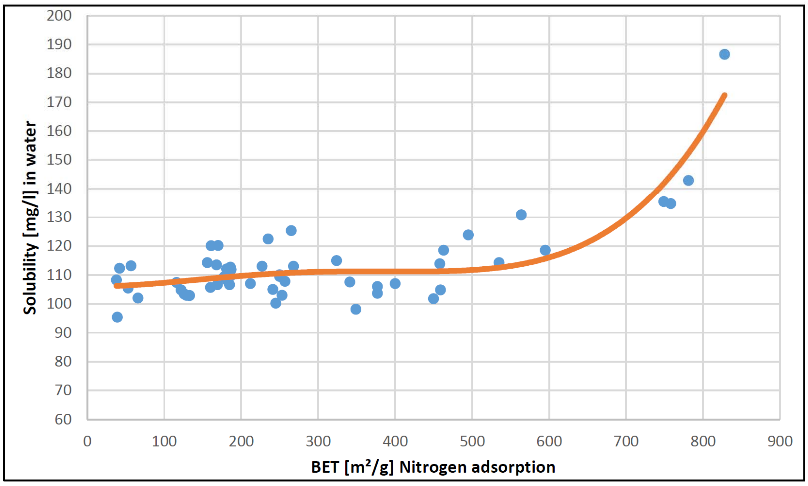

Figure 3: *Water solubility of precipitated SAS and Silica Gel (Wet route manufacturing process). The yellow curve is a calculated trend line, based on the individual measured data to illustrate that the measured data of individual products are correlated to the surface area.*

One company also tested colloidal silica. As stated before, colloidal SAS is a dispersion of discrete nanoparticles in a solvent, mainly water. Thus, the water is therefore saturated with dissolved silica in the form of ortho-silicic acid. The test method applied is photometry as described in Enhanced OECD 105 Test Guideline chapter 5. However, the pH value of the tested colloidal products exceeds pH 8, therefore the OH-concentration in the system leads to a higher solubility as calculated using the solubility surface area correlation for the wet production, see Figure 4. The solubility of the precipitated and dried SAS from a colloidal dispersion is shown in Figure 4. The solubility is increasing linearly with the surface area of the material in a linear mode, the first measurement is considered as slightly too high (re-evaluation will be done). The increase in surface are is created by a decrease of the particle diameter starting at 22 nm and ending at 5 nm for the monodisperse system. The increase of the solubility with decreasing particle size is in-line with the description in literature, i.e. [Iler (1979)]. Besides the higher solubility, which may lead for a short time to an oversaturated solution, the dissolution time also decreases with decreasing particle diameter.

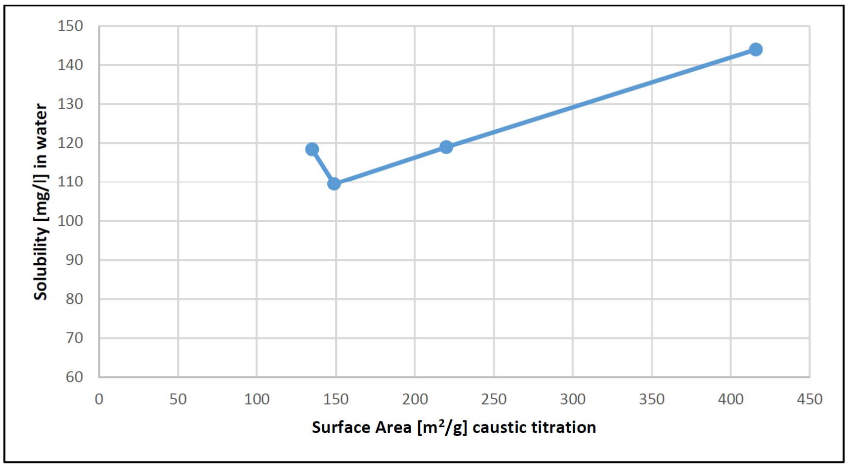

Figure 4: *Water solubility of colloidal SAS, dried material (Wet route manufacturing process).*

Figure 5 is the expected solubility of SiO_2 in the dispersion medium anticipating a similar pH of 8.95 to 9.25. Actually, the pH of the fourth grade with a BET over 400 m^2/g is 9.7 and 10.3 and exceeding the limit concentration of OH- groups in the solvent equal to pH 9. According to Alexander *et al.* [Alexander *et al.* (1954)] the solubility of SAS at a pH of 10 is 3 to 5 times higher compared to pH 9. This ratio was exactly found in the measurement of a product from one company with a pH above 10.

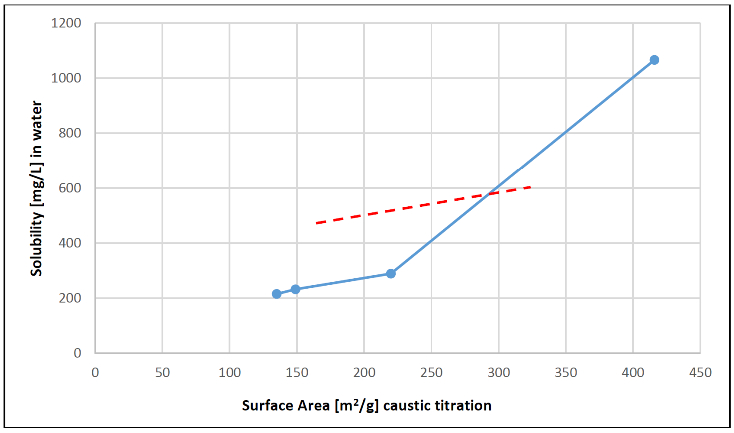

Figure 5: Water solubility of colloidal SAS, dissolved material in water (Wet route manufacturing process).

In summary, the **solubility for hydrophilic SAS is above 100 mg/L for all production routes – thermal and wet**. The experimental results of products used are fully in-line with the literature.

The following conclusions on solubility testing were drawn by the Applicant on hydrophilic SAS (Thermal and wet production process)
Using the Enhanced OECD Test Guideline 105 on Solubility for SAS, it can be demonstrated in more than 50 conducted tests that the solubility of all hydrophilic SAS products, pyrogenic SAS, precipitated SAS, silica gel and colloidal SAS is 100 mg/L or higher. The test results concur with the published literature on the solubility of SAS. Different independent literature sources describe the solubility of SAS in the range of 100 to 150 mg/L or more precise between 130 mg/L to 150 mg/L. Based on the tests performed and results in comparison with the literature, it can be concluded that hydrophilic SAS is soluble in water and therefore is outside the scope of the nanomaterial definition provided in the Cosmetics Regulation (EC) No 1223/2009 Article 2 (1) (k):

Consequently, hydrophilic pyrogenic SAS, precipitated SAS, silica gel and colloidal SAS are not a nanomaterial based on the Cosmetics Regulation (EC) No 1223/2009.

SCCS Comment:
Referring to the solubility terms in Table 1 corrected by the SCCS, the SCCS acknowledges that conventional chemical substances with solubility in the range of 100-1000 mg/L are generally regarded as 'very slightly soluble', and those with solubility less than 100 mg/L as 'insoluble'.

Hydrophobic SAS

As mentioned before, surface treatment is achieved by covalently coupling different silanes with the surface silanol groups of SAS. This reaction takes place at the surface only, the bulk inner surface of the aggregates is not affected by this modification. Due to steric hindrance, a certain amount of silanol groups (up to 50 %) (see Figure 6) remain unreacted on the surface and are being shielded by the bulky organic treatment agent (see Figure 7).

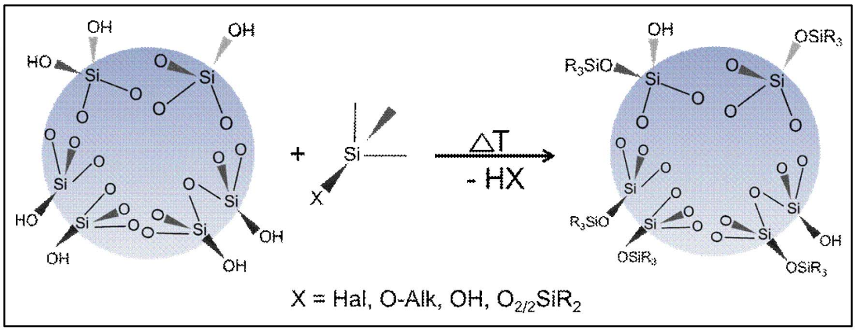

Figure 6: *Schematic view of surface modification.*

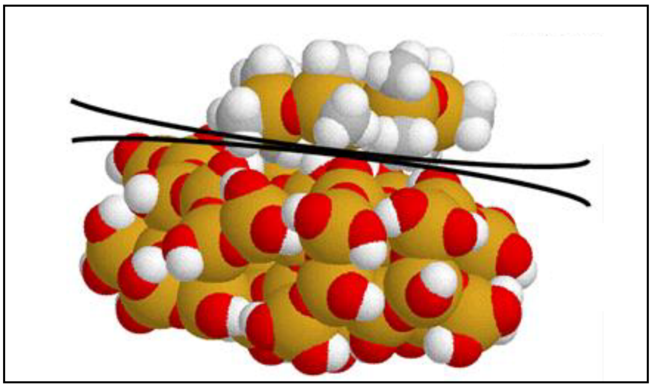

Figure 7: *Molecular model of surface-treated SAS (shielding effect). Depicted in white are hydrogen atoms, in red oxygen atoms, in grey carbon atoms and in brown silicon atoms. The lower part of the figure represents a model of the silica surface, the upper part illustrates a model of the surface treatment agent shielding the surface area. Some Si-OH groups are remaining unreacted*

Depending on the degree of hydrophobicity of the organic group the whole SAS/organic surface complex will show more or less pronounced hydrophobic behaviour. **Hence, the determination of the solubility of surface-treated SAS in water is either hardly reproducible or even impossible.** Hence, there is no OECD test guideline or commonly recognized method available to determine the solubility of hydrophobic surface-treated SAS.

The following working hypothesis was provided by the Applicant

If surface-treated SAS can be wetted, it should exhibit a certain solubility in water (kinetics will be different from non-surface-treated SAS). This hypothesis is supported by the literature on the degradation behaviour of silica in water and biological systems [Croissant *et al.* (2017), Cauda *et al.* (2010)].

In order to accomplish wetting of SAS, several routes are possible. It was decided to follow the NanoGenoTox protocol [NanoGenoTox (2011)], i.e. pre-wetting the samples with ethanol, followed by dispersion in water. **While the NanoGenoTox protocol proposes to use 0.5% of ethanol, this is not sufficient for most hydrophobic SAS products**. Instead a fixed concentration of 10% ethanol was chosen.

This mixture was used for the determination of the aforementioned Enhanced OECD 105 Test Guideline being followed in all other aspects. For comparison, the solubility of hydrophilic SAS was determined at the same ethanol concentration. As access of the solvent to the Si-OH surface is sterically hindered, it was found, that it takes more than four weeks until the maximum solubility or a plateau is reached.

One company tested several representative samples of SILICA DIMETHYL SILYLATE, SILICA SILYLATE, SILICA DIMETHICONE SILYLATE and SILICA CAPRYLYL SILYLATE (see Figure 8). Unsurprising, the solubility of non-treated, i.e. hydrophilic SAS in 10 % ethanol/water (dotted line in orange) was found to be slightly below the non-treated, i.e. hydrophilic SAS in pure water (straight line in blue).

Due to the variable nature of base materials, treatment agents, and process conditions, there is no clear relationship with e.g. the BET surface area to be observed. However, all hydrophobic SAS products analyzed so far exhibit a solubility between 100 and 160 mg/L in 10 % ethanol/water (grey points in Figure 8). It is expected that other products not tested so far will be found to fit into that range.

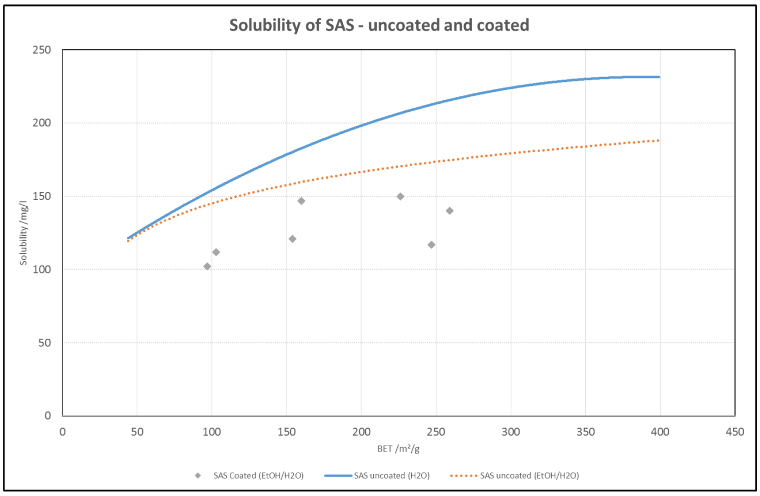

Figure 8: *Solubility of surface-treated SAS in ethanol/water (points, grey). For comparison, the lines show the solubility of non-treated SAS in water (straight, blue) and ethanol/water respectively (dotted, orange).*

The following conclusions on solubility testing were drawn by the Applicant on hydrophobic SAS:

Applying a modified method to accomplish sufficient material wetting all hydrophobic SAS products analysed so far exhibit a solubility between 100 and 160 mg/L in 10% ethanol/water. It is expected, that other products not tested so far will also fit into that range. Thus, it can be concluded that the solubility of hydrophobic SAS does not differ from the results of hydrophilic SAS.

Consequently, hydrophobic SAS is not a nanomaterial based on the Cosmetics Regulation (EC) No 1223/2009

SCCS Comment:
Referring to the solubility terms in Table 1 corrected by the SCCS, the SCCS acknowledges that conventional chemical substances with solubility in the range of 100-1000 mg/L are generally regarded as 'very slightly soluble', and those with solubility less than 100 mg/L as 'insoluble'.

Solubility test performed in pure ethanol
According to the Applicant's Dossier, the solubility of SAS has been tested by one company in pure ethanol for two different products produced through the wet route. Based on the broadly accepted theory that the OH-concentration is the driver for solubility of SAS, a much lower concentration is expected in ethanol. Ethanol has no tendency to dissociate OH-groups which are needed to act as catalyst for solubility and to form ortho-silicic acid ($Si(OH)_4$).
The measurements in both cases delivered a solubility slightly above 1 mg/L based on the *Enhanced* OECD 105 Test Guideline for SAS using pure ethanol instead of water:
Precipitated SAS BET: 36.7 m^2/g: < 1.07 mg/L SiO_2 (Photometer) and
Silica Gel BET: 346.5 m^2/g: < 1.07 mg/L SiO_2 (Photometer).

Therefore, as expected, the solubility of SAS in pure ethanol is much lower due to the absence of a sufficient OH-concentration and based on Table 1, only slightly soluble (at the very low range). The BET seems to have no impact on solubility, only the OH-concentration in the solvent.

SCCS comment:
Based on Table 1 corrected by the SCCS, both types of the tested SAS materials can be considered as being insoluble in pure ethanol.

SCCS Overall Comments:

SAS materials specifications:
Where information was provided in the dossier, the specifications of the SAS materials ranged between:
- hydrophilic SAS (amorphous silica and hydrated amorphous silica) and hydrophobic SAS (surface-treated amorphous silica)
- 2 to 24 months for aging of the materials,
- 30 to 828 m^2/g for surface areas of the materials**,**
- 2 to 1000 micrometres for the median of the particle size distribution (d_{50})

Solubility test protocol used:
Where information was provided, the various conditions/parameters used for solubility tests were as follows:
pH: 3 to 8
Temperature: 19.5°C to 20.5°C
Test duration: from 3 to 49 days
Liquid media: 0.5 % ethanol – modified enhanced TG 105 protocol for hydrophilic SAS.
10% ethanol – modified enhanced TG 105 protocol for surface treated hydrophobic SAS.

Solubility results:
The experimental solubility values for the tests carried out under different conditions have been reported to range from 95 to 225 mg/L. Estimated or calculated values for solubility have also been reported to range from 104 to 228 mg/L. For some SAS materials, the solubility values have not been provided.

It is well known that solubility of a substance is dependent on a number of physicochemical factors, the nature of the solvent, and the specific conditions under which solubility was tested.
In this regard, the SCCS has noted that the solubility values reported previously for SAS materials (Table 1, SCCS/1545/15 [SCCS/1545/15 (2015)]) were between 54.3 and 112.9 mg/L for hydrophilic precipitated SAS materials, and between 22.6 and 91.8 mg/L for hydrophilic pyrogenic silica when tested using the OECD TG 105 and when measured by using ICP-AES. The solubility values for hydrophobic pyrogenic silica were reported to be between 0.4 and 15.7 mg/L (by using the ICP-AES method).
A comparison between the previously reported and the currently provided solubility values has revealed large differences. This is particularly obvious in the higher solubility values reported in the dossier for some hydrophobic materials - up to a factor of 173, following the modified enhanced OECD TG 105 (10% ethanol for hydrophobic SAS), and a factor of 10 for some hydrophilic SAS following enhanced OECD TG 105 (0.5% ethanol).
These values also do not correspond with the general range of solubility reported for SAS materials in the literature, and most likely reflect the influence of the changed test protocol used for measuring solubility in the current dossier.

3.1.7 Additional physical and chemical specifications

No information has been provided.

3.1.8 Particle size

According to the Applicant's Dossier, particle size is not considered further, as it can influence the speed of dissolution, but not the solubility (e.g. Otterstedt and Brandreth (1998)).

SCCS comment:
The median of the particle size distribution (d_{50}) has not been provided for 20 out of the total 159 materials included in the submission. Particle size is known to influence the speed of dissolution and solubility of silica materials (Alexander, 1957; Braun *et al.*, 2016; Diedrich *et al.*, 2012; ECETOC, 2006; Gun'ko *et al.*, 2005; Herting *et al.*, 2014; Rimstidt and Barnes, 1980; Roelofs and Vogelsberger, 2004; Tarutani,1989) and should have been provided according to the Guidance on the Safety Assessment of Nanomaterials in Cosmetics (SCCS/1484/12) and the Checklists for Applicants submitting dossiers on Cosmetic Ingredients to be evaluated by the SCCS (SCCS/1588/17).

3.1.9 Microscopy

The following information on microscopy was provided by the Applicant:

An electron microscope investigation of the test solutions from two representative grades with low primary particle size has been conducted (Annex III - Electron microscope investigation – Applicant's Dossier). There is no validated protocol for this procedure and drying of the filtrate on the grid results in a re-precipitation of dissolved silica, with morphologies comparable to precipitated silica itself. Quantification of "undissolved" versus "re-precipitated" particles therefore is not possible with this method.

A small number of aggregate fragments, but no isolated primary particles were detected on the sample grid. A rough geometrical estimation indicates that the amount of aggregates detected on the grid does not exceed 1 mg SiO_2/L, which is well below the sensitivity of the Tyndall device.

High surface area SAS samples (wet and pyrogenic route) were used for this provisional check (non GLP study), following the OECD 105 enhanced protocol. After 4 days of shaking at room temperature in water, solutions were filtered using a 0.45 µm nylon membrane. Pure water samples were run in parallel as a control.

In duplicate, one droplet from each bottle was taken and placed on a separate transmission electron microscopy (TEM) grid (diameter = 3 mm) which is coated by a nanometer-thin carbon film which is transparent to high-energy electrons in the TEM-investigations. The grid was carefully tapped on its edge, on a filter paper to remove supernatant fluid/solution. The individual grid was then air dried at ambient conditions in an open Petri-dish then transferred into a TEM-grid container with a tight closing lid.

TEM images were taken of structures present and their morphology inspected. Chemical composition of the structures was determined using EDX spectra.

In contrast to the blank samples, measured as background reference, the SAS solutions contained typical aggregates of silica besides diffuse background structures of potentially re-precipitated silica. This is confirmed and reproduced by duplicate determination.

The images suggest that a smaller particle size fraction (equivalent circular diameter (ECD) of 40 nm [pyrogenic SAS], and 20 nm [precipitated SAS], respectively) might be present with the larger sizes cut off by filtration. However, no isolated primary particles were observed.

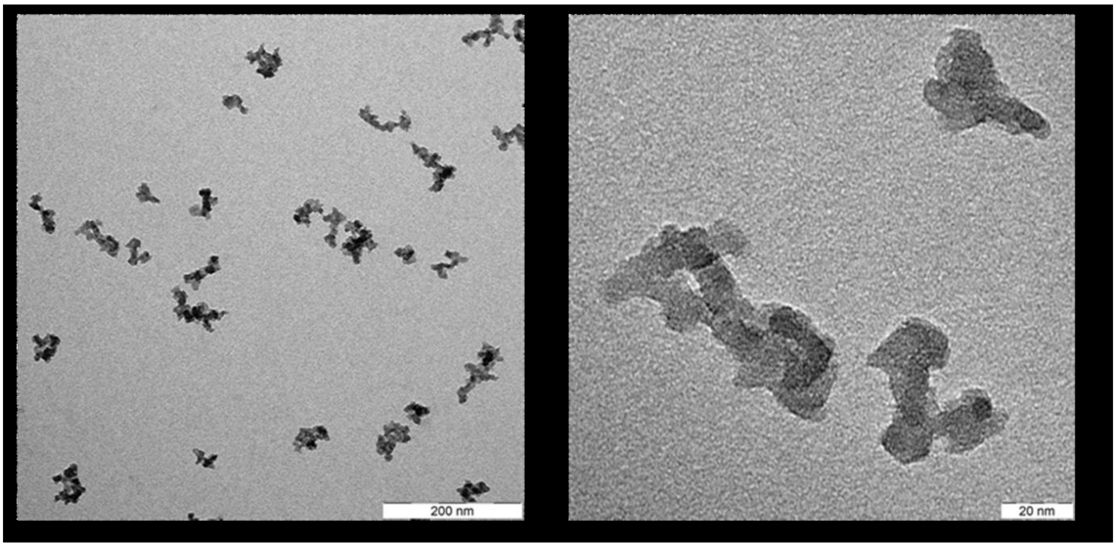

Figure 9: Aggregates/fractions of pyrogenic SAS; average equivalent circular diameter of the aggregates is around 40 nm. The picture at higher magnification shows the intergrowth/sintered structure of example aggregates.

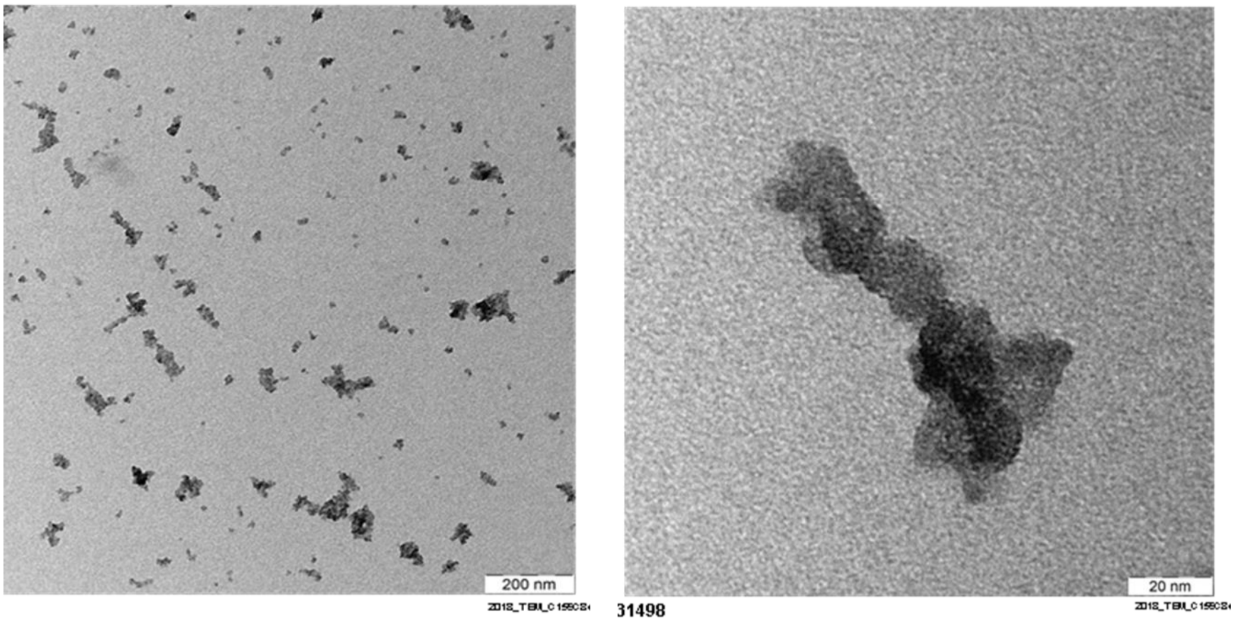

Figure 10: Aggregates/fractions of precipitated SAS; average equivalent circular diameter of the aggregates is around 20 nm. The picture at higher magnification again illustrates the intergrowth/sintered structure of example aggregates.

Although the experiment cannot give exact quantitative amounts of silica found in the filtrate, the number of aggregates/fragments on the grid is not very high as shown in Figures 9 and 10. It should be noted that this is for two specific grades and there may be some variance with other grades.

A simple geometrical calculation shall help to compare this with the solubility data:
Assumptions:
1 mg SiO_2/L passing the filter and being not detected by the Tyndall device; Amount of filtrate on the grid: 50 µL spread over the grid (7.07 x *10^6 µm²); Silica density: 2.1 g/cm³
Using the equivalent circular diameters of the aggregates found on the grid, we could expect to see ca. 100 particles /µm² for the 40 nm species (pyrogenic SAS) and ca. 800 particles/µm² for the 20 nm species (precipitated SAS). Comparing these figures with the attached example pictures, it is consistent with the claimed accuracy of the Tyndall device in literature (Frese *et al.*, 2016) that the amount of particular silica in the filtrate is below 1 mg/L.

SCCS comments:
The SCCS has noted that after 4 days of shaking of high surface area SAS samples (manufactured by wet and pyrogenic route) at room temperature in water using the enhanced TG 105 protocol (with 0.5 % ethanol) and filtration of the solution using a 0.45 µm nylon membrane, the SAS solutions contained typical aggregates of silica but no isolated primary particles exhibiting an equivalent circular diameter of 40 nm [pyrogenic SAS] and of 20 nm [precipitated SAS]. Based on such dimensions, these aggregates have to be considered as nanomaterials.

The SCCS has also noted that the amount of aggregates detected by TEM investigations does not exceed 1 mg SiO_2/L, corresponding to the detection limit of the Tyndall device.

3.1.10 Crystal structure

No information provided in the Dossier.

SCCS comment:
Silica is claimed to be amorphous but no information on structural characterisation (X-ray Diffraction patterns, SAED / TEM patterns) has been provided. Only TEM bright field images have been provided without any electron diffraction patterns.

3.1.11 UV absorption

No information provided in the Dossier.

3.1.12 Surface characteristics

The following information on surface characteristics was provided by the Applicant:

The surface treating agents are included in the company confidential specific parts of Annex II from the Applicants Dossier. Some silanes used for the surface treatment will hydrolyze in water/ethanol. This property, the reactivity with OH-groups, can be used to convert hydrophilic into hydrophobic silica. The reactive silane species couples to the Si-OH group of the respective core silica. The production process is controlled in a manner that no more reactive silanes are present in the final product.

SCCS's comment:
Surface treatments converting hydrophilic into hydrophobic silica can only be expected to decrease the solubility of the materials.

3.1.13 Homogeneity and stability

The following information was provided by the Applicant:

Specific Information on colloidal SAS:
Colloidal SAS consists of spherical and non-porous silica particles in the nano-size range, dispersed in a liquid phase, usually water. Often, such suspensions are stabilized electrostatically. The particles may remain dispersed, or alternatively, aggregation processes may remove the material from the liquid phase. In practice, even apparently stable dispersions will gradually aggregate out of the aqueous phase over time. The size-range of the colloidal silica particles defines them as nanoparticles under the ISO and recommended EU definition (Recommendation on the definition of a nanomaterial (2011/696/EU)).

Specific information on hydrophobic SAS:
SILICA DIMETHYL SILYLATE, SILICA SILYLATE, SILICA DIMETHICONE SILYLATE, SILICA CAPRYLYL SILYLATE and SILICA CETYL SILYLATE are surface-treated SAS (also referred to as silanated or silylated silicon dioxides, or hydrophobic SAS). The surface-treatment affects only the outermost layer of the SAS and preserves the aggregate structure; it has no effect on the properties of the core material. After the treatment, the original treating agent is no longer detectable on the product surface, and the core (base) material is still SAS. Therefore, the term "surface-treated" is used in this dossier.

The surface treating agents are included in the companie's confidential parts of Annex II of the Applicants Dossier. Some silanes used for the surface treatment will hydrolyze in water/ethanol. This property, the reactivity with OH-groups, can be used to convert hydrophilic into hydrophobic silica. The reactive silane species couples to the Si-OH group of

the respective core silica. The production process is controlled in a manner that no more reactive silanes are present in the final product.
As the surface functionality of all hydrophobic SAS grades used in cosmetics is either "alkyl" or "silyl", the hydrolysis stability of the treatment agent itself is not relevant in this context.

When surface treated SAS is contacted with water or water/ethanol mixtures, at some stage the core silica starts to dissolve and so release part of the organic coating. This effect can be detected by comparing between UV-VIS (molybdate) and ICP-OES solubility data.

The UV-VIS method only detects dissolved ortho-silicic acid, and solubility plateaus. In contrast, the ICP-OES results continue to increase because of a release of coating ("hydrolysis"), fragments of which are found in solution. An example is given in the Figure 11 below. When this effect was observed, only solubility results from UV-VIS were reported.

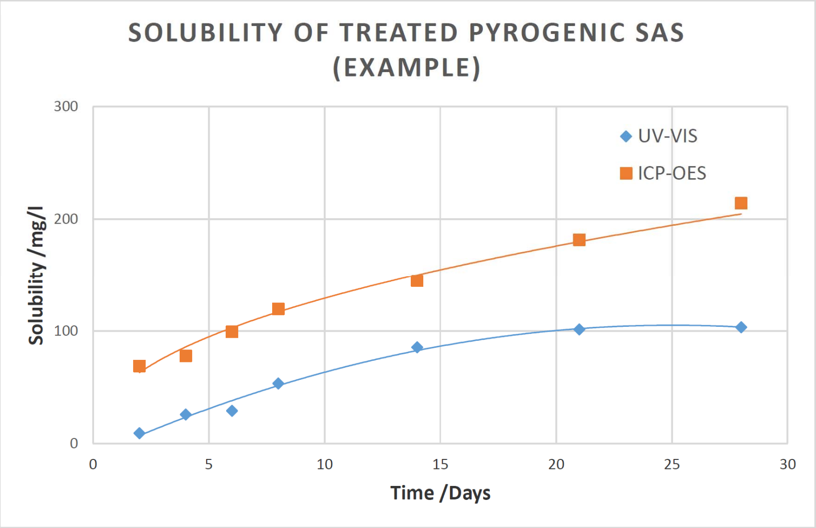

Figure 11: Comparison of the solubility data of surface treated pyrogenic SAS (example) measured by UV-VIS and ICP-OES. UV-VIS data reached a plateau, whereas ICP results did not. This suggests that fragments of the surface coating are released into the solution.

In general, most wet processed silica such as gels and precipitated grades include a hydrothermal ageing step during the manufacturing process and so will not show significant solubility changes with increasing age of material.

Pyrogenic silica may show a very slow decrease of solubility with age that is associated with the rearrangement of silanol- and siloxane groups, and which is influenced by the storage conditions of the material. However, no significant effects are seen within the recommended shelf life of the products stored under recommended conditions. Annex I of the Applicant's Dossier, covering an age range from 2 to 20 months, shows no relationship between sample age and solubility.

SCCS comment:
The SCCS has noted that there is no observed relationship between sample aging and solubility in the case of pyrogenic SAS. Information should have been provided on the recommended conditions corresponding to the suggested shelf life of pyrogenic SAS.

3.1.14 Other parameters of characterisation

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3.1.15 Summary on supplementary physicochemical characterisation

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4. FUNCTION AND USES

The following information was provided by the Applicant:

Hydrophilic SAS: SILICA and HYDRATED SILICA
Hydrophobic SAS: SILICA DIMETHYL SILYLATE, SILICA SILYLATE, SILICA DIMETHICONE SILYLATE, SILICA CAPRYLYL SILYLATE and SILICA CETYL SILYLATE SILICA, HYDRATED SILICA, SILICA DIMETHYL SILYLATE, SILICA SILYLATE, SILICA DIMETHICONE SILYLATE, SILICA CAPRYLYL SILYLATE and SILICA CETYL SILYLATE are used in leave-on and rinse-off skin and oral care formulations, in eye, nail and lip products, and in cosmetic sprays. Highest levels of hydrophilic SAS are found in formulations for skin products (up to 65 % in powder foundation), and in toothpaste (up to 40 %). Spray products with incidental inhalation exposure, e.g., deodorant or antiperspirant sprays, usually contain very low amounts of SAS

Specific information on colloidal SAS:
Colloidal SAS consists of spherical and non-porous silica particles in the nano-size range, dispersed in a liquid phase, usually water. Often, such suspensions are stabilized electrostatically. The particles may remain dispersed, or alternatively, aggregation processes may remove the material from the liquid phase. In practice, even apparently stable dispersions will gradually aggregate out of the aqueous phase over time. The size-range of the colloidal silica particles defines them as nanoparticles under the ISO and recommended EU definition (Recommendation on the definition of a nanomaterial (2011/696/EU)).

Specific information on hydrophobic SAS:
SILICA DIMETHYL SILYLATE, SILICA SILYLATE, SILICA DIMETHICONE SILYLATE, SILICA CAPRYLYL SILYLATE and SILICA CETYL SILYLATE are surface-treated SAS (also referred to as silanated or silylated silicon dioxides, or hydrophobic SAS). The surface-treatment affects only the outermost layer of the SAS and preserves the aggregate structure; it has no effect on the properties of the core material. After the treatment, the original treating agent is no longer detectable on the product surface, and the core (base) material is still SAS. Therefore, the term “surface-treated” is used in this Dossier.

5. DISCUSSION

SCCS general comments:

5.1. Review of SAS solubility

According to the literature review submitted as part of the Dossier, the solubility of SAS material is below 150 mg/L. This means that the materials can be regarded as ranging from insoluble (below 100 mg/L) to very slightly soluble (ranging from 100 to 1000 mg/L) according to solubility terms based upon USP38 and USP 38 NF33 (see corrected Table 1).

A review of the open literature carried out by the SCCS on the solubility of SAS materials indicated that solubility of amorphous silica in aqueous media is affected by a number of factors, such as particle size, specific surface area, the type and content of impurities, temperature, pH, pressure, duration of test, salt content, and aging (Table 2). It is therefore important that information on these parameters is also taken into consideration when comparing data on the solubility of various SAS materials.

The SCCS has noted that estimated/ calculated solubility values for SAS have also been provided in the Dossier. As a principle, where experimentally-measured values for a parameter are available, they take precedence over estimated/ calculated values. In such a situation, the use of the latter would require a strong justification on scientific grounds.

Parameters shown to influence the dissolution rate/solubility of silica materials	References
Particle size	Alexander (1957), Braun *et al. (*2016), Diedrich *et al. (*2012), ECETOC (2006), Gun'ko *et al.* (2005), Herting *et al.* (2014), Rimstidt and Barnes (1980), Roelofs and Vogelsberger (2004), Tarutani (1989)
SAS composition	Chappex and Scrivener (2012), Iler (1973), Lillicrap *et al.* (2014), SIDS OECD (2004), Vogelsberger *et al.* (2008)
Surface treatment	ECETOC (2006), Fruijtier-Pölloth (Review) (2012), Iler (1973)
Silica aging	Willey (1980)
pH	Alexander (1957), Chan (1989), Correns (1926), Correns (1941), Diedrich *et al. (*2012), Eikenberg (1990), Fleming (1986), Gun'ko *et al.* (2005), Herting *et al.* (2014), Kato and Kitano (1968), Kitahara (1960), Krauskopf (1956), Lenher and Merril (Review) (1917), Lillicrap *et al.* (2014), Löbbus *et al.* (1998), Mazer and Walther (1994), Mitra and Rimstidt (2009), Okamoto *et al.* (Review) (1957), Pelmenschikov *et al.* (2001), Plettinck *et al.* (1994), Seidel *et al. (*1997), Tarutani (1989), Vogelsberger *et al.* (1992), Vogelsberger *et al.* (2002) Vogelsberger and Schmidt (2018), Yamamoto *et al.* (2018)
Temperature	Alexander (1957), Chan (1989), Chen and Marshall (1982), Fournier and Rowe (1977), Gunnarsson and Arnorsson (2000), Kitahara (1960), Marshall (1980a), Marshall (1980b), Marshall and Chen (1982), Mazer and Walther (1994), Morey *et al.* (Review) (1964), Niibori *et al.* (2000), Okamoto *et al.* (Review) (1957), Rimer *et al.* (2007), Rimstidt and Barnes (1980), Tarutani (1989), Vogelsberger (Review) (2003), Vogelsberger and Schmidt (2018), Willey (1980), Yamamoto *et al.* (2018)
Solution (ionic/ organic content)	Alexander (1957), Bai *et al.* (2009), Braun *et al.* (2016), Chan (1989), Chen and Marshall (1982), Dandurand and Schott (1987), Dove (2008), Fournier and Marshall (1983), Herting *et*

	al. (2014), Icenhower and Dove (2000), Kato and Kitano (1968), Marshall (1980a), Marshall and Warakomski (1980), Marshall (1980b), Marshall and Chen (1982), Plettinck *et al.* (1994), Rimstidt and Barnes (1980), Tarutani (1989), Vogelsberger *et al.* (1992), Vogelsberger and Schmidt (2018), Willey (1980)
Pressure	Chan (1989), Fournier and Rowe (1977)
Duration of the test	Seidel *et al.* (1997), Vogelsberger *et al.* (2008), Vogelsberger and Schmidt (2018)

Table 2: SCCS literature review "parameters shown to influence the SAS solubility value"

The SCCS acknowledges that conventional chemical substances with solubility ranging from 100 mg/L to 1000 mg/L are generally regarded as 'very slightly soluble', and those with solubility less than 100 mg/L as 'insoluble'. Although such values have not yet been established for nanomaterials, the SCCS can accept the same for nanomaterials in consideration that solubility is an inherent property of a material.

The definition of a nanomaterial under the Cosmetics Regulation indeed relates to insoluble materials, in conjunction with other size/particle related parameters. However, the question relating to solubility of a nano-structured material in the context of nanomaterial definition relating to cosmetics use needs to be seen in perspective. For nano-structured materials, with the exception of the materials that are completely soluble, it is important to establish whether a proportion of these materials would still exist in undissolved form comprising nanoparticles at a given use level in a cosmetic formulation.

5.2. SAS particles specifications

SAS specification	Production route	INCI	Surface area (m^2/g)	Particle size d_{50} (µm)	Aging (Months)	Typical pH
A -1* Fumed Silica – Hydrophilic [4 products]	Pyrogenic	Silica	89.4 to 411.5	102 to 207	4 to 10	4.05 to 4.15
A – 2** Fumed silica – hydrophilic [20 materials]	Pyrogenic	Silica	130 to 380	90 to 99 (2 materials only)	not provided	4.00 to 4.05
A – 3 Fumed silica – hydrophobic [5 materials]	Pyrogenic surface treated	-Silica Dimethyl silylate -Silica Silylate -Silica Dimethicone Silylate	105 – 135 to 205 - 245	47 to 195 (3 materials only)	7 to 8 (3 materials only)	5.5 (1 material only)
B – 1 [29 materials]	Precipitated	Hydrated silica	45 to 500	3 to 500	2 to 7 (8 materials only)	6.0 to 7.7
B – 2 [14 materials]	Pyrogenic	Silica	50 to 380	15 to 27	not provided	4.1 to 6.5
B – 3 [10 materials]	Pyrogenic Surface Treated	-Silica Silylate -Silica Dimethyl silylate -Silica Dimethicone	100 to 260	10 to 19	16 to 23 (7 materials only)	4.0 to 7.3

		Silylate -Silica Caprylyl Silylate				
C – 1 [14 materials]	precipitated	hydrated silica	38 to 210	10 to 18	3 to 8 (2 materials only)	4.0 to 8.0
C – 2 [26 materials]	gel	hydrated silica	250 to 828	3.1 to 500	3 to 20 (5 materials only)	3.0 to 9.6
C – 3 [3 materials]	Colloïdal	hydrated silica	110 to 400	7 to 22 nm	Not provided	9.0 to 10.3
D – 1 [19 materials]	Precipitated	hydrated silica	30 – 150 to 330-570	2.0-3.5 to 500 - 1000	4 to 8 (4 materials only)	5.5 to 8.0
D – 2 [3 materials]	Gel	hydrated silica	260 to 360	53 – 180 to 106 -500	8 (1 material only)	5.5 to 7.5
E [5 materials]	Precipitated	hydrated silica	55 to 250	3.5 to 10	3 (1 material only)	7 to 7.5
F – 1 [2 materials]	Pyrogenic	Silica	200 to 300	ca. 600 to 680	5 to 7	3.8 to 4.3
F – 2 hydrophobic [4 materials]	Pyrogenic surface treated	Silica Dimethyl Silylate	200 to 300	ca. 350 to 450	12 to 24 (3 materials only)	3.8 to 6.8
F – 3 Hydrophobic [1 material]	Pyrogenic surface treated	Silica Silylate	150	ca 220	5	6.5 to 8

Table 3: Specifications of the SAS materials collated from the submission. SAS specifications - Surface area determined by BET (m²/g) by multiple point nitrogen adsorption, Particle size distribution determined by Laser Diffraction (Dry powder – Microtrac method) - data generated from volume weighted distribution Mean (µm), if available. For the SAS specifications A-1* and A-2**, the solubility has been measured and estimated, respectively.

Aging of SAS particles

The aging of 118 SAS particles out of the 159 total has not been provided. For the materials for which the aging duration has been provided, no information on the storage conditions has been provided.

Particle size distribution d_{50}

The median of the particle size distribution d_{50} has not been provided for 20 out of 159 materials.

5.3. Solubility results

The solubility values provided by the Applicant are listed in Table 4. Company names have been anonymised at the request of Applicant.

Company code, SAS type, [total number of materials]	pH during test	Temperature °C	Test Duration (days)	Solubility (mg/L)
Hydrophilic SAS				
A -1 [4 materials]	5 to 6	20°C to 20.5°C	3 to 4	155.6 to 225.0
A – 2 [20 materials]	Not provided	Not provided	Not provided	175.76 to 227.97 (Estimated values)
B – 1 [29 materials]	3 to 8 (8 materials)	19.5 to 20.5 (8 materials)	3 to 4 (8 materials)	107 to 119 (8 materials) 106 to 109 (Estimated values for 19 materials)
B – 2 [14 materials]	5 to 7 (10 materials)	19.5 to 20.5 (10 materials)	3 to 8 (10 materials)	118 to 132 (10 materials) 227 (Estimated value for 1 material)
C – 1 [14 materials]	6.0 to 6.93 (2 materials)	19.5 to 19.9 (2 materials)	3 (2 materials)	95.4 to 113.2 (6 materials) 104 to 108 (Calculated values)
C – 2 [26 materials]	5 to 7.6 (5 materials)	19.7 to 20.4 (5 materials)	3 to 4 (5 materials)	98.1 to 142.9 (12 materials) 108 to 145 (Calculated values for 14 materials)
C – 3 [3 materials]	Not provided	Not provided	Not provided	107.8 (1 material) 120 to 137 (Calculated values for 2 materials)
D – 1 [19 materials]	6 (4 materials)	20.0 to 20.5 (4 materials)	3 to 7 (4 materials)	102 to 107 (4 materials) 106 to 109 (Estimated values for 15 materials)
D – 2 [3 materials]	6 (1 material)	20.0 (1 material)	6 (4 material)	115 (1 material) 109 (Estimated values for 2 materials)
E [5 materials]	6 (1 material)	20 (1 material)	3 (1 material)	109.5 (1 material) 106.3 to 108.4 (Estimated value for 4 materials)
F – 1 [2 materials]	5 - 6	20.0 to 20.5	3	210 to 223
Hydrophobic Surface Treated SAS				
A – 3 [5 materials]	4.1 to 4.6 (3 materials)	19.5 – 20.5 (3 materials)	11 to 18 (3 materials)	135 to 164 (3 materials)
B – 3 [10 materials]	Not provided	19.5 to 20.5 (7 materials)	21–28 to 35–49 (6 materials in 10% ethanol) 3-7 (1 material in water)	102 to 150 (6 materials in 10% ethanol) 195 (1 material in water)
F – 2 [4 materials]	Not provided	Not provided	3	150 to 180 (3 materials)
F – 3 [1 material]	Not provided	Not provided	3	110

Table 4: Solubility test protocol and solubility values

In brief, for the total 159 SAS materials, the solubility was:

- measured for 63 materials (39.6%)
- estimated for 61 SAS materials (38.4%)
- calculated for 24 SAS materials (15.1%)
- not provided for 11 SAS type (6.9%)

5.3.1 Solubility test protocol used

i) pH :
For 119 out of the total 159 SAS types, the pH during solubility tests has not been provided.

ii) Temperature
OECD TG 105 (1995) states that the test is preferably run at 20 ± 0.5 °C. If a temperature dependence is suspected in the solubility (>3% per °C), two other temperatures at least 10 °C above and below the initially chosen temperature should also be used *(EU Method A.6 Water Solubility)*.
As shown by Fruijtier-Pölloth (2012), and mentioned by ASASP (2012), the solubility of pyrogenic silica is strongly dependent on temperature. The water solubility (saturation) has been reported to be equal to 144–151 mg/L at 37 °C and pH 7.1–7.4, and equal to 15–68 mg/L at 20 °C and pH 5.5–6.6. This shows that, for at least pyrogenic silica, the temperature dependence is higher than 3% per °C. Therefore, the SCCS considers that the tests did not follow the requirements of OECD TG 105 in terms of providing solubility results at three different temperatures.

iii) 10% ethanol - modified enhanced TG 105 protocol
The OECD TG 105 method was designed for conventional chemicals and has been regarded as not suitable for measuring the solubility of nanomaterials by the OECD (1995). The "enhanced OECD TG 105" method (or the modified "enhanced OECD TG 105") used for measuring solubility of SAS is industry's own proposed method, and is as such not an accepted method.
Instead of using 0.5% ethanol, as defined in the OECD protocol (enhanced - TG 105), the Applicants have used 10% ethanol for determining the solubility of hydrophobic SAS. Such use of a 10% ethanol-water medium is 20 times higher than the 0.5% ethanol concentration specified by the EU projects NanoReg, ENPRA, NanoGenoTox and PROSPEcT.

Further issues in this regard have been identified by the NanoReg project. Concerning the rate of dissolution and equilibrium solubility, it is clear that the optimal dissolution analyses are provided if reliable *in situ* time-resolved analyses are made of the dissolved matter, but this is not always feasible. It was also observed that harmonisation of procedures in regard to the definition and control of the atmospheric and temperature test conditions is necessary. Moreover, for risk assessment, the dissolution (or time-fixed solubility) should not be studied in water alone. It is recommended in the NANoREG report (D2.08) that dissolution studies should be conducted **in a series of relevant media that represent or simulate key biological and environmental compartments and conditions**.

The determination of water solubility according to OECD TG105 may not be appropriate, especially for nanomaterials with low and/or slow water-solubility. Section R.7.1.7 of the parent ECHA Guidance on information requirements and chemical safety assessment; OECD No. 62 and OECD No. 29 are considered applicable for the determination of the dissolution rate over one-week to 28 days, respectively. However, it is noted that methods for nanomaterials are currently under development by the OECD. It is also recommended to perform tests in specifically relevant biological and environmental media.

Hartmann *et al.* (2015) stated: "the critical issues are whether the chemical used for pre-wetting significantly changes relevant physicochemical ENP (engineered nanoparticles) properties or whether the compound in itself or by degradation products induce important biological side-effects. For the 0.5% ethanol concentrations used in the ENPRA, NANOGENOTOX, and PROSPEcT, such effects are still not noted or reported."

It is recommended that dissolution studies should be conducted either in a series of relevant media that represent or simulate key biological and environmental compartments and conditions (NanoReg), or in media which has to be equivalent to the one used for *in vitro* tests (NanoGenotox, ENPRA and PROSPEcT - Hartmann *et al.* (2015).

The protocol using water with 10% ethanol, as well as the protocol using pure ethanol, in which the solubility tests were performed by the Applicant are not in line with the above recommendations. The SCCS considers that these test conditions also do not correspond to conditions that are relevant to cosmetic formulations.

It is well known that solubility is dependent on a number of physicochemical factors, the nature of the solvent, and the specific conditions under which solubility was tested. A comparison between previously reported and currently provided solubility values reveals large differences. This is particularly obvious in the higher solubility values reported in this Dossier for some hydrophobic materials - up to a factor of 173, following the modified enhanced OECD TG 105 (10% ethanol for hydrophobic SAS), and a factor of 10 for some hydrophilic SAS following the enhanced OECD TG 105 protocol using 0.5% ethanol. These values do not correspond with the general range of solubility reported for SAS materials in the literature, and reflect the influence of changes in the test protocol used for measuring solubility.

iv) Duration of the test:
For the majority of the SAS materials (107 out of 159) included in the Dossier, the duration of the solubility tests has not been reported. This makes it difficult to consider the data in relation to solubility of SAS materials as such, and in relation to their use in cosmetic applications. Where this information is provided, it shows that the test durations range from 3 days up to 49 days in the case of hydrophobic SAS. This information is not only insufficient to be applicable to all SAS materials included in the submission, but also needs to be interpreted in the context of duration of a typical cosmetic application, which is generally not more than a few hours up to a day (for leave-on products).

5.3.2. Measured solubility values

Measured solubility values have been reported only for less than 40% of the SAS materials included in the Dossier. They range from 95.4 to 225 mg/L. 14% of the mean measured solubility values (i.e. 9 SAS materials) are below 100 mg/L. However, as mentioned before, many of the measurements are not comparable to each other because they have been performed using considerably different durations (ranging from 3 to 49 days) or under different test conditions.

The SCCS has also noted that in the two TEM images provided (High surface area SAS samples obtained by wet and pyrogenic routes), the SAS particles remain even after shaking for 4 days in water at room temperature (following the enhanced OECD TG 105). This needs to be considered in relation to the duration of cosmetic applications that are generally only for a few hours up to a day (for leave-on products).

5.3.3 Estimated and Calculated solubility values

Estimated and calculated solubility values have been reported in the Dossier for >53% of SAS materials. These are based on extrapolations from measured values. As noted before, where measured values are available, the estimated/calculated values can only be considered if a strong scientific reasoning is provided for the need for their use. Furthermore, material specifications and solubility test conditions for many SAS materials have not been reported, which does not allow a direct comparison of estimated/calculated values with experimental values provided for the SAS materials. In view of these limitations, the calculated/estimated values have not been considered in this Opinion.

5.3.4. Solubility data not provided or not determined

For 11 SAS materials, the solubility values have not been provided or not determined. These materials are therefore excluded from the SCCS Opinion. These materials include: CAB-O-SIL® TS620, CAB-O-SIL® TS622, SIPERNAT® 22 PC, SIPERNAT® 2200, AEROSIL® R 8200, AEROSIL® 200, AEROSIL® 300 Pharma, AEROSIL® 380, AEROSIL® R972 Pharma, AEROSIL® R 972V, HDK® H20.

For 4 SAS materials, the final report on the solubility test was mentioned as being not available, and the solubility test results can change slightly. These materials include: HDK® H15, HDK® H30, HDK® H18, HDK® H2000.

5.3.5 Summary

In view of the discrepancies in the methods used for solubility testing noted above, and in consideration of the data provided in this Dossier and that available in published literature, the SCCS is of the view that the solubility of hydrophilic SAS can be considered to range from 22 mg/L to 225 mg/L (i.e. insoluble to very slightly soluble) and of hydrophobic SAS from 0.4 up to 180 mg/L (i.e. insoluble to very slightly soluble) under the following conditions:

- hydrophilic SAS: Silica and hydrated silica when solubilised in aqueous media containing up to 0.5% ethanol,
- hydrophobic surface treated SAS: when solubilised in aqueous media containing up to 10% ethanol,
- at temperature: between 19.5 up to 20.5°C,
- pH: between 3 and 8,
- over a period of 3 days (hydrophilic SAS) up to 49 days (hydrophobic SAS).

It is worth highlighting that the above solubility values may not be valid in situations where SAS materials are used under conditions that are different from those specified here - e.g. when formulated/used in a less/non aqueous formulation or at a lower temperature.

6. CONCLUSION

1. Does the SCCS consider that Synthetic Amorphous Silica (SAS) are soluble (100 mg/L or higher) or degradable/non-persistent in biological systems, in light of the nanomaterial definition of the Cosmetic Regulation?

Having considered the data provided in this Dossier and that available in published literature, the SCCS concludes that:

i) the solubility values for hydrophilic SAS materials have been reported to range from 22 mg/L to 225 mg/L for the solubility tests performed in aqueous media, or following the enhanced OECD TG 105 (0.5% ethanol). The latter protocol has been noted to increase the solubility by a factor of 10 for some hydrophilic SAS materials.

ii) the solubility values of hydrophobic surface-treated SAS materials have been reported to range from 0.4 to 180 mg/L for solubility tests performed in aqueous media, or following a modified enhanced OECD TG 105 protocol (i.e. using 10% ethanol). The latter protocol has been noted to strongly increase the solubility of some hydrophobic SAS materials (by a factor up to 173).

The hydrophilic and hydrophobic SAS materials can therefore be regarded as “insoluble” (i.e. below 100 mg/L) to “very slightly soluble” (i.e. 100 mg/L to 1000 mg/L) by the SCCS based upon the terminology used in USP38 and USP 38 NF33 (Table 1 corrected by the SCCS).

In regard to the nanomaterial definition in the Cosmetic Regulation, none of the SAS materials (hydrophilic or hydrophobic) included in the dossier can be regarded as soluble. In fact, the Applicant had mistakenly interpreted the SAS materials as soluble on the basis of the solubility of some of the materials being 100 mg/L or higher. The threshold for regarding a material 'soluble' is 33.3 g/L under the USP38 and USP 38 NF33 categorisation (not 100 mg/L as claimed by the Applicant).

No data were provided to help establish whether the SAS materials could be regarded as degradable/non-persistent in biological systems.

2. Can the SCCS indicate to which kind of Silica this solubility applies?

The solubility values reported in the dossier are applicable when SAS materials are subject to the following conditions:

- hydrophilic SAS: Silica and hydrated silica when solubilised in aqueous media containing up to 0.5% ethanol,
- hydrophobic surface treated SAS: when solubilised in aqueous media containing up to 10% ethanol,
- at temperature: between 19.5 up to 20.5°C,
- pH: between 3 and 8,
- over a period between 3 days (hydrophilic SAS) and up to 49 days (hydrophobic SAS).

3. Does the SCCS have any further scientific concerns with regard to solubility of Synthetic Amorphous Silica (SAS)?

The solubility values considered by the SCCS in this Opinion may not be valid in situations where the SAS materials are formulated/used under conditions that are different from those used in the solubility tests - e.g. when used in a less/non aqueous formulation, or at a different temperature.

In the context of the definition of a nanomaterial under the Cosmetics Regulation, which relates to insoluble materials in conjunction with other size/particle related parameters, the question of solubility of a nano-structured material needs to be seen in perspective for use in cosmetics. For nano-structured materials, with the exception of the materials that are completely soluble, it is important to establish whether a proportion of these materials would still exist in undissolved form comprising nanoparticles at a given use level in a cosmetic formulation.

The SCC has noted that the protocols used for solubility tests have a strong influence on the solubility of SAS materials.

7. MINORITY OPINION

None

8. REFERENCES

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