EUROPEAN CHEMICALS AGENCY

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For Silicon dioxide, CAS No 7631-86-9 (EC No 231-545-4)

Addressees: Registrant(s) of Silicon dioxide

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent for comment, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants holding active registrations on the day the draft decision was sent are *not* addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by Bureau REACH on behalf of the Ministry of Infrastructure and the Environment as the Competent Authority of the Netherlands (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 4 April 2013, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of the Netherlands has initiated substance evaluation for Silicon dioxide, CAS No 7631-86-9 (EC No 231-545-4) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to the substance characterisation, nanoparticles and toxicity of different forms of the substance, Silicon dioxide was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2012. The updated CoRAP was published on the ECHA website on 29 February 2012. The Competent Authority of the Netherlands was appointed to carry out the evaluation.

The evaluating MSCA considered that further information was required to clarify the above mentioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 27 February 2013.

On 4 April 2013 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 6 May 2013 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA considered the comments received from the Registrant(s) and the dossier updates. The information contained therein is reflected in the Statement of Reasons (Section III) whereas minor amendments to the Information Required (Section II) were made.

In accordance with Article 52(1) of the REACH Regulation, on 4 September 2014 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of the draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, four Competent Authorities of the Member States and ECHA submitted 23 proposals for amendment to the draft decision.

On 10 October 2014 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

On 20 October 2014 ECHA referred the draft decision to the Member State Committee.

By 10 November 2014, in accordance to Article 52(2) and Article 51(5), the Registrant(s) provided comments on the proposals for amendment. The Member State Committee took into account the comments the Registrants made on the proposals for amendment (PfAs).

After discussion in the Member State Committee meeting on 8-11 December 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 11 December 2014.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

The Evaluating MSCA has conducted a targeted evaluation that does not include a full evaluation of all elements of the registration dossiers. The evaluation is targeted to the characterisation of the substance, human health hazard assessment in relation to the inhalation route and exposure assessment of the registered synthetic amorphous silica.

Based on the current information in the registration dossiers, the information as requested in section II is required. Evaluation of the information submitted in response to these requests might reveal that the safety of all forms of SAS[1] still cannot be adequately assessed and might lead to additional requests for information.

II. Information required

Synthetic amorphous silica (excluding surface-treated forms)

Pursuant to Article 46(1) of the REACH Regulation each Registrant shall submit the following information using the indicated test methods/instructions and the registered substance subject to the present decision:

1. Information on the following physicochemical properties of each individual SAS form[1] that is manufactured, imported and/or placed on the market, using the indicated test method(s) under standardised conditions that are fully described:
   a. The granulometry, which shall include primary particle size, aggregate/agglomerate size, and particle size distribution (number-based). Method for powders is Transmission Electron Microscopy (TEM) combined with Energy Dispersive X-ray (EDX), Laser Diffraction and Sieving; method for suspensions is Transmission Electron Microscopy (TEM) combined with Dynamic Light Scattering;
   b. The specific surface area (by volume). Method: for powders BET (ISO 9277:2010); for suspensions calculation based on theoretic model;
   c. The hydroxylation state. Method: infrared spectroscopy;
   d. The water solubility. Method: enhanced OECD 105 Flask Method for SAS including Tyndall effect measurement of the solution;
   e. The density. Method: OECD 109 Density of Liquids and Solids, pour and tap method for solids and immersed body method for liquids;
   f. The dustiness. Method: rotating drum method (prEN 15051-2);
   g. The point of zero charge. Method: microelectrophoresis or electrophoretic light scattering to be performed at three salt concentrations and at fixed particle concentration.

The information on the physicochemical properties shall be provided for each individual SAS form covered by the registration of silicon dioxide and shall be provided for the substance forms as produced, processed and placed on the market. Only the Registrant(s) of the substance know the details of each of its forms necessary for their characterisation. Based on this knowledge, they may consider that a test method requested by ECHA is not suitable in order to characterise each form of the substance. Nevertheless, it is the Registrant(s)' exclusive responsibility 1) to ensure that ECHA is in a position to characterise precisely each form of the substance and 2) to justify the reasons for the use of another test method instead of a method explicitly required in the present decision.

As an alternative, grouping may be used to provide information on physicochemical properties of SAS forms. In such case the Registrant(s) shall provide a clear justification and documentation as further specified in section III.

[1] See Annex I for abbreviation and terminology.

2. Sub-chronic toxicity study (90-day; OECD 413), in rats via the inhalation route with the following four [redacted] SAS forms as manufactured that represent:
   i. the lowest specific surface area with the lowest number of hydroxyl groups,
   ii. the lowest specific surface area with the highest number of hydroxyl groups,
   iii. the highest specific surface area with the lowest number of hydroxyl groups,
   iv. the highest specific surface area with the highest number of hydroxyl groups,

and the following modifications:

   a. Two additional recovery groups of animals shall be included for each form: one group of 5 animals/sex with a 13-week recovery period after exposure and one group of 5 animals/sex with a 26-week recovery period after exposure;
   b. Clinical pathology and ophthalmological examination may be excluded;
   c. Gross pathology and histopathology shall be conducted on the lungs, trachea; nasopharyngeal tissues, nasal associated lymphoid tissue and larynx; other organs and tissues may be excluded from examination;
   d. The aerosols shall have a maximum mass median aerodynamic diameter (MMAD) of 3 µm. There will be no lower size limit;
   e. Bronchoalveolar lavage (BAL) shall be conducted and the following parameters shall be included: total and differential leukocyte counts, total protein, lactate dehydrogenase and pro-inflammatory cytokines/chemokines;
   f. Collagen content shall be measured in lungs and associated lymph nodes.

As an alternative, in case for one of the identified forms a sub-chronic toxicity study (90-day, via inhalation) is available (taking into account the modifications to OECD 413 indicated above), and the tested form[3] is fully characterised according to request 1 of this Decision, this information may be provided to cover the information request for this one form.

3. Information on the uses of each individual form of SAS[2] that is manufactured, imported and/or placed on the market.

Surface-treated SAS

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit for the registered substance:

4. Information on the following physicochemical properties of each individual surface-treated SAS form[2] that is manufactured, imported and/or placed on the market, using the indicated test method(s) under standardised conditions that are fully described:
   a. The granulometry, which shall include primary particle size, aggregate/agglomerate size and particle size distribution (number-based)
   Method for powders is Transmission Electron Microscopy (TEM) combined with Energy Dispersive X-ray (EDX), Laser Diffraction and Sieving; method for suspensions is Transmission Electron Microscopy (TEM) combined with Dynamic Light Scattering;
   b. The specific surface area (by volume). Method: for powders BET (ISO 9277:2010); for suspensions calculation based on theoretic model;
   c. The hydroxylation state. Method: infrared spectroscopy;
   d. The surface treating agent(s), including chemical identity (IUPAC name and numerical identifiers (CAS and EC)) and type of reaction with the SAS surface;

[2] See Annex I for abbreviation and terminology.

e. The water solubility. Method: enhanced OECD 105 Flask Method for SAS including Tyndall effect measurement of the solution;
f. The density. Method: OECD 109 Density of Liquids and Solids, pour and tap method for solids and immersed body method for liquids;
g. The dustiness. Method: rotating drum method (prEN 15051-2);
h. The point of zero charge. Method: microelectrophoresis or electrophoretic light scattering to be performed at fixed low salt concentration and at fixed particle concentration.

The information on the physicochemical properties shall be provided for each individual surface treated SAS form of silicon dioxide and shall be provided for the substance forms as produced, processed and placed on the market. Only the Registrant(s) of the substance know the details of each of its forms necessary for their characterisation. Based on this knowledge, they may consider that a test method requested by ECHA is not suitable in order to characterise each form of the substance. Nevertheless, it is the Registrant(s)' exclusive responsibility 1) to ensure that ECHA is in a position to characterise precisely each surface treated form of the substance and 2) to justify the reasons for the use of another test method instead of a method explicitly required in the present decision.

As an alternative, grouping may be used to provide information on physicochemical properties of SAS forms. In such case the Registrant(s) shall provide a clear justification and documentation as further specified in section III.

5. All toxicological information on surface-treated SAS as manufactured, imported and/or placed on the market as available to the Registrant(s). This includes all exposure routes, all toxicological endpoints and all forms of surface-treated SAS. Further, a scientific justification shall be provided that substantiates if and why the toxicological information on untreated SAS can be used for safety assessment of surface-treated SAS.

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **20 March 2017**, 24 months from the date of the decision, an update of the registration dossiers containing the information required by point 1-5 of section II.

III. Statement of reasons

According to the current EU-definition, a nanomaterial is a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm (EU, 2011). According to the questions and answers on the Commission Recommendation on the definition of nanomaterial[3], the definition also includes aggregates and agglomerates of nanoparticles. Agglomerated or aggregated particles may or may not exhibit the same properties as unbound particles. Moreover, there can be cases during the life cycle of a nanomaterial where the particles are released from weakly bound agglomerates or under certain conditions even from more strongly bound aggregates. The definition in the Recommendation therefore includes particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm - 100 nm (European Commission, Questions and Answers on the Commission Recommendation on the definition of Nanomaterial[3]). Where technically feasible and requested in specific legislation, compliance with the definition as mentioned above may be determined on the basis of the specific surface area by volume. A material should be considered as falling under the definition as mentioned

[3] http://europa.eu/rapid/press-release_MEMO-11-704_en.htm

above where the specific surface area by volume of the material is greater than 60 m^2/cm^3 (EU, 2011). However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition even if the material has a specific surface area lower than 60 m^2/cm^3 (EU, 2011).

Nanomaterials are being engineered for their specific physicochemical and biological characteristics, meaning that their reactivity and/or behaviour (such as their interaction with their environment) will depend on these characteristics. Due to their specific physicochemical properties, small nanoscale particles can have specific characteristics that distinguish them from the non-nanoparticles and from other nanoparticles of the same material. Although the toxicological profile of the chemical components of a given nanomaterial may be well known, there may be cases where its specific properties raise concerns about the specific potential to harm humans and the environment (SCENIHR, 2010). It is further concluded in this SCENIHR report that the reaction rate of nanoparticles often relates to the available surface area. Consequently, chemical reactivity per mass dose increases with decreasing particle size.

In addition, nanomaterials can change during their life cycle. Parameters such as size, aggregation states, surface charge, coatings and other properties may change in different solvents, test media, and biological environments (SCCS, 2012).

To ensure a high level of protection of human health and the environment, the REACH Regulation imposes the determination of hazards, exposures and risk irrespective of the form of the substances concerned. This includes more specifically nanoforms of substances, which may trigger specific hazardous properties and risks, as already highlighted by various institutions, including the European Parliament[4].

1. Physicochemical properties

Establishing the concern

SAS is a nanostructured material and four types of SAS can be distinguished, which are pyrogenic SAS, precipitated SAS, silica gel and colloidal SAS (Fruijtier-Pölloth, 2012). Of each of these four types, multiple forms are produced, processed and placed on the market, each with specific purposes and functional properties and characteristic interactions with their environment. These differences in properties and characteristics between the forms can be attributed to differences in their physicochemical properties (Napierska et al., 2010).

The registration dossiers include information on several physicochemical characteristics, including granulometry, water solubility, density and surface area. This information is mostly provided for each of the four SAS types only and not for each of the individual forms of SAS.

Under the REACH Regulation, different forms can be considered within a single registration of a substance. There is a concern that the safety of all registered forms of SAS cannot be ensured based on the registered information.

Justification why new information is needed

The information included by the Registrant(s) of the substance SAS in their respective dossiers is not sufficient to identify and characterise the individual forms of the substance

[4] Recital D of European Parliament Resolution of 24 April 2009 on Regulatory aspects of nanomaterials (2008/2208(INI)), pages 267-275 of the document available at http://www.europarl.europa.eu/RegData/seance_pleniere/textes_adoptes/provisoire/2009/04-24/P6_TA-PROV(2009)04-24_EN.pdf.

manufactured, imported or placed on the market by their respective legal entities. Consequently, the scope of the registered substance cannot be verified and therefore safe use of the substance is not demonstrable based on the information provided. Therefore, physicochemical characteristics for the individual forms of SAS are required to draw appropriate conclusions on possible similarities or expected equalities in characteristics, behaviour and potential interactions with their environment.

The need for individual characterisation of all registered forms is further emphasised by the fact that both the mammalian and environmental toxicology of SAS are significantly influenced by their physicochemical properties (ECETOC, 2006). Differences in toxicity between forms of SAS have been demonstrated by [redacted]).

[redacted] performed a 13-week inhalation study in rats exposed to 1, 6 or 30 mg/m^3 [redacted] and 30 mg/m^3 [redacted]. The study revealed that 30 mg/m^3 [redacted] ([redacted] induced more severe changes in the lungs as compared to 30 mg/m^3 [redacted]. Additionally, only a part of the effects induced by 30 mg/m^3 [redacted] reversed during the post-exposure period, while effects induced by [redacted] were all reversible. Focal interstitial fibrosis was observed 13 weeks after exposure in both the [redacted] (9/10 rats exposed to 30 mg/m^3) and [redacted] (1/10 rats) exposure groups. This effect disappeared in the [redacted] exposure group during the subsequent post-exposure period but persisted and became more severe in the 30 mg/m^3 [redacted] exposure group up to 52 weeks after exposure (at the end of the study). Focal interstitial fibrosis was already observed in 1/10 rats exposed to 1 mg/m^3 [redacted]. Various other repeated dose inhalation studies available in the registration dossiers indicate that fibrosis is only associated with exposure to [redacted] SAS. In a study by Johnston et al. (2000), rats were exposed to [redacted] for 13 weeks at a concentration of 50 mg/m^3. Histopathology data revealed fibrosis in the alveolar septae, which subsided during a recovery period (≥ 3 months). Further, signs of (collagenic) fibrosis were observed by Groth et al. (1981), Klosterkötter (1969) and Schepers et al. (1957a, 1957b), although the reliability of some of the results was questioned and doses were relatively high. No fibrosis was observed in any of the available inhalation studies with [redacted] SAS or [redacted], apart from the single finding by [redacted] for [redacted], as mentioned above.

The available inhalation studies indicate differences in toxicity and potency between different types of SAS, with [redacted] SAS showing a higher toxic potential than [redacted] SAS and [redacted] gel. These differences in potency between SAS types are inextricably bound up with differences in physicochemical characteristics. Physicochemical properties vary significantly between SAS types, but also between different SAS forms within one SAS type[5]. Considering this dependency of toxicity on physicochemical characteristics, identification of the individual forms of SAS for their physicochemical characteristics is required.

The information request

The information in the registration dossiers about the physicochemical characteristics is provided for only a few forms[5] of SAS or limited to combined ranges for multiple forms, and thus insufficient to distinguish the individual forms of SAS for their physicochemical properties. Therefore, each respective Registrant shall include the requested information for each representative form of SAS manufactured/imported/placed on the market in its updated respective registration dossier. Each representative form (by SAS type) shall be

[5] See Annex I for abbreviation and terminology.

reported as a separate composition in Section 1.2 of the dossier submitted by each Registrant and the corresponding characterisation data for each form included in section 1.4 of the respective dossiers. The Registrant(s) shall ensure that each form of the substance is taken into account for all data included in sections 2-11 of the technical dossier as per REACH requirements. The Registrant(s) may take note of the IUCLID user manual on how to include information on nanomaterials in IUCLID dossiers[6] as this will help structure the dossier such that information on the various forms of the registered substance can be structured consistently and transparently in all the sections of the IUCLID dossier.
In addition, the information required must be provided for all SAS forms covered by the registration.

Key parameters that are expected to play a decisive role in toxicology of nanomaterials or specifically SAS are particle size, particle size distribution, aggregation and agglomeration state, specific surface area, surface hydroxylation state, water solubility, density, dustiness and surface charge (ECETOC, 2006; SCENIHR 2010, REACH Guidance R7a).

- Granulometry: Despite the importance of granulometry (i.e. particle size and particle size distribution) in identifying nanomaterials like SAS, the current registration dossier includes only limited information on this parameter. Primary particle size was not included in the current dossier, despite it being a part of the identity of SAS. It was described that primary particles do not exist in isolation in SAS and that the smallest particles are aggregates with a size of > 100 nm. However, no evidence for this was provided within the registration dossier. Also with primary particle size being a part of the identity of SAS, information on this parameter shall be provided, irrespective of potential exposure to primary particles. The primary particle size could be of influence on characteristics of the agglomerate/aggregate states of SAS. Information on the aggregate/agglomerate state and the size distribution of these particles are of influence on the assessment of the effects after inhalation exposure. Particles smaller than 10 µm are respirable and can reach the alveolar regions of the lungs. Therefore, information on the primary particle size and the particle size distribution of the registered substance is required.

- Specific surface area: The specific surface area has impact on the solubility and reactivity of materials. Especially nanomaterials, including nanostructured materials, have an increased surface-to-volume ratio. The European Commission, therefore, included in its recommendation that a material should be considered as falling under the definition when it has a large specific surface area by volume (i.e. > 60 m^2/cm^3; EU, 2011). This parameter was chosen because specific surface area is considered to be an important factor which influences toxicity (OECD, 2010; SCENIHR, 2010). For powders, the surface area can be determined by Brünauer, Emmett and Teller (BET) measurements on gas adsorption; for suspensions the surface area can be estimated based on particle size distribution and density.

- Hydroxylation state: The hydroxylation state (number of silanols at the surface) influences amongst others the surface reactivity of SAS. The hydrophilicity of a silica material increases with the number of surface silanols, or silicon-bonded hydroxyl groups, capable of forming hydrogen bonds with water molecules. This may affect the behaviour and reactivity of silica towards its environment (ECETOC, 2006; Razzaboni, 1990).

[6] Nanomaterials in IUCLID 5.2, http://iuclid.eu/index.php?fuseaction=home.documentation. The manual can be downloaded directly with this link:
http://iuclid.eu/download/documents/usermanual/IUCLID_User_Manual_Nanomaterials_v1.0.pdf

- Water solubility: In general, water solubility is a significant parameter, as summarised in section R.7.1.7.1 of ECHA's REACH Guidance on Information Requirements and Chemical Safety Assessment, e.g. because water soluble substances gain access to humans and other living organisms. The water solubility is an intrinsic property of a SAS particle, depending on e.g. particle size, specific surface area, hydroxylation state.

- Density: the density of SAS may affect the deposition of particles in the lungs. The density is also required to determine the specific surface area for suspensions.

- Dustiness: the dustiness of SAS is important to determine particle size distribution in the air. The particle size distribution of the airborne fraction will be different to that determined for the non-airborne substance.

- Point of zero charge: the surface charge is a determining property for the tendency of a material to agglomerate, and is therefore relevant both in terms of potential for exposure and hazard. The property may be used in a relative manner to assess in which order different SAS types and forms tend to agglomerate/aggregate. Surface charge is not an intrinsic property as it depends on the testing conditions. In order to compare the surface charge of different SAS types the point of zero charge shall be determined, performed under standardised conditions for particle concentration and salt concentration.

Summary of Registrant(s)'s comments and response to comments

- The Registrant(s) have commented on the selection of physicochemical parameters and the methods that shall be used. Based on the comments, one parameter was removed from the request and methods were adapted according to the Registrant(s)'s comments.

- The Registrant(s) commented that SAS is not a new substance and has been produced and marketed for decades without significant changes in its physicochemical properties. However, it is noted that REACH is based on the principle that manufacturers, importers and downstream users must ensure that a substance does not adversely affect human health or the environment. For such an assurance a scientific justification based on information on the properties and hazards of the substance shall be provided. Although SAS may have been produced and marketed for decades, this does not provide a guarantee that SAS is a safe substance during its whole life cycle.

- According to the Registrant(s), the "sameness" of SAS produced as pyrogenic SAS, precipitated SAS, silica gel and colloidal SAS has been demonstrated. Concerning physicochemical properties, the Registrant(s) state that the term "sameness" applies only to the parameters listed in table 3.1 in ECHA`s "Guidance for Identification and Naming of Substances under REACH (and CLP)" (Version June 2007 and 1.2, March 2012).

  ECHA does not agree that the sameness of SAS has been demonstrated within the registration dossier. SAS is a nanomaterial that is manufactured in many types and forms, which may vary largely in physicochemical characteristics.
  Also key parameters that are not mentioned in the "Guidance for Identification and Naming of Substances under REACH (and CLP)", including particle size, particle size distribution, aggregation and agglomeration state, specific surface area, surface hydroxylation state, water solubility, density, dustiness and surface charge, may play

a decisive role in the exposure, kinetics and toxicology of nanomaterials or specifically SAS. Information on these characteristics is therefore of high importance for risk assessment of SAS and to evaluate sameness or differences between SAS types and forms.

- According to the Registrant(s), substance identity parameters should not extend to product grades. REACH is a substance-based regulation and not a product/grade-based regulation. According to ECHA, the registration dossiers comprise SAS, in all its types and forms manufactured. The dossier information shall cover all different forms, referred to as grade by the Registrant(s), to demonstrate safe use of SAS. Moreover, the forms of SAS could differ in physicochemical properties. To justify that the current dossier information, especially the toxicological information, is relevant for all registered forms of SAS and to enable evaluation of safe use, the physicochemical properties of each form shall be described in the registration dossiers.

- According to the Registrant(s), the Draft Decision is disproportionate. SAS is a substance that has been reviewed over a long period of time, in different and diverse frameworks such as OECD programs or EU-related programs, which did not result in any findings that would indicate concerns to be tackled further. However, ECHA interprets the data from the OECD program as indicating a low priority for further work but not the absence of risks. Moreover, the OECD concluded that SAS possesses properties indicating a hazard for human health (repeated inhalation toxicity). Further, the Cefic LRI program includes studies performed with [redacted] SAS, while the focus of the concern is primarily related to exposure to [redacted] SAS. Moreover, it is emphasised that the registration dossiers are evaluated within the scope of REACH; conclusions on potential hazard as made in other frameworks do not automatically apply for the registration in REACH.

It is requested that information on physicochemical properties of all individual forms of SAS shall be provided. As described above, the Registrant(s) have commented on the sameness of SAS and mentioned that SAS is not a new substance and has been produced and marketed for decades. These comments are not sufficient to dispel the initial concerns. Therefore, informal interaction between the Registrant(s) and the evaluating MSCA was initiated to further discuss the requests. These interactions have led to a suggestion for grouping by the Registrant(s) as displayed in Tables 1, 2 and 3.

Table 1. Proposal for grouping as suggested by the Registrant(s) at 18 Dec 2013

SAS type	**Specific surface area range**	**Grade 1**	**Grade 2**	**Grade 3**
Pyrogenic	50-500 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Precipitated	30-700 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Gel	200-800 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Colloidal	BET cannot be directly measured but is calculated based on particle size.	[redacted] nm primary particle size, [redacted] wt% in aqueous medium	[redacted] nm primary particle size, [redacted] wt% in aqueous medium	[redacted] nm primary particle size, [redacted] wt% in aqueous medium

Table 2. Proposal for grouping as suggested by the Registrant(s) at 12 May 2014. The candidates for physicochemical testing are presented in the table.

SAS type	Specific surface area range	Grade 1	Grade 2	Grade 3
Pyrogenic	50-500 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Precipitated	30-800 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Gel	200-800 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Colloidal	50-800 m^2/g (BET calculated based on particle size; Sauter)	[redacted] m^2/g([redacted] nm primary particle size, [redacted] wt% in aqueous medium	[redacted] m^2/g ([redacted] nm primary particle size, [redacted] wt% in aqueous medium	[redacted] m^2/g ([redacted] nm primary particle size, [redacted] wt% in aqueous medium)

Table 3. Proposal for grouping as suggested by the Registrant(s) at 24 June 2014.

SAS type	Specific surface area range	Grade 1	Grade 2	Grade 3
Pyrogenic	50-500 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Precipitated	30-800 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Gel	200-800 m^2/g	[redacted] m^2/g	[redacted] m^2/g	[redacted] m^2/g
Colloidal	80-480 m^2/g (BET calculated based on particle size; Sauter mean diameter)	[redacted] m^2/g ([redacted] nm, in aqueous medium	[redacted] m^2/g ([redacted] nm, in aqueous medium	[redacted] m^2/g ([redacted] nm, in aqueous medium)

The suggested grouping is based on the four SAS types, related to the production process (not further specified by the Registrant), and the specific surface area of each SAS form.

ECHA has considered this suggestion for grouping. Although ECHA agrees that grouping is important for the assessment of nanomaterials, the scientific reasoning behind the grouping is as yet insufficient.

ECHA considers that the grouping approaches proposed by the Registrant(s) do not demonstrate how the properties of each form of the registered substance can be predicted from the available information in the registration dossier. More specifically, by analogy to Section 1.5 of Annex XI of the REACH Regulation, which sets out the conditions to be met by alternative methods, equivalent information on all forms shall be obtained. The grouping strategy proposed by the Registrant(s) does not fulfil those conditions, both in relation to 1) the documentation provided and 2) the scientific rationale of the grouping approach.

1) The documentation of the grouping approach:

By analogy to Annex XI, 1.5, "adequate and reliable documentation of the applied method shall be provided." More specifically, a prerequisite for a decision to take any position on a grouping approach is that the Registrant(s) provide adequate and reliable documentation. In the present case, ECHA notes that the documentation submitted is inadequate in relation to the determination of the grouping.

The definition of each group of forms is a fundamental aspect of the grouping approach. However, ECHA's ability to evaluate the grouping approach is hampered by the lack of clarity in the definition of the groups, but to the extent that it is possible to draw

conclusions on the adequacy and reliability of the documentation, the following should be addressed:

- **Definition of the grouping approach.** The Registrant(s) have based their grouping approach on the four different types of SAS and secondarily on the specific surface area. However, for this approach there is insufficient information available in the registration dossier on the production processes, how the production processes are linked to the various grades and how the production process relates to the differences in characteristics of the SAS forms covered by the registration. The Registrant(s) have not clearly explained which criteria will be used to define the groups in such a way that each form can unambiguously be assigned to a specific group. Further, the proposed groups do not cover the whole specific surface area range as described by the Registrant(s). In the comments provided by the Registrant(s) these information gaps were not solved. Further, there are no data on the specific surface area of each SAS form and there is no information on how all SAS forms covered by the registration are distributed and arranged into the defined groups.

- **Key parameters.** The grouping of forms of the substance must be justified for each hazard endpoint separately. By analogy to the rules for adaptation set out for grouping in Annex XI, 1.5 of the REACH Regulation, results shall "have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)", i.e. test data using the corresponding test method (or studies of comparable coverage) needs to be available for each group of the forms, in order to establish a justified grouping approach for an endpoint.

  ECHA considers that it has not been sufficiently demonstrated that other parameters can be disregarded in the grouping approach. ECHA considers the hydroxylation state to be an important parameter for the surface reactivity; e.g. ECETOC (2006) indicates the relevance of the number of silanol groups for the reactivity of the SAS types. There is no justification why this crucial parameter was not included in the grouping proposal from the Registrant(s).

2) Scientific assessment of the grouping approach:

By analogy to Annex XI, 1.5, the application of the grouping concept to different forms of the same substance requires that human health effects can be predicted from data for reference form(s) of that substance by interpolation to other forms of that substance.

Based on the same principle, the relevant hazard properties of all the forms in a group shall be predicted from the properties of the reference form(s) within that group. Such a prediction may be a result of a constant pattern in the changing of the potency of the properties across each group. However, to the extent that the case for grouping is currently set out by the Registrant(s), ECHA considers that the Registrant(s) have failed to demonstrate that the human health effects of all forms of the substance can be predicted from reference forms within each group.

In view of that, ECHA asks for the information as indicated in section II (request 1). The Registrant(s) may fulfil the requests of section II, request 1, using a grouping approach provided that the grouping is done according to a sound scientific reasoning that shall be provided when the dossier is updated. In particular, the following justifications must be made and supported by documented evidence:

- Justification how each form can be allocated to a specific group. As noted, in the current dossier allocation to the various groups is not possible due to the absence of information of the individual forms and due to the absence of information on the production process leading to various grades.
- Also, for allocating each form to a group, all forms shall be covered. It is noted that in the current grouping proposal there are gaps in the proposed surface area ranges, e.g. for [redacted] are not covered by the current groups.
- Justification why the grouping is sufficient to cover all individual SAS forms, and why these parameters were chosen.
- Justification how all requested parameters relate to the specific surface area and the SAS type. In particular, what is the range of the hydroxylation state or primary particle size within each of the proposed groups?
- Justification how these groups are linked to the inhalation toxicity of SAS. Differences in toxicity between SAS types were observed and may also occur between different SAS forms. The results of the key inhalation study [redacted] indicate that different types of SAS have different potencies to interact with biological materials, that cannot be simply explained by exposure to particles (see 'Toxicological data'). Therefore, toxicity shall be distinguished between SAS forms and linked to the grouping of the forms.

It is the responsibility of the Registrant(s) to ultimately define the groups based on reliable information which shall be used in a way that does not underestimate hazards of the forms of the substance in relation to each endpoint.

Consideration of proposals for amendment and Registrant(s)'s comments on them

a. ECHA Secretariat made a proposal for amendment by including the grouping approach, i.e. the possibility to group several individual SAS forms as an alternative to provide information on physicochemical properties, in section II. Additionally, ECHA Secretariat made a proposal for amendment of including a reference in Section III to the grouping and read-across criteria as established in Annex XI, 1.5. of the REACH Regulation, clearly indicating which of the individual conditions have not been met by the grouping suggested by the Registrant(s). The Registrant(s) supported these proposals for amendment.
The evaluating MSCA agreed to refer to an alternative grouping approach in section II and amended the Draft Decision accordingly. The methodology for grouping substances set out in Annex XI, 1.5 can, even though not referring explicitly to nanomaterials yet, apply by analogy to grouping of SAS forms. It is of high importance that the basic information on physicochemical properties is provided and only a specified grouping approach will be sufficient to address all relevant information. The evaluating MSCA has amended section III by including a reference to the grouping approach and indicated the limitations of this approach.

b. A Member State Competent Authority (MSCA) made a proposal to ask for data representative of production, to indicate variability within and between batches of production. The Registrant(s) did not agree with this proposal for amendment, stating that the production of [redacted] SAS is a continuous process or based on a stable and robust process, leading to stable formation of SAS forms and meeting the quality specifications. The variation is checked on a regular basis and lot-to-lot variation has been demonstrated to be statistically insignificant.

The evaluating MSCA agreed with this MSCA that data representative of production are of importance to enable a proper risk assessment for all registered forms of SAS. In the Draft Decision that was sent to the MSCAs and ECHA, it was already requested

to provide information of the SAS form 'that is manufactured, imported and/or placed on the market'. This takes into account that information shall be representative for SAS forms as manufactured. Therefore, the evaluating MSCA did not amend the Draft Decision.

c. The MSCA made a second proposal for defining the pre-treatment and condition of tests (dry module or in a precised solvent) along with DLS data. The Registrant(s) agreed with this proposal for amendment and agreed to define a standard operation procedure (SOP) for sample preparation and appropriate devices to measure the nanoscale.

   The evaluating MSCA agreed that the test conditions are important to take into account when performing DLS. It was suggested that the Registrants shall perform the studies according to a standardised approach that is fully described, to enable proper comparison of the study results. This was amended in the Draft Decision as follows: '...using the indicated test method(s) under standardised conditions that are fully described'.

d. The MSCA made a third proposal for using measurement of tap and pour density (for example CIPAC 186), instead of requesting the density according to OECD 109. The Registrant(s) did not agree with this proposal for amendment, amongst others stating that the CIPAC 186 method requires only a limited number of taps, leading to inconsistent results.

   The evaluating MSCA agrees with the proposal for amendment to further specify the method used for measuring the density. It is further agreed that a limited number of taps may lead to inconsistent data. Therefore, the test method shall be performed with a sufficient number of taps, reaching a stable density measurement. Further, it is emphasized that the tap and pour density (and the difference between them) shall be measured. The Draft Decision was amended accordingly.

e. Another MSCA made a proposal for amendment to justify the methods requested for measuring the particle size distribution, or delete the request or leave the choice of method up to the Registrant(s). The Registrant(s) agreed with this MSCA regarding the analytical challenges due to a lack of standardized methods, as reported in a recent JRC publication and support the suggestion to delete the data request.

   The evaluating MSCA commented that the specified methods were determined in consultation with the Registrant(s). The combination of methods is considered to be sufficient to determine the particle size distribution of the different SAS forms. In addition, in section III it was included that the Registrant(s) may consider that a requested test method is not suitable in order to characterize the substance and that it is the Registrant(s)' responsibility to precisely characterize their substance and justify the reasons in case another test method is used. In addition, the Registrant(s) indicated in their comment on the PfA from another MSCA (Section II, point 1), related to granulometry, that variation is checked and no statistically significant differences were demonstrated. This implies that reliable methods do exist and are used.

f. The same MSCA further proposed to delete the request for information on the surface area and hydroxylation state, arguing that it is not clear how it will be used for regulatory purposes. The Registrant(s) agreed to delete the requests and refer to a linear correlation between hydroxylation state and surface area. Further, the Registrant(s) indicated that a comprehensive dataset for all physicochemical

parameters requested in the Draft Decision has been provided in the dossier.

The evaluating MSCA did not agree with deleting the requests. The surface area is of high importance for the toxicity of nanomaterials. Further, the specific surface area is part of the current EU recommendation for the definition of nanomaterial, where the surface area is included as an alternative parameter (alternative to particle size) to decide whether a material falls under the definition. Moreover, the Registrant(s) use the specific surface area to distinguish between (some of) their forms, as the many different SAS forms differ mainly in specific surface area. The reactivity of SAS is dependent on the chemistry of the surface, including the number of hydroxyl (silanol) groups at the surface (Razzaboni, 1990). Surfaces with a low number of silanol groups will be relatively unreactive, while surfaces with a higher number of silanol groups may react with components of the surrounding media, or with other SAS particles to form agglomerates. Therefore, the hydroxylation state is expected to be an important parameter in relation to the toxic potential of SAS forms and thus required to assess the risk of SAS.

The Registrant(s) referred to data that suggest a linear relationship between the hydroxylation state and the specific surface area of SAS. However, data that were obtained via the SEARS methods are based on a direct correlation between the hydroxylation state and the surface area and therefore hydroxylation state is not measured independently. Similarly, data obtained with another method (using $LiAlH_4$) only show a constant relationship between hydroxylation state and specific surface area for sufficiently aged SAS (which may take a year). Clearly such aged SAS does not correspond to the material as produced. Further, information from Mathias and Wannemacher (1988) indicates that the SiOH density on the surface is dependent on the temperature during the production process, i.e. a higher temperature will lead to a lower SiOH density as for example can be seen for the [redacted]. SAS forms with the same surface area may therefore differ in SiOH density, dependent on the production process.

The current registration dossiers contain information on several, but not all, requested parameters. Further, data were often provided in ranges for each SAS type. As indicated in the Draft Decision, there is a concern based on the possible differences in toxicity between SAS forms, due to differences in physicochemical properties. Without information on the individual SAS forms, it cannot be determined if the SAS forms with the highest potential toxicity are tested and represented by the dossiers. Therefore, the current dossier information is insufficient to assess the safety of all registered SAS forms.

Conclusion

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to submit information on the following physicochemical properties of each individual SAS form[7] that is manufactured, imported and/or placed on the market, using the indicated test method(s) under standardised conditions that are fully described:

a. The granulometry, which shall include primary particle size, aggregate/agglomerate size and particle size distribution (number-based). Method for powders is Transmission Electron Microscopy (TEM) combined with Energy Dispersive X-ray (EDX), Laser Diffraction and Sieving; method for suspensions is Transmission Electron Microscopy (TEM) combined with Dynamic Light Scattering;
b. The specific surface area (by volume). Method: for powders BET (ISO 9277:2010); for suspensions calculation based on theoretic model;
c. The hydroxylation state. Method: infrared spectroscopy;

[7] See Annex I for abbreviation and terminology.

d. The water solubility. Method: enhanced OECD 105 Flask Method for SAS including Tyndall effect measurement of the solution;
e. The density. Method: OECD 109 Density of Liquids and Solids, pour and tap method for solids and immersed body method for liquids;
f. The dustiness. Method: rotating drum method (prEN 15051-2);
g. The point of zero charge. Method: microelectrophoresis or electrophoretic light scattering to be performed at fixed low salt concentration and at fixed particle concentration.

The information on the physicochemical properties shall be provided for each individual SAS form covered by the registration of silicon dioxide and shall be provided for the substance forms as produced, processed and placed on the market. Only the Registrant(s) of the substance know the details of each of its forms necessary for their characterisation. Based on this knowledge, they may consider that a test method requested by ECHA is not suitable in order to characterise each form of the substance. Nevertheless, it is the Registrant(s)'s exclusive responsibility 1) to ensure that ECHA is in a position to characterise precisely each form of the substance and 2) to justify the reasons in case another test method is used instead of a method explicitly required in the present decision.

As an alternative, grouping may be used to provide information on physicochemical properties of SAS forms. In such case the Registrant(s) shall provide a clear justification and documentation as further specified above.

2. Toxicological data

Establishing the concern

The current registration dossiers contain various repeated dose toxicity inhalation studies, however, they do not cover all registered forms. As a consequence, the relevancy of the test results for all forms of SAS cannot be evaluated for the individual endpoints. From the registration dossiers, it cannot be verified to whether the most potent forms of the [redacted] have been tested for the various toxicity endpoints and to what extent the provided data are representative for all forms produced, processed and placed on the market. Neither can it be verified how the test results can be applied to the safety assessment of the SAS forms that were not tested. Consequently, an underestimation of the hazards cannot be excluded and the risks during exposure to the registered substance may not be adequately controlled.

Justification why new information is needed

The request for new information is justified based on the findings by [redacted] who performed a 13-week inhalation study with three different SAS forms [redacted]). Differences in the toxicity profile were clearly demonstrated, with the main difference in the incidence of focal interstitial fibrosis. Rats were exposed to 1, 6 or 30 mg [redacted]/m^3, to 30 mg [redacted] /m^3 or to 30 mg surface-treated [redacted]/m^3. Separate exposure groups were included for recovery periods of 13, 26, 39 and 52 weeks. A low incidence of fibrosis was observed 13 weeks post-exposure in rats exposed to [redacted] and to [redacted]; at 26 weeks post-exposure no fibrosis was observed in rats exposed to [redacted] and in 1/10 rats exposed to [redacted]. In contrast, higher incidences of fibrosis in the [redacted] exposure groups were observed which were very consistent: 1) the increase in the incidence of fibrosis was clearly concentration-related with a nearly 100% incidence at the highest exposure concentration and 2) four independent recovery exposure groups at all three concentrations tested showed comparable incidences.

Considering the much higher incidence of fibrosis following exposure to [redacted] as compared to [redacted] and [redacted], and the fact that fibrosis occurs already at low exposure concentrations of [redacted], the fibrosis cannot be attributed to just a particle (over)load of the lungs. This is further substantiated by the fact that [redacted] reported lower silicon content in the lung of rats exposed to [redacted] than in the lung of rats exposed to the other SAS forms; the silicon clearance from the lung appeared to be faster in [redacted] exposed rats.

These data suggest that the observed differences in the occurrence of focal interstitial fibrosis between these SAS forms are due to differences in specific characteristics of the three SAS forms.

This is in line with the findings in various other repeated dose inhalation studies available in the registration dossiers that indicate that fibrosis is only associated with exposure to [redacted] SAS (Johnston et al., 2000; Groth et al., 1981; Klosterkötter, 1969; Schepers et al., 1957) although the reliability of some of these data was questioned and doses were relatively high. No fibrosis was observed in any of the available inhalation studies with precipitated SAS or silica gel, apart from the single finding by [redacted] for [redacted] as mentioned above.

Conclusions of a chemical safety assessment should cover all forms in a registration. When data from one form of a substance are used in demonstration of the safe use of other forms, a scientific justification should be given on how the data from a specific test or other information can be used for all other forms of the substance, applying the rules for grouping and read-across.

Occupational exposure measurements as reported by ECETOC (2006) indicate that exposure concentrations could reach up to 10 mg/m^3 total silica in the 1980s and 1990s, of which approximately 20 to 40% was respirable (i.e. up to 3.4 mg/m^3 respirable SAS). Data that are more recent (1996 – 2003) displayed SAS concentrations of up to 3 mg/m^3 inhalable dust and up to 1 mg/m^3 respirable dust. Total dust concentrations were not described. In comparison, the exposure concentrations tested in the study by [redacted] inducing pulmonary fibrosis are similar to these industrial exposure concentrations of respirable SAS. This shows that occupational exposure potentially causes a risk to human health. However, only a limited number of SAS forms are toxicologically tested and the relevancy of these test results for all other SAS forms is unknown. Therefore, further investigation is required to determine the SAS form with the highest potential for the induction of pulmonary fibrosis and to determine a NOAEC for this effect that accounts for all forms of SAS. This information is a prerequisite for further safety assessment of SAS, especially for the derivation of safe exposure levels for workers and the general population potentially exposed by inhalation to SAS.

The behaviour and reactivity of nanomaterials are dependent on their physicochemical properties that are subject to change due to the influence of factors such as the manufacturing process, and storage conditions (SCENIHR, 2010). It has been described that the hydrophilicity of a silica material increases with the number of silicon-bonded hydroxyl groups, capable of forming hydrogen bonds with physical water molecules (Napierska et al., 2010). [redacted], produced at high temperature, is almost entirely dehydroxylated. However, depending on storage conditions, [redacted] SAS can become more hydroxylated over time, resulting in the formation of hydrogen bonds and agglomeration of particles. This can affect the physicochemical properties and the toxicological potency of the substance. In case such hydroxylation occurs before a physicochemical or toxicological test is performed, the test results will not be representative for the substance as it exists during the production process or as it is placed on the market. Information on the storage time and the

storage conditions of the substances prior to testing is therefore considered important to enable assessment of the appropriateness and usability of the study.

The information request

Toxicological studies performed via the inhalation route and with fully characterised forms of SAS are required. The induction of pulmonary fibrosis as main toxicological endpoint needs to be examined, since the available information indicates that it is the most critical adverse effect [redacted]. Further, different forms of SAS with reasonable extreme values for specific physicochemical parameters need to be tested to 1) obtain basic information on the relationship between physicochemical characteristics and the toxic potency and 2) to assure that the test results can be applied to non-tested, different forms of SAS. The main physicochemical characteristics for SAS in relation to potential toxicity are considered to be the specific surface area and the hydroxylation state (see also section III, request 1). Since fibrosis in the lungs was not observed before 13 weeks post-exposure to relatively low SAS concentrations, at least a 13-week exposure period followed by a recovery period is considered adequate for the determination of a NOAEC. Therefore, a 28-day toxicity study would be insufficient for detecting such adverse effects. The concentrations of the substances to be tested shall be comparable to the concentrations as used in the study by [redacted]. At least one dose shall be the same as tested by [redacted], clearly resulting in adverse effects in the lungs, and the other concentrations chosen as such that a NOAEC can be derived.

Summary of Registrant(s)' comments and response to comments

- According to the Registrant(s), the interpretation of available data is incomplete and unbalanced as the content of the Draft Decision suggests that not all available data have been considered in the evaluation and subsequent development of the Draft Decision.

  All repeated dose toxicity inhalation studies available in the dossiers have been taken into account. In the Draft Decision the key study by [redacted] was selected to indicate the induction of fibrosis in lungs upon inhalation exposure to [redacted] SAS at low doses. However, several other studies that are included in the registration dossiers, although of less quality than the key study by [redacted], also indicated possible induction of fibrosis upon exposure to [redacted] SAS. No fibrosis was observed in any of the studies with [redacted] SAS or [redacted], apart from a single finding with [redacted] SAS in the [redacted] study. The information of all repeated dose inhalation studies indicates that [redacted] SAS is hazardous (induction of pulmonary fibrosis), and it shows that the toxicity potential differs between the different SAS types.
- In addition to the comments submitted, the Registrant(s) indicated at one of the informal meetings with the evaluating MSCA that there is a linear relationship between the specific surface area and the hydroxylation state. Low specific surface area equates to lowest number of hydroxyl groups; highest specific surface area equates to highest number of hydroxyl groups. The requested toxicity tests will therefore lead to duplicate testing of the same SAS form. A figure was provided, showing that the number of hydroxyl groups at the surface is 1.8 OH/nm^2, irrespective of the specific surface area. For this correlation, the specific surface area was determined with the SEARS method (Sears, 1956).

  According to ECHA, the SEARS method can be used to determine the specific surface area, based on a titration of the surface with sodium hydroxide. At pH 9, a specific number of hydroxyl groups is adsorbed per nm^2 of surface and is thereby a measure for the specific surface area. The correlation between these two parameters is

therefore intrinsic to the method and not suitable to determine the correlation of surface area with the hydroxyl groups of SAS as manufactured and/or placed on the market. Further, no reference was provided for the data presented in the figure. In addition, Mathias and Wannemacher (1988) and Gazzano et al. (2012) have shown differences in the overall Si-OH density between different [redacted] forms [redacted] which could be attributed to differences in flame temperature during the production.

The hydroxylation state is an important parameter that affects the reactivity and agglomeration state of SAS and can differ between SAS forms. The effect of the surface conditions, including the number of hydroxyl groups, is also shown by the differences in toxic potential between untreated and surface treated SAS [redacted]. Therefore, the current request is considered relevant and of importance.

- According to the review of prof. Dekant and Colnot (2013), the histopathological changes observed (including fibrosis) are in line with findings related to the well described "lung overload" phenomenon.

  However, ECHA interprets the results by [redacted] differently, and does not see the fibrosis as a result of a high particle load. [redacted] measured the total amount of silicon (Si) in the lungs. The results show that Si levels were lowest for [redacted], in comparison to [redacted] and [redacted]. Further, [redacted] was more rapidly cleared from the lungs; no or only minimal levels of silicon were detected at 13 weeks post exposure and thereafter. Si levels in rats treated with [redacted] and [redacted] were still detected at 39 weeks post exposure. In case the observed fibrosis was caused by a high particle load, Si levels should have been highest in lungs of rats exposed to [redacted] that showed the highest incidence of fibrosis. Further, fibrosis would also have been observed in rats exposed to [redacted], which caused higher Si levels than [redacted]. The data by [redacted] clearly show that there is no correlation between the incidence of fibrosis and the silicon content in the rat lung. Further, fibrosis was already observed at low levels of 1 mg/m^3 [redacted] and 6 mg/m^3 [redacted]; the incidence observed at 1 mg/m^3 is comparable to the incidences observed at 30 mg/m^3 for [redacted] and [redacted]. This further contradicts that the fibrosis is due to exposure to high particle numbers. These data altogether show that it is highly unlikely that fibrosis was caused by a relatively high pulmonary particle load but that it is due to specific characteristics of [redacted] SAS.

Considerations of proposals for amendment and Registrant(s)' comments on them

a. Proposals for amendment were made by ECHA Secretariat, indicating to provide information in Section II on the possibility to provide already available information for repeated dose toxicity inhalation (90-day) and information for repeated dose toxicity inhalation (90-day) on different forms than those specified by the evaluating MSCA. Further, proposals for amendment were made by a MSCA proposing to clarify or delete a statement that another parameter (other than hydroxylation state or specific surface area) may be of higher importance for the reactivity and/or toxicity of SAS and that information from request 1 shall be taken into account. The Registrant(s) did not share ECHA's concern on repeated dose toxicity via inhalation. They did agree with the evaluating MSCA that the proposed testing is not scientifically justified. Further, they requested a stepwise approach to consider the physicochemical test results (request 1), in the decision for any additional inhalation toxicity study.

   In request 2, a study shall be performed with four specific forms of SAS, but it is not clear yet which specific forms of SAS these will be. These four SAS forms can only be

identified after information of request 1 becomes available. Currently, there is no information on the physicochemical properties of each registered SAS form. It is therefore not known which SAS forms have the lowest/highest specific surface area and the lowest/highest hydroxylation state. Potentially one of the requested SAS forms for testing may already have been examined in a 90-day toxicity study, including sufficient characterization. This study may even already be included in the registration dossier. In such a case, additional testing may not be necessary. It should be noted, however, that in the studies provided so far, a full characterisation of the SAS form tested is lacking. Section II of the Draft Decision was amended. Further, according to the REACH regulation all available information shall be included in the registration dossier(s). The proposal by ECHA may imply that this was not done yet or that all information shall only be included when specifically requested in a decision.

The eMSCA agreed that the statement may lead to uncertainty in the request. Based on the available information, it considered the specific surface area and the hydroxylation state to be the most important parameters that influence the toxicity of the different SAS forms, which is further specified in section III, request 1. Therefore, a 90-day study with the indicated SAS forms is requested. ECHA considers this as essential information to clarify the initial concern. Based on the first PfA by the MSCA mentioned above, the Draft Decision was amended only in section III, making clear that a 90-day study is requested with the indicated SAS forms. The statement in section III that different SAS forms may be used was deleted from the Draft Decision.

b. Another proposal for amendment was made by ECHA Secretariat, proposing to provide in section III a justification on the request in relation to the concern and the specified forms. The Registrant(s) agreed with ECHA Secretariat that a sound scientific justification for the request for 90-day inhalation studies is missing.

   The registration dossiers include many different forms of SAS that have not been characterised. Moreover, the toxicity studies lack adequate information regarding the characteristics of the substance that has been tested. As a consequence, based on the current dossier information, it cannot be verified if the most potent forms of SAS have been tested and are covered by the dossier information. If the dossier information is not representative for the most potent forms of SAS, this may mean that the current DNEL is not protective for all registered SAS forms. Based on the available information and expert judgement, the specific surface area and hydroxylation state are considered to be the most important physicochemical properties that may influence the toxic potency of SAS. The specific surface area may impact the solubility and reactivity of SAS; the hydroxylation state influences the surface reactivity and exposure of SAS (see section III, request 1).
   The data described by [redacted] indicate that induction of fibrosis by SAS will only occur upon long-term treatment of at least 90 days with an additional recovery period. To examine the induction of fibrosis and the possible differences in potency between SAS forms, toxicity studies with shorter exposure times (such as a 28 day study) will not be sufficient. Therefore, 90-day toxicity study with sufficient recovery times is requested.

c. One MSCA did not consider that the requested inhalation toxicity studies will contribute additional useful information on the hazard identification and risk management, and made a proposal for amendment to reject the requested studies. They stated that the current data are sufficient to support classification of SAS for repeated dose toxicity and the lung effects are in their opinion consistent with

particle overload. The Registrant(s) supported this MSCA's proposal to reject the request for new data. In their comments on this proposal and ECHA's proposal they referred to the many studies that are performed since the 1950s and considered the data set complete, supported by external experts and the outcome of the OECD HPV program. They considered the justification for inhalation toxicity studies to be based on misunderstanding and overestimation of the [redacted] data. They agreed on the MSCA's comments on classification.

The concern addressed in this decision is related to the large number of SAS forms that are registered within one joint registration. Based on the current dossier information it is not clear whether the available data are representative for [redacted] SAS form and whether the derived DNEL is applicable to all registered forms of SAS.

The most severe effect observed upon treatment to [redacted] SAS by inhalation is fibrosis. In the study by [redacted] the occurrence of fibrosis in exposure to [redacted] was very consistent: i) there was a clear concentration-related increase in incidence of fibrosis and ii) four independent recovery exposure groups at all three concentrations tested showed comparable incidences of fibrosis. Further, this study showed differences in treatment-related effects between SAS types and between untreated and surface-treated SAS, showing that untreated [redacted] SAS was the most potent SAS type for the induction of fibrosis. These differences in toxicity between the SAS types and between untreated and surface-treated [redacted] SAS are related to differences in physicochemical properties. Such variation in physicochemical properties also exists between different SAS forms of the same SAS type. Therefore, it cannot be ruled out that [redacted] SAS forms, other than [redacted], may be more potent in inducing pulmonary fibrosis.

The current data are insufficient for risk management, as it is not clear whether the data are representative for all registered SAS forms. To address the concern, information on the most potent forms of SAS is required. Therefore, additional inhalation information on the four indicated forms is requested to ensure that the most potent forms are studied. It cannot be ruled out that another form of SAS than the ones currently tested may be more potent and induce fibrosis at a lower concentration, resulting in a lower DNEL. Therefore, it is highly relevant to perform the requested 90-day toxicity study with the requested forms.

The evaluating MSCA did not agree with the MSCA that submitted a proposal for amendment that the observed changes in the lungs are consistent with particle overload. The observed fibrosis cannot just be attributed to the number of SAS particles for the following reasons:

1. Fibrosis is already observed at 1 mg/m^3 [redacted] SAS (the lowest concentration tested), but not at exposure to 30 mg/m^3 of [redacted] or [redacted] SAS, although the number of particles will have been considerably higher in the latter two exposures.
2. Lung silicon content is lowest for [redacted] SAS as compared to the other two SAS types tested. All three types had similar exposure concentrations of approximately 30 mg/m^3.

[redacted] measured the total amount of Si in the lungs. The results showed that silicon levels were lowest for [redacted], in comparison to [redacted] and [redacted]. Further, [redacted] was quickly cleared from the lungs; no or only minimal levels were detected at 13 weeks post exposure and longer. Si levels in rats

treated with [redacted] and [redacted] were still detected at 39 weeks post exposure. If the fibrosis would have been solely caused by a high particle load, pulmonary fibrosis would also have been expected in rats exposed to [redacted], for which significantly higher Si levels in the lung were observed than for [redacted]. The lung silicon contents for [redacted] and [redacted], as observed in the [redacted] study, therefore support the conclusion that the fibrosis is not caused by particle overload but is specific for [redacted] SAS. Further, fibrosis was already observed at low levels of 1 mg/m3 and 6 mg/m3 [redacted]. These data altogether suggest that it is highly unlikely that pulmonary fibrosis in rats exposed to [redacted] is the result of particle overload.

The evaluating MSCA did therefore not agree to reject the requested studies and did not see a reason to amend the Draft Decision.

The evaluating MSCA did agree with the MSCA that the statement regarding classification is at this moment premature and has amended in the Draft Decision.

As previously indicated in section III.1 (response to comment of Registrant(s) on request 1), the Cefic LRI program includes studies performed with [redacted] SAS, while the focus of the concern is related to exposure to [redacted] SAS. Further, the OECD HPV program clearly states that SAS possess properties indicating a hazard for human health (repeated inhalation toxicity). Only based on exposure information, priority is set as low. This does however not indicate that SAS is not hazardous. In addition, none of the studies performed with SAS are performed with a proper characterization of the test substance.

d. A proposal for amendment was made by a MSCA to measure the hydroxylation state of the substance prior to testing, to understand the influence of storage time and storage conditions. The Registrant(s) did not agree with this proposal, stating that the hydroxylation state does not alter over time.

   The evaluating MSCA agreed that the measurement of the hydroxylation stage provides useful information on the possible changes in properties during storage. In the Decision, it was included in section III that the test substance shall be fully characterised prior to testing according to request 1. This shall be performed shortly before testing to take account of the possible changes in properties during storage.

   The evaluating MSCA did not see any evidence in the provided formal documents that the hydroxylation state of all SAS types does not alter over time. Information on the hydroxylation state over time was provided informally, however, the data were obtained via the SEARS methods, in which the hydroxylation state is directly related to the surface area and not measured independently.

e. A proposal for amendment was made by a MSCA, proposing to examine the collagen content in the required 90-day toxicity studies. The Registrant(s) did not dispute this proposal, however, they also emphasized that they do not support the request for additional 90-day inhalation toxicity studies.

   The evaluating MSCA accepted the proposal of the MSCA to include collagen content as an additional endpoint to measure in the 90-day toxicity studies and amended the Draft Decision accordingly.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit for the registered substance that is manufactured, imported and/or placed on the market a sub-

chronic toxicity study (90-day; OECD 413), in rats via the inhalation route, with the four [redacted] SAS forms as manufactured that represent:

i. the lowest specific surface area with the lowest number of hydroxyl groups,
ii. the lowest specific surface area with the highest number of hydroxyl groups,
iii. the highest specific surface area with the lowest number of hydroxyl groups,
iv. the highest specific surface area with the highest number of hydroxyl groups.

and the following modifications:

1. Two additional recovery groups of animals shall be included: one group of 5 animals/sex with a 13-week recovery period after exposure and one group of 5 animals/sex with a 26-week recovery period after exposure;
2. Clinical pathology and ophthalmological examination may be excluded;
3. Gross pathology and histopathology shall be conducted on the lungs, trachea, nasopharyngeal tissues, nasal associated lymphoid tissue and larynx; other organs and tissues may be excluded from examination;
4. The aerosols shall have a maximum mass median aerodynamic diameter (MMAD) of 3 µm. There will be no lower size limit;
5. Bronchoalveolar lavage (BAL) shall be conducted and the following parameters shall be included: total and differential leukocyte counts, total protein, lactate dehydrogenase and pro-inflammatory cytokines/chemokines;
6. Collagen content shall be measured in lungs and associated lymph nodes.

The test substance shall be fully characterised shortly before testing according to request 1 as presented above. The granulometry shall additionally be analysed by using Scanning Mobility Particle Sizer (SMPS) (ISO 15900:2009; ISO 10808:2010; ISO 28439:2011) combined with Aerodynamic Particle Sizer (APS). Further, Registrant(s) shall provide the date of manufacture of the substance and the date(s) of performance of the physicochemical and toxicity tests (including information on storage time and storage conditions in between tests).

The four SAS forms to be tested can only be identified on the basis of information provided under request 1. In case for one of the identified forms a subchronic toxicity study (90-day, via inhalation) is available (taking into account the modifications to OECD 413 indicated above), and the tested form[9] is fully characterised according to request 1 of this Decision, this information may be provided.

In absence of any existing toxicological information in the registration dossiers on the most potent SAS form, ECHA takes the view that testing of these four extremes of SAS will provide sufficient information to assess whether the most potent forms of SAS are represented by the registration dossiers. Provided that the Registrant(s) submit a well documented scientific justification that less than the four indicated SAS forms are sufficient to cover the most potent forms of [redacted] SAS, the test may be performed on these form(s). The evaluating MSCA will examine the information provided by the Registrant(s). In case the concern is still not clarified or new information raises further concerns, additional testing may be requested in a new decision based on the information that is provided in response to the current decision.

3. Uses of SAS

Establishing the concern

In the registration dossiers a list of uses of SAS by industrial workers, professional workers and consumers is included. The uses are applicable to SAS as one substance; no information is provided on the uses of each individual SAS type or each SAS form[8]. [redacted] and the potential high exposures, there is a concern about the risk of SAS and information on the exposure to SAS is therefore in demand.

Justification why new information is needed

The registration dossiers do not contain any exposure assessment and risk assessment. According to the Registrant(s), SAS is not a hazardous substance and they state that in line with REACH further exposure assessment and risk characterisation are not required.

However, ECHA does not agree with the conclusion of SAS not being hazardous. The study by [redacted] demonstrates that pulmonary fibrosis is induced upon treatment to [redacted] SAS at a dose level of ≥ 1.3 mg/m^3. According to ECHA, the findings of the available inhalation studies, including the severity of the effect (fibrosis) and the dose level at which the effect is seen, could be considered for classification of SAS for repeated dose toxicity.

SAS is used in a wide variety of industrial applications (ECETOC, 2006). Exposure to silica can occur for workers in industrial settings, professional workers and consumers. The route of exposure and concentrations to which humans are exposed will depend on the type of application and use, including the life cycle phase in which exposure takes place. In the current available information in the registration dossier, the uses are described without further specification to the SAS types and/or SAS forms that it applies to.

Further, the registration dossier claims that, in the commercial products, the fraction of particles in the whole-size range of air-borne particles that is potentially able to reach the thoracic and alveolar site is [redacted]. This claim is based on the analysis of only four SAS forms[9], without further grounds to support that these four forms are representative for all other registered SAS forms. Moreover, it does not address the full life cycle of these forms. Therefore, the claim is insufficiently founded in the dossier.

Furthermore, exposure measurements described by ECETOC (2006) indicate that occupational exposure levels could reach up to 10 mg/m^3 total silica, of which 3.4 mg/m^3 as respirable SAS, indicating that more than 30% of the SAS present in air at the workplace can be respirable. Data that are more recent (1996 – 2003) displayed SAS concentrations of up to 3 mg/m^3 inhalable dust and up to 1 mg/m^3 respirable dust. Total dust concentrations were not described. These data indicate potential exposure to respirable SAS at a level that may result in pulmonary toxicity and show the need for more detailed information about potential inhalation exposure scenarios for SAS and subsequent risk characterisation.

The information request

It is requested to provide information on the uses of each individual form of SAS. Based on the provided information, a selection of relevant exposure scenarios and relevant SAS forms can be made. To ensure safe use of SAS, it may be necessary to provide exposure

[8] See Annex I for abbreviation and terminology.
[9] See Annex I for abbreviation and terminology.

estimations in a follow up of the present decision. Such an estimation shall include the exposure levels to respirable SAS and to inhalable SAS.

Summary of Registrant(s)' comments and response to comments

In the initial draft decision that was sent out to the Registrant(s) information on inhalation exposure and exposure scenarios for all the SAS types and forms were requested. The Registrant(s) considered the request for inhalation exposure assessment of all uses and for each form of SAS not appropriate. According to them, the registration dossiers demonstrate that SAS requires no hazard classification and therefore does not require any exposure scenario to be developed.

The Registrant(s) were informed that the substance evaluation process, which focuses on specific concerns, allows to request information from Registrant(s) that goes beyond the basic information requirements of REACH, and as such also information on exposure on various uses could be requested. Moreover, according to the eMSCA, the information in the registration dossiers clearly indicates that SAS is a hazardous substance due to its repeated dose toxicity via inhalation. Therefore, information on the specific uses of SAS and exposure estimations are of high relevance.

Upon discussion with the Registrant(s), the eMSCA reconsidered and adapted its request. As a first step, more information on the uses of the individual SAS forms is required, to enable a targeted exposure assessment for only a selection of SAS types/forms and scenarios.

Considerations of proposals for amendment and Registrant(s)'s comments on them.

A proposal for amendment was made by a MSCA to include the assessment of human exposure and risks in section II. The Registrant(s) did not agree with this proposal. They stated that this proposal contradicts with the REACH Regulation, in which it is specified that exposure and risk assessment are only required where a substance is hazardous.

ECHA agrees that there is a need for human exposure information to assess the potential risks of exposure to SAS. However, prior to any information on human exposure more information on the uses of the individual SAS forms is required. Based on the uses information, it can be further decided if and to what extent additional information on exposure is required to address the concerns.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit for the registered substance that is manufactured, imported and/or placed on the market information on the uses of each individual form of SAS[10] that is manufactured, imported and/or placed on the market.

4. Physicochemical properties on surface-treated SAS

Establishing the concern

The registration dossiers of synthetic amorphous silica covers several types of silica, which are pyrogenic SAS, precipitated SAS, silica gel, colloidal SAS and surface-treated SAS. As surface treatment may affect the characteristics of the registered substance, an underestimation of the hazards cannot be excluded based on the available data.

[10] See Annex for abbreviation and terminology.

Consequently, the risks during exposure to surface-treated SAS may not be adequately controlled.

Justification why new information is needed

Purposely applied and environmentally acquired coatings can have a major impact on nanomaterial interaction with biological systems. The type of coating on the outer surface of a given nanomaterial determines its stability to degradation or aggregation in a given medium. In addition, the choice of coating is usually application driven and has a direct influence on the binding of the nanomaterial with e.g. biomolecules, lipids, or proteins, and thus can affect the interaction of the nanomaterial with biological systems. The coating and core together control the properties of a given nanomaterial. Each combination of a nanomaterial and a coating has to be considered as an individual case when safety evaluation of a specific nanomaterial is considered (SCENIHR, 2010).

[redacted] have studied [redacted] and [redacted], which is surface-treated [redacted], in a repeated dose toxicity study. The results showed that [redacted] induces toxicity in the lungs, but with differences in effects as compared to [redacted], including lower lung collagen content, no/less fibrosis, higher silicon content in the lungs and additionally granuloma-like lesions (not seen for [redacted]). These data indicate that differences in toxicity between surface-treated and non-treated SAS can be expected.

No information on characteristics of surface-treated SAS was included in the dossiers. To enable safety assessment of all registered SAS forms, all available information on surface-treated SAS shall be included in the dossiers.

The information request

As a first step in safety assessment, information on physicochemical properties of surface-treated SAS shall be provided. Since no information was included in the dossier, surface-treated SAS were dealt with separately from untreated SAS in this substance evaluation. The relevant physicochemical properties are the same as requested for untreated SAS. In addition, information on the surface treating agent(s) is necessary to evaluate the safety of the specific combination of the nanomaterial and the surface treating agent.

As indicated for request 1, REACH allows for substances to be assessed by the use of grouping approaches. By analogy to Section 1.5 of Annex XI of the REACH Regulation, which sets out the conditions to be met by alternative methods, equivalent information on all forms shall be obtained in such a grouping approach. The grouping strategy shall fulfil those conditions, both in relation to 1) the documentation provided and 2) the scientific rationale of the grouping approach. The information that shall be addressed is further explained in Section III, request 1.

Summary of Registrant(s)' comments and response to comments

- According to the Registrant(s), following the direction provided by ECHA in FAQ 6.3.8, surface-treated SAS does not have to be registered separately from the non-surface-treated SAS under REACH.

  According to ECHA, the published FAQ explicitly limits the applicability of the FAQ to 'macroscopic particles', i.e. it does not apply to nanomaterials. Furthermore, the answer to FAQ 6.3.8. clearly states that any specific hazards or risks of the surface treated substance should be appropriately covered by the chemicals safety assessment. Surface treatment may alter the characteristics of materials. Especially in case of SAS, that consists of primary particles in the nanoform and may have a large specific surface area. Surface treatment of SAS may therefore cause other

toxicity and/or has a different potential than untreated SAS, as was demonstrated by [redacted]. Based on the current information in the registration dossier it is not clear if surface-treated SAS is used safely. Information on the characteristics and toxicity is required to properly evaluate the risks of all forms of SAS, including surface-treated SAS. Finally, the substance evaluation is a risk-based process and is not restricted to the standard REACH requirements.

- According to the review of prof. Dekant and Colnot (2013), the available data indicate no significant differences in alveolar particle accumulation between surface-treated and non-surface-treated SAS. However, in the study by [redacted] the same [redacted] SAS, with and without surface treatment was studied, showing clear differences in the toxicity profile, both qualitatively and quantitatively. The results of the additional two 90-day inhalation studies that were discussed in the review (surface-treated pyrogenic, precipitated SAS) do not refute these conclusions.

Considerations of proposals for amendment and Registrant(s)' comments on them.

a. Proposals for amendment were made by ECHA Secretariat, who proposed to include the grouping approach in Section II and in Section III, including a reference in Section III to the read-across criteria as established in Annex XI, and to include a paragraph with additional information as was also included in request 1. The Registrant(s) supported ECHA Secretariat 's proposal to include the grouping approach in Section II and agreed with the proposal to indicate in section III why the current grouping proposal is not sufficient. The Registrant(s) did not agree with the proposal to include the specified paragraph with additional information in Section III, because the paragraph specifically requires physicochemical properties for each form of surface treated SAS. In addition, the Registrant(s) did not agree that only the Registrant(s) of the substance know the details of each of its forms necessary for their characterization.

The evaluating MSCA agreed with the proposals made by ECHA Secretariat and amended the Draft Decision. Therefore, an additional paragraph was included to indicate the possibility for a grouping approach, see also request 1. This grouping could also addresses the Registrant(s)' comment made on the characterization of each individual surface treated form of SAS. ECHA Secretariat's PfA lead to some additional arguments why the above mentioned FAQ 0038 (formerly FAQ 6.3.8) is in this case not applicable:

As noted by the Registrant(s) on page 24 of their comments, the surface treatment of particles is not specific for nanomaterials. In order to ensure adequate reporting of surface treated substances in view of their hazard assessment, a REACH FAQ was developed in 2008 by ECHA, the Member States, the Commission and stakeholder organisations.[11]

While drafts of the FAQ did include carbon black, calcium carbonate, kaolin and silica as examples of materials that are surface treated and where the FAQ would be applicable, there is no reference to "nanomaterials" in any of the documented consultations during the review process.

The documented supporting rationale for removing the example is "*As naturally occurring silica is exempt from registration (according to Annex we feel that the given example is not correct.*" Based on this, it can be concluded that the Rehcorn review process was considering silicas such as sand and not SAS as implied by the Registrant(s)[12]. From the absence of any documented discussion on nanoforms, it can be understood that the

[11] FAQ 6.3.8 "Do I have to register chemically **surface treated** substances?"

[12] Final report on FAQ 2.2 update; REHCORN/14/2008

phrasing of the FAQ to refer to surface treatment of "macroscopic particles" is an explicit exclusion of nanomaterials.

Moreover, the interpretation of this FAQ must be seen in light of the objectives of REACH. In that respect, ECHA considers that the provisions of an FAQ developed for "macroscopic particles" whose "surface makes a minor contribution to the substance" does not address particles that would fulfil the criteria to be considered nanomaterials according to the Recommendation on the definition of nanomaterial.

The impact that surface treatment may have on the properties of forms that fulfil the Recommendation on nanomaterial is also explicitly reflected in the recent Guidance notes on sample preparation for the safety testing of nanomaterials published by the OECD[13] where the relevance of surface treatment for hazard assessment of nanomaterials is explicitly addressed:

> *"such modifications have been shown to significantly affect the chemical reactivity of a nanomaterial and thereby its potential effects on (or interactions with) living organisms and the environment."*
>
> *"therefore the surface functionality of a nanomaterial is likely to have a strong impact on its (eco)toxicological behaviour"*

In addition the OECD Working Party on Manufactured Nanomaterials (WPMN) listed surface treatment as an endpoint for phase 1 testing of nanomaterials at the level of "nanomaterial information/identification".[14].[15]

b. Proposals for amendment were made by two MSCAs.
A proposal from the first was to add the DLS method in the request for surface-treated SAS. The Registrant(s) did not agree with this proposal, as the method is not standardized for surface treated SAS.
The evaluating MSCA suggests to use the same methods as are indicated for non-treated SAS, in request 1. According to the evaluating MSCA, the combination of methods is considered to be sufficient to determine the particle size distribution of the different SAS forms. In addition, in section III it is included that the Registrant(s) may consider that a requested test method is not suitable in order to characterise the substance and it is the Registrant(s)' responsibility to precisely characterise their substance and justify the reasons in case another test method is used. The Draft Decision was amended.

All other proposals for amendment on request 4 from these MSCAs were the same as the proposals from these two MSCAs for request 1. The comments of the Registrant(s) were also the same as provided for request 1. A reference is made to the responses and explanations as made for request 1 (see Considerations of proposals for amendment and Registrant(s)'s comments on them).

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[13] No. 36 - ENV/JM/MONO(2012)40 available at http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono(2012)40&doclanguage=en

[14] No. 27 - ENV/JM/MONO(2010)46 available at http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono(2010)46&doclanguage=en

[15] ENV/CHEM/NANO(2009)4/ADD6 available at: http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=ENV/CHEM/NANO(2009)4/ADD6&docLanguage=En

Conclusion

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit for the registered substance information on the following physicochemical properties of each individual surface-treated SAS form[16] that is manufactured, imported and/or placed on the market, using the indicated test method(s) under standardised conditions that are fully described:

a. The granulometry, which shall include primary particle size, aggregate/agglomerate size and particle size distribution (number-based). Method for powders is Transmission Electron Microscopy (TEM) combined with Energy Dispersive X-ray (EDX), Laser Diffraction and Sieving; method for suspensions is Transmission Electron Microscopy (TEM) combined with Dynamic Light Scattering;
b. The specific surface area (by volume). Method: for powders BET (ISO 9277:2010); for suspensions calculation based on theoretic model;
c. The hydroxylation state. Method: infrared spectroscopy;
d. The surface treating agent(s), including chemical identity (IUPAC name and numerical identifiers (CAS and EC)) and type of reaction with the SAS surface;
e. The water solubility. Method: enhanced OECD 105 Flask Method for SAS including Tyndall effect measurement of the solution;
f. The density. Method: OECD 109 Density of Liquids and Solids, pour and tap method for solids and immersed body method for liquids;
g. The dustiness. Method: rotating drum method (prEN 15051-2);
h. The point of zero charge. Method: microelectrophoresis or electrophoretic light scattering to be performed at fixed low salt concentration and at fixed particle concentration.

The information on the physicochemical properties shall be provided for each individual surface-treated SAS form of silicon dioxide and shall be provided for the substance form as produced, processed and placed on the market. Only the Registrant(s) of the substance know the details of the surface treatment, if any, of these forms. Based on this knowledge, the Registrant(s) may consider that a test method requested by ECHA is not suitable in order to characterise a specific SAS surface-treated form. Nevertheless, it is the Registrant(s)'s exclusive responsibility 1) to ensure that ECHA is in a position to characterise precisely each surface-treated form of the substance and 2) to justify the reasons in case another test method is used instead of a method explicitly required in the present decision.

As an alternative, grouping may be used to provide information on physicochemical properties of SAS forms. In such case the Registrant(s) shall provide a clear justification and documentation as further specified in section III request 1.

5. Toxicological data on surface-treated SAS

Establishing the concern

The registration of synthetic amorphous silica covers several types of silica, which are pyrogenic SAS, precipitated SAS, silica gel, colloidal SAS and surface-treated SAS. However, no information on toxicological data on surface-treated SAS was included in the dossiers. As surface treatment may affect the toxicity of the registered substance, an underestimation of the hazards cannot be excluded based on the available data. Consequently, the risks during exposure to surface-treated SAS may not be adequately controlled.

[16] See Annex I for abbreviation and terminology.

Justification why new information is needed

As described above for request 4 (section III), each combination of a nanomaterial and a coating has to be considered as an individual case when safety evaluation of a specific nanomaterial is considered (SCENIHR, 2010). More specifically for SAS, differences in toxicity were observed between [redacted] and the [redacted] (which is [redacted].

The results by [redacted] raise concerns about the adequacy of the current available dataset (on untreated SAS) for the surface-treated SAS. The results showed that [redacted] induces toxicity in the lungs, but with differences in effects as compared to [redacted], including lower lung collagen content, no/less fibrosis, higher silicon content in the lungs and additionally granuloma-like lesions (not seen for [redacted]). These data indicate that differences in toxicity between surface-treated and non-treated SAS may be expected. The hazard of the registered substance may be underestimated, and subsequently risks may not be adequately controlled.

The information request

All available toxicological information on surface-treated SAS shall be provided, to enable the evaluation of all SAS forms and determine on the safe use of SAS. Together with the information on characteristics, the toxicological data on surface-treated SAS will be evaluated further to determine if any safety concerns will remain. Further studies can be required on surface-treated SAS depending on the quality of the toxicological information submitted.

Considerations of proposals for amendment and Registrant(s)'s comments on them

A proposal for amendment was made by a MSCA. They proposed to indicate in section II that further studies can be required on surface-treated SAS depending on the quality of the toxicological information submitted. The Registrant(s) rejected the proposal for amendment. They mention that a justification for the comparability of untreated SAS and treated SAS is described in a review by Prof. W. Dekant and Prof. T. Colnot, which fulfils the information request.

The evaluating MSCA does not agree with the Registrant(s) that the review of Prof. Dekant and Prof. Colnot provides sufficient justification to conclude that non-treated SAS and surface-treated SAS are equivalent in their toxicological profiles. In the study by [redacted], the same [redacted] SAS with and without surface-treatment was examined. The differences in the toxicity profiles clearly show that surface-treatment can considerably alter the toxicity of a SAS type or form. The results of the additional two 90d-inhalation studies as discussed by Prof. Dekant (surface-treated [redacted], precipitated SAS) do not refute these conclusions.

The evaluating MSCA agreed to amend the Draft Decision according to the proposal of the MSCA.

Conclusion

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit for the registered substance that is manufactured, imported and/or placed on the market all toxicological information on surface-treated SAS as available to the Registrant(s). This includes all exposure routes, all toxicological endpoints and all forms of surface-treated SAS. Further, a scientific justification shall be provided that substantiates if and why the toxicological information on untreated SAS can be used for safety assessment of surface-treated SAS.

Considerations of other proposals for amendment and Registrant(s)' comments on them.

A proposal for amendment was made by ECHA Secretariat to grant more time to Registrant(s) to comply with the requests, at least an additional 3 months. The Registrant(s) agreed with the proposal to grant more time and suggested a minimum of 24-30 months or a minimum of 36 months.

The evaluating MSCA agreed with ECHA Secretariat that an additional 3 months, resulting in 24 month is more appropriate in view of the requested information.

A second proposal for amendment was made by ECHA Secretariat to delete the Section 'Adequate identification of the composition of the tested material' of the decision. The Registrant(s) did agree or had no comments on this proposal.

The evaluating MSCA agreed to delete the Section 'Adequate identification of the composition of the tested material' of the decision and amended the Draft Decision accordingly.

IV. Avoidance of unnecessary testing by data- and cost- sharing

Avoidance of unnecessary testing and the duplication of tests is a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between Registrant(s). Since several Registrant(s) of the same substance are required to provide the same information, they are obliged to make every effort to reach an agreement for every endpoint as to who is to carry out the test on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation.

If ECHA is not informed of such agreement within 90 days, it shall designate one of the Registrant(s) to perform the tests on behalf of all of them. If a Registrant performs a test on behalf of other Registrant(s), they shall share the cost of that study equally and the Registrant performing the test shall provide each of the others concerned with copies of the full study reports.

This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments/draftdecisioncomments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

V. General requirements regarding Good Laboratory Practice

ECHA always reminds Registrant(s) of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as

adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above. [17]

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

Leena Ylä-Mononen
Director of Evaluation

Annex I: Abbreviations and terminology

Annex II: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

[17] OECD, 2012, Guidance on sample preparation and dosimetry for the safety testing of manufactured nanomaterials, Series on the Safety of Manufactured Nanomaterials No. 36, JT03332780, ENV/JM/MONO(2012)40, 18-Dec-2012

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Annex I- Abbreviations and terminology

SAS	synthetic amorphous silica (excluding surface-treated forms)
SAS types	pyrogenic silica, precipitated silica, silica gel and colloidal silica
SAS forms	all individual size grades and trade names that can be identified separately per SAS type, based on differences in characteristics.
Surface-treated SAS	surface modified SAS by a chemical or physical reaction
Grades	different forms of SAS, referred to as grades by the Registrant(s).