Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide

EC Number: 272-697-1

CAS Number: 68909-20-6

CLH-O-0000006735-67-01/F

Adopted

5 December 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILANAMINE, 1,1,1-TRIMETHYL-N-(TRIMETHYLSILYL)-, HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide
EC number: 272-697-1
CAS number: 68909-20-6
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Japan	Japan Business Machine and Information System Industries Association	Industry or trade association	1

Comment received

Japan Business Machine and Information System Industries Association (JBMIA) appreciates the opportunity to give our comments on the proposal for Harmonized Classification and Labelling for silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

In the CLH report for silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide, classification of the substance as STOT RE 2 is proposed.

The classification of the substance as STOT RE 2 is proposed based on the results of the 90-d inhalation rat study for Aerosil R 974 which is an analogous substance (IIIA6.4.3_01).

However, in the same report it is also stated that "all the observed effect were characteristic of an inflammation and were reversible" and "the effect could be mainly related to a pulmonary overload and no dose-response relationship could be established" for the study.

These effects are not intrinsic to the substance but are considered to be common to PSLT. Classification of substance in the CLP Regulations should not be given based on these results.

About JBMIA:
Japan Business Machine and Information System Industries Association (JBMIA) is the industry organization which aims to contribute the development of the Japanese economy and the improvement of the office environment through the comprehensive development of the Japanese business machine and information system industries and rationalization thereof.
The advancement of information technology has brought about sophistication of the age of digitalization and networking and resulted in significant changes in the office environment accordingly. In response to the shift of business emphasis from the hardware to total business solutions including products, JBMIA carries out active committee/group activities regarding important issues that the industries are confronting in and outside Japan by conducting investigations and researches regarding the policy proposals, international cooperation, prevention of warming, environment preservation, standardization, product safety, etc., by deepening the association with the sales and software-related companies, as well as the manufacturers.

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Dossier Submitter's Response

It has been considered that these effects were directly related to the nature of the active substance since these are the direct consequences of SiO_2 inhalation after a 90-d exposure period.
We agree that this kind of effect is not specific to silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

RAC's response

RAC reviewed various inhalation studies with silanamine, both acute and chronic. In all studies a prominent and consistent clinical symptom observed in animals was respiratory distress. Histopathological findings supported local inflammation, as well as congestion and oedema. Indications of tissue remodelling (increase in collagen content) and tissue injury (increased LDH, NAG activity) were also available, despite the fact that the main histopathological finding of fibrosis was reviewed (Weber *et al.*, 2018) and downgraded to fibrogenesis. These adverse findings, although reversible and adaptive (for inflammation), explain and account for the breathing difficulties, which may persist after the end of exposure. The response to silanamine repeated exposure via inhalation appears to be quite substance specific. All in all, the respiratory distress varying from difficulties in breathing to slight dyspnea and shortness of breath is attributed to silanamine exposure via inhalation. Clearly symptoms are observed both after acute and repeated exposure, with considerably lower doses after repeated exposure.
Regarding the PSLT (poorly soluble low toxicity) particle properties please refer to comment #5 below. In addition, SAS is indeed cleared from the lung through the lymph

nodes, although not that rapidly and when cleared, inflammation progresses from the lung to the mediastinal lymph nodes.

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Belgium	Association of Synthetic Amorphous Silica Producers (ASASP)	Industry or trade association	2

Comment received

The Members of the Association of Synthetic Amorphous Silica Producers, ASASP, a Cefic Sector Group, hereby take the opportunity to provide input to the public consultation on the proposed hazard classification of Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica (EC No. 272-697-1), i.e. AEROSIL® R 812 S, in the following abbreviated as 'HMDZ surface-treated SAS', as STOT RE 2 (H373) by the French Competent Authority.
During a careful review of the CLH proposal, ASASP realised that not all critical and up to date information pertaining to the inhalation hazard of HMDZ surface-treated SAS may have been considered by the French Competent Authority during their report drafting. ASASP requests for including the more recent information that was not presented in the original active biocide application for HMDZ surface-treated SAS under the Biocidal Products Directive 1998/8 for considering the French CLH proposal. Full references are provided in the accompanying reference list.
General comments:
The French Competent Authority justifies its proposal to classify HMDZ surface-treated SAS as STOT RE 2 (H373) based on effects reported for a 90-day rat inhalation toxicity study with AEROSIL® R 974, which was carried out by the contract laboratory TNO (TNO, 1987). AEROSIL® R 974 is a hydrophobic synthetic amorphous silica (SAS) and has been surface-treated with dichlorodimethylsilane (DDS). In 1991, based on material from the original study, TNO reported slight to moderate increase of lung collagen content with signs of focal interstitial fibrosis, granuloma like lesions and septal cellularity in the lungs of rats after inhalation exposure to AEROSIL® R 974 (Reuzel et al., 1991). The French Competent Authority considered these findings to meet the classification criteria for STOT RE 2 (H373). No further data or information was presented in the CLH Report for supporting the classification proposal.

Recently, a re-analysis of the lung tissue slides of the original TNO study was conducted by an expert pathology working group (PWG). This was carried out according to the current criteria for pathology assessment (EPL, 2016; Weber et al., 2018). This re-analysis clearly demonstrated that focal interstitial fibrosis, an irreversible disease, was not present in the lungs of the AEROSIL® R 974 exposed rats at any point in time. The study pathologist of the original TNO study, Dr. Ruud Woutersen, agreed with the outcome of the PWG's re-evaluation of the original lung slides in a subsequent statement (Woutersen, 2017).
The effects observed with AEROSIL® R 974 represent markers of typical inflammatory responses of the rat lung after continued high exposures to particles, which may persist over a long time (ECETOC, 2006). Ultimately, all effects of AEROSIL® R 974 were fully reversible and cannot be termed adverse according to WHO/IPCS definitions (WHO, 2004). Accordingly, the conditions that would trigger a STOT RE 2 classification as detailed in Paragraph 3.9.2.7.3 (Annex I) of the CLP Regulation (EC, 2008) and related ECHA guidance documents (ECHA, 2017) have not been met. ASASP thus disagrees with the French Competent Authority's interpretation of the TNO study and their conclusion

that the effects observed in this study meet the CLP STOT RE 2 (H373) classification criteria.
ASASP also points out that, in addition to the incomplete interpretation of the TNO (1987) study, the CLH report does not consider the value of existing animal inhalation studies with similar SAS materials or epidemiological studies done in SAS production plants. The CLP Regulation requires the consideration of the weight of evidence of all relevant information pertaining to the hazard of a substance including physico-chemical properties, animal data or occupational exposure data. In particular, regarding HMDZ surface-treated SAS, the key information requiring consideration when assessing repeated dose toxicity via the inhalation route is
• SAS is rapidly cleared from the lung. SAS is soluble under physiological conditions and therefore has little persistence in the lung. Clearance occurs by hydrolysis or phagocytosis by alveolar macrophages.
• No intrinsic toxicity of SAS. There is no indication of systemic toxicity following repeated inhalation of SAS including AEROSIL® R 974 at the sole exposure concentration of 34.7 mg/m3.
• Effects induced in the lung by SAS-inhalation are reversible, hence adaptive and not adverse. Numerous inhalation toxicity studies have been conducted with hydrophilic and hydrophobic SAS, including AEROSIL® R 974. All SAS grades show a similar pattern of toxicity during inhalation toxicity studies, representing an adaptation of the lung to high and sustained particle exposure (e.g., transient increases in inflammation, markers of cell injury, and lung collagen content; macrophage accumulation). Both, hydrophilic and hydrophobic SAS do not induce progressive fibrosis in the lung. Hence, all effects are limited and fully reversible with no severe consequences on organ function.
• Epidemiological studies demonstrate absence of effects of worker exposure to SAS on lung function. SAS have a long history of production and use. No indication of pneumoconiosis or other exposure-related pulmonary diseases were observed in epidemiological studies. The particle sizes of commercial SAS handled do not penetrate the lung.
Considering all information, it is obvious to ASASP that HMDZ surface-treated SAS does not warrant a classification for specific target organ toxicity following repeated inhalation exposure. The proposal for a classification as STOT RE 2 (H373) by the French Competent Authority is neither based on a thorough evaluation of all available as well as up to date scientific information pertaining to the inhalation toxicity of SAS materials, nor on the appropriate consideration of the CLP criteria for a STOT RE 2 (H373) classification.
More detail, in particular with regard to the re-evaluation of the Reuzel study by the PWG, is provided in the attached pdf document entitled "ASASP1090a-CLH surface treated SAS PBS". ASASP hereby explicitly refers to the expert reviews conducted and submitted to this public consultation by Professors W. Dekant and L. Levy.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ASASP1090a-CLH surface treated SAS PBS.pdf

Dossier Submitter's Response

The study from Weber *et al*. has been published in November 2018 and therefore was not available when the CLH report of silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide has been provided by FR. Moreover, the CLH report is in line with the Assessment Report endorsed at EU level in November 2016 in the frame of the approval of the active substance under Regulation 528/2012.
Moreover, as stated in the document, the epidemiological data available were not considered fully reliable to be taken into account.

RAC's response
Regarding the overall assessment of silanamine toxicity via inhalation, please refer to RAC's response to comment #1. More specifically: • SAS is indeed cleared from the lung through the lymph nodes, although not rapidly and when cleared, inflammation progresses to the mediastinal lymph nodes. • Hydrophobic SASs, silanamine included, cause death by inhalation based on the studies discussed by RAC in the opinion that were included in the ECETOC and OECD reviews, which were specifically refered to in the CLH report. Additional key elements from studies in the open literature, such as Becker *et. al*. (2013), Pölloth (2012), EPA (2011) and JRC, are also discussed in the opinion, all providing evidence for the inhalation toxicity of silanamine. • Despite the fact that the histopathological effects induced in the lung by hydrophobic SAS-inhalation are reversible, and could be regarded as adaptive, at least for the part that included inflammation, they cannot be considered not adverse, as a persistent and consistent clinical symptom of respiratory distress is observed both in acute and repeated dose inhalation studies at various doses. Breathing disorders are not expected to disappear immediately after cessation of exposure and in the context of another pathological condition, such as an infection, could prove to be detrimental to health. Therefore, they cannot be ignored. In addition, the increase in lung collagen content (the specific Van Gieson stain was not used in the re-evaluation of Weber *et al.*, 2018, OH-proline was not re-measured) and the septal cellularity and alveolar broncholisation, still present at the end of the recovery period, reported as original findings in 1987, along with the high LDH and NAG activity in the lung lavage fluid (ECETOC, 2006; Wacker, 1998), have not been questioned. These findings could account for exposure-related fibrogenesis, tissue injury and structural remodelling of the lung, which are reversible but cannot be excluded as an adverse effect that could progress to fibrosis, if exposure persists and occurs in the presence of other detrimental pathology, such as an infection.

Date	Country	Organisation	Type of Organisation	Comment number
10.04.2019	Germany		Individual	3
Comment received				
The available rat inhalation toxicity study for AEROSIL® R 974, a hydrophobic synthetic amorphous silica (SAS), and a reevaluation of the reported lesion according to current standards were examined regarding consequences of the results for classification and labeling. In addition, relevant epidemiological data were evaluated. Classification of AEROSIL® R 812 S as STOT-RE 2 H373 is proposed based on results after repeated inhalation exposures of rats to AEROSIL® R 974 applying read-across. AEROSIL® R 974 inhalation was reported to induce the typical responses of the rat lung to high particle loads and focal interstitial fibrosis was diagnosed to be present in recovery groups sacrificed 13 and 26 weeks, but not 52 weeks after the termination of inhalation exposure. Slides from the study were reanalyzed applying current standards. The reanalysis of the original study sections clearly show that pulmonary effects following inhalation exposures to AEROSIL® R 974 were reversible after termination of exposure. AEROSIL® R 974 inhalation did not induce progressive fibrosis of the lung or systemic toxicity. As other SAS, AEROSIL® R 974 was rapidly cleared from lungs and lymph nodes after the end of the inhalation exposure periods. In addition, effects observed in the toxicity studies with AEROSIL® R 974 represent biomarkers of the reversible inflammation processes caused by the high particle loads. Therefore, changes in the lungs of AEROSIL® R 974-exposed animals are not adverse as they are reversible; "serious changes to the biochemistry or hematology of the organism" are not produced. A large number of occupational epidemiology studies do not give any indication for adverse lung				

effects in workers with occupational exposure to SAS. Due to the reversibility, the absence of any toxicity on other organs then the lung and of biochemical and hematological changes in experimental animals, and absence of adverse effects in the lungs of workers exposed to SAS, a classification of AEROSIL® R 812 S as STOT-RE 2 H373 is not warranted and is inconsistent with the guidance in EU legislation.
For details see uploaded pdf file.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment SAS-CL-March-2019-ECHA.pdf

Dossier Submitter's Response

The study from Weber *et al*. has been published in November 2018 and therefore was not available when the CLH report of silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide has been provided by FR. Moreover, the CLH report is in line with the Assessment Report endorsed at EU level in November 2016 in the frame of the approval of the active substance under Regulation 528/2012.

Moreover, as stetd in the document, the epidemiological data available were not considered fully reliable to be taken into account.

RAC's response

For a general assessment of silanamine toxicity via inhalation, please refer to RAC's response to comments #1 and #2.
RAC would also like to note that in the case of silanamine (SAS-HMDS), some alterations in pulmonary function (breathing) are consistent among the majority of the repeated dose inhalation studies with similar hydrophobic SASs. Hydrophobic SAS induced treatment-related effects reflecting inflammation of lung tissue, associated with a slight morphological tissue reaction (hypertrophy, partial hyperplasia of the bronchiolar epithelium, collagen remodelling). The vast majority of the effects disappeared during recovery, showing clear signs of reversibility. These effects could be regarded as adaptive (compensatory) changes (for inflammation), but the adversity of consequences and clinical toxicity (i.e. impaired breathing) upon cessation of exposure is not disputed. Similar effects (the clinical symptom of laboured breathing and respiratory distress) with the same target organ (lungs) are observed after single exposure to silanamine at doses not leading to mortality, but close (~ ½) to the LC_{50}. More specifically, the most common necropsy finding is darker lungs and white/red areas (discoloration) in the lungs (210 mg/m^3), depicting congestion and pulmonary haemorrhages, depending on the extent of discoloration (López, A. The Respiratory System, Mediastinum and Pleura: In, Pathological Basis of Veterinary Disease, 5th Edition. McGavin, Zachary Eds. Mosby. 2012). All effects are transient and are connected with the respiratory system, both the upper respiratory tract and the lungs themselves. The mechanism involved it is believed to be local inflammation, as suggested by the findings of the mechanistic study of the CLH dossier (A6.10 2005) and the histopathology. These effects are observed also in the repeated exposure inhalation studies clearly at significantly lower doses than the single exposure studies (even at 10.01 mg/m^3 in the Wacker (1998) study).

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	4
Comment received				
We note that the CLH-report is not a stand-alone document. A non-confidential Annex I is lacking, only a confidential annex Doc IIIA is available. Available studies in the report are only very briefly described, not allowing independent assessment and conclusion by the reader.				
Dossier Submitter's Response				
The CLH report is based on the documents initially presented in the Competant Authority Report (CAR) for this active substance prepared in the frame of the Regulation 528/2012. The Documents IIIA issued from the CAR present the study summaries related to the different study reports submitted in the dossier for approval of the active substance. These documents IIIA were submitted with the CLH report.				
RAC's response				
RAC reviewed the studies mentioned in the CLH report and all studies included in the references of the CLH report (CAR, ECETOC and OECD reviews), along with studies from the open literature (Becker *et. al*., 2013; Pölloth, 2012; EPA, 2011 and JRC) and the studies provided during public consulation (Weber *et al*. 2018).				

Date	Country	Organisation	Type of Organisation	Comment number
30.04.2019	Netherlands	<confidential>	Company-Importer	5
Comment received				
The proposal's scope is not made clear enough, and without more clarification, it will give rise to confusion among stakeholders, such as manufacturer, importers, and users of the substance identified with CAS 68909-20-6. It is quite reasonable to limit the scope only to the "nano" form of the substance, as only the respirable particulate is expected to cause the adverse effect under discussion. If so, then the proposal, if made into regulation, should give much a clearer definition and the boundaries and not just the IUPAC names, EC No and CAS No for the substance for which the proposed regulation will apply. In line with the scope definition used in Table 1 on page 2 (Primary particle size - range covered by this dossier: 6.9-8.6 nm; shape of primary particles - spherical), exactly the same narrowing of the substance specification properties should be applied in the section 2.1 that summarizes the proposed harmonized classification and labelling in Table 5 at the bottom of page 5. In the column "Notes", the line "Resulting Annex VI entry if agreed by RAC and COM" should be amended by both qualifiers of primary particle size and shape of primary particles. In addition, there should be guidance for the regulatory community how to apply the definition of the scope, including how to measure the parameters by which the business can determine whether the substance in question is in the scope or out of the scope. If no such guidance is given, then the purpose of "harmonized" classification and labelling will not be achieved, as each responsible party may apply the scope in different ways. Insofar it is necessary in our opinion not only to mention the required test equipment (TEM - Transmission Electron Microscopy) itself but also to specify the exact test method to be applied. The ideal standard would be a universally applicable OECD method for nano				

particles. In absence of such specific OECD method for TEM, ECHA should define the method(s) that is/are fully accepted for determination of the nano particle size in the EU.
Dossier Submitter's Response
We intended to redact this CLH dossier for the coumpounds refered as aerosil R812 and aerosil R812S as indicated in table 1 under the information "other name". This CLH report is not intended to apply to other coupounds that could be identified by the names and cas number reported in table 5. owever, the CLH template does not enable to clarify the diferenciation. The only criteria on nano form or only primary particule size and shape is not enough to define the substance classified.
RAC's response
The various forms of SASs are characterized by several physicochemical parameters such as SiO_2 content (%wt), carbon content (%wt), density (g/cm^3), loss on drying (%), water solubility (saturation) (mg/l, at ambient temperature and at 37°C and pH 7.1-7.4), pH (1:1 water:ethanol), specific surface area, B.E.T. (m^2/g), particle size measured by laser diffraction, behavior towards water etc., and the values thereof are reviewed in the literature *(*ECETOC, 2006; Polloth, 2012; Becker *et al.*, 2013; OECD SIDs, 2004). The substance covered by this CLH opinion belongs to the surface treated SASs with the chemical name "silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide" (EC: 272-697-1; CAS: 68909-20-6), with a molecular formula of $[SiO_2]_n$-$[OSi(CH_3)_3]_m$, where n > m. The m corresponds to the surface treatment of silica with methyl (alkyl) groups. It is a synthetic amorphous silica (SAS), which has been modified with hexamethylsilazane (HMDS, CAS 999-97-3) to give a hydrophobic SAS due to the trimethylsilyl-surface modified silica. The DS included in the SID the primary particle size, namely 6.9-8.6 nm, which is derived from the experimental data provided in the CAR by the applicant and covers specifically the products from this supplier. However, there are other major suppliers of similar products on the market, with product identifiers sharing the same CAS number, the same chemical name and similar primary particle size, at a range 5-20 nm (all relevant commercial products included) (Pölloth, 2012). These extra physicochemical parameters are necessary to describe a nanomaterial since size, shape and surface characteristics of a nanoform may cause the substance to exhibit a different behaviour compared to the non-nanoform of a material with the same composition (*Guidance on information requirements and chemical safety assessment; Appendix R.6-1 for nanomaterials*). These will be taken into consideration when RAC evaluates the results from the various testing protocols. In order to be fully compliant with Regulation 1272/2008/EC (CLP) and the description of the entries in Annex VI of CLP, RAC decides to include in the SID only the name and the EC and CAS numbers, i.e. **"silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide" (EC: 272-697-1; CAS: 68909-20-6)**.

Since in the name of the substance the material is clearly defined as a "nano", RAC is of the view that there is no need to define the particle size.

In the opinion and the Background Document an extensive description of several parameters is provided.

Date	Country	Organisation	Type of Organisation	Comment number
29.04.2019	Netherlands		MemberState	6
Comment received				

Read-across for environmental toxicity endpoints
The current proposal for no classification for environmental hazards is based on a read across. NL notices that the read across justification (beginning of section 10) is only based on physico/chemical characteristics of the substance (particle size, coating etc.). According to "Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals" a robust read-across justification should be based on more aspects like toxicity, fate and toxicokinetics. For ecotoxicity there is no data for the target substance, this, together with the differences in coating, particle size and hydrophobicity, would normally make the read across not acceptable. However, it is noticed that the ecotoxicity endpoints for the read across substance are > 10 000 mg/L, these values are far above any trigger for environmental classification. Taken into account that the hydrophobicity of the target substance is higher than that of the read across substances which reduces the bioavailability for water organisms and as such probably also reduces the toxicity, it is considered unlikely that the target substance will show any toxicity in the considered tests. Nevertheless we are in the opinion that a more robust read-across justification should be provided with reference to Appendix R.6-1 as mentioned above. When a more proper and more robust scientific justification is provided, we will agree with the proposal for no classification for environmental hazards.

Read-across for human toxicity endpoints.
The classification proposal is partly based on a read across with other surface treated, synthetic amorphous, nano surface treated silica. The substitute aerosil R 972 or R 974 differ in surface modification, i.e. with dichlorodimethylsilane instead of hexamethyl-silazane, however this is not believed to affect its toxicity because these groups have no particular activity themselves. However, it is unclear whether the coating is stable when the particles are taken up by the lysosomes of macrophages and, if not, whether different substances are formed within the microsomes. In addition, there may be differences in the rate at which the surface treatment is removed and the non-surface treated particles are present in the lysosomes. Please explain.
In addition, it should be explained to what extent the 'slightly lower' methyl-densities of the substitute aerosils (however, not defined), affect the available silanolgroups and whether this is of influence on the activity of these substances.

Like silanamine, aerosil R972 and R974 consist of spherical particles, however, these appear to be somewhat larger (12-16 nm compared to 6.9-8.6 nm according to the specifications) resulting in a smaller surface area. Though this could potentially result in a negative effect regarding inhalatory toxicity, with regard to the limited data available, and the precaution in drawing conclusions on the studies with aerosil R972 and R974, NL

agrees with applying read-across if the questions above are sufficiently answered.

Dossier Submitter's Response

Regarding read-across for human toxicity endpoints, there is no available information regarding the behaviour of the coating when the particules are taken up by lysosomes of macrophages. This point has not been investigated further.

RAC's response

The substance whose CLH is evaluated is the result of the reaction of synthetic amorphous silica treated with hexamethylsilazane (HMDS), leading to a silica characterised by CAS No 68909-20-6 and marketed under various trade names. The CLH report, as well as the opinion, do not apply to other non-surface treated silica, or crystalline silica.

The surface modification of the hydrophilic silica with dichlorodimethylsilane [DDS, CAS No. 75-78-5] results in a dimethylsilyl-surface modified silica [Silica dimethyl silylate, CAS No. 68611-44-9], abbreviated **SAS-DDS,** which is somewhat less hydrophobic than SAS-HMDS due to the lower density of surface methyl groups. These latter substances are used as read across in the CLH report, as well as in the opinion, since they are structurally similar to silanamine and share physical, chemical and toxicological properties.

The surface modification of the hydrophilic silica with polydimethylsiloxane (PDMS, CAS # 9016-00-6) results in a dimethylsilyl-surface modified silica [Silica dimethicone silylate, CAS 67762-90-7,], abbreviated **SAS-PDMS,** which is somewhat less hydrophobic than SAS due to the lower density of surface methyl groups. These latter substances are used as read across in this opinion, from studies found in the open literature and as supporting evidence to the key studies presented in the CLH report.

Thus, **SAS-HMDS** is the substance whose CLH is evaluated and **SAS-DDS** and **SAS-PDMS** are similar surface modified SASs used as read across substances (Table 1, below).

Table 1. Compilation of data specifications for the three hydrophobic silica either evaluated or used as read across in the opinion (ECETOC 2006; Polloth 2012; Becker *et al.* 2013; OECD SIDs 2004)

Property (units)	SAS-HMDS	SAS-DDS	SAS-PMDS
CAS	68909-20-6	68611-44-9	67762-90-7
Surface treatment	Hexamethyldisilazane HMDS	Dimethyldichlorosilane DDS	Polydimethylsiloxane PDMS
SiO_2 content (%wt)	≥ 99.8	≥ 99.8	≥ 99.8
Carbon content (%)	2.0-4.6 %	0.6-2.6	3.5-5.0
Loss on drying, (%)	< 1.0	< 1.0	< 1.0
Density (g/cm^3)	2.2	2.2	2.2
Water solubility (saturation), (mg/l) at 37°C and pH 7.1-7.4			
pH (1:1 water:ethanol)	4.5-8.0	3.6-5.0	4.0-7.0
Specific surface area, B.E.T. (m^2/g)	190-290	90-330	100-230
Behavior towards water	Hydrophobic	Hydrophobic	Hydrophobic
Particle size measured by laser diffraction			
Primary particle (nm)	5-20	5-20	5-20

Agreggate (µm)	0.1-1.0	0.1-1.0	0.1-1.0
Agglomerate (µm)	Mostly > 125	Mostly > 125	Mostly > 125

In order to evaluate human health toxicity, the biological reactivity and the toxicokinetics, availability in water systems included, are of major importance. Oral administration of SAS-PDMS to rhesus monkeys lead to expiration in the breath and excretion in the urine with a half-life of 24 hours, while after 92 hours more than 90% was recovered in the faeces. Inhalation of SAS-DDS by rats led to distribution in the lungs and mediastinal lymphnodes after 24 hours, while after three month > 80% of the test substance was eliminated (Becker *et al.*, 2013). The chemical structure of the hydrophobic SASs bears similarities enough to substantiate comparable biological reactivity (low hydroxylation state, di- and tri- methyl substituted silyl surface groups).

Toxicokinetics depend on water solubility. There is no established protocol to date to determine the solubility of hydrophobic powders and applying either the standard, or enhanced, OECD TG 105 methods show a high scatter of results or no real result. However, a recent report of Roelofs and Vogelsberger, 2004, reviewed in the Scientific Committee on Consumer Safety (SCCS), Opinion on the solubility of Synthetic Amorphous Silica (SAS), European Commission 2019, provided data on solubility and dissolution of hydrophobic SASs, based on the working hypothesis that if surface-treated SAS can be wetted, it should exhibit a certain solubility in water (kinetics will be different from non-surface-treated SAS). This hypothesis is supported by the literature on the degradation behaviour of silica in water and biological systems (Croissant *et al.,* 2017; Cauda *et al.,* 2010). The modified NanoGenoTox protocol (NanoGenoTox 2011) was used (ethanol 10% instead of 0.5%). The results showed that all hydrophobic SAS products analyzed so far exhibit a solubility between 100 and 160 mg/L in 10 % ethanol/water. It is expected that other surface-treated products not tested so far will be found to fit into that range. In that sense, taking into consideration the chemical structure similarity of the hydrophobic SASs (i.e. the dimethylsilyl moiety of SAS-DDS and SAS-PDMS should not alter the aforementioned properties when compared to the trimethylsilyl moiety of SAS-HMDS) and the similar behaviour in water described above, the read-across for the human health hazards can be substantiated.

At the same time, caveats exist. More specifically, there is lack of data regarding the human toxicity endpoints in order to compare the biological stability, behaviour and reactivity of the three surface treated SASs used in the opinion.

With regards to the environmental toxicity endpoints, under normal environmental conditions, silicon dioxide is an inert substance with no known degradation products. At ambient temperature and pH, hydrophobic SASs are practically insoluble in water. SASs are not volatile and have no lipophilic character. SASs are also photostable and there is no reason to believe that the slight differences in the surface of the SAS will alter the photoreactivity/stability of the SAS polymorphs. Thus, the hydrophobic SASs will settle mainly into soils/sediments and weakly into water. SiO_2 is expected to combine indistinguishably with the soil layer or sediment due to the chemical similarity with inorganic soil matter. Thus, although there is no experimental data to prove the same environmental behaviour/fate of the substance whose CLH is evaluated with the read across substances,

RAC believes that at ambient temperatures the surface coatings should be more stable than in the biological medium, and their environmental reactivity should be similar, while any differences between the di- and the tri- substituted coatings should be insignificant.

In addition, it is noted that a similar grouping approach has been widely accepted and used in the open literature for the three hydrophobic, surface treated polymorphs of SAS used in the opinion (i.e. SCCS, 2019; Becker *et al.*, 2013; Pölloth, 2012; EPA, 2011; ECETOC, 2006; OECD, 2004).

Regarding the non-treated, hydrophilic SASs, although they are used as read across for certain hazard endpoints in the CLH report, RAC decides not to consider them in the CLH evaluation of the SAS-HMDS classification based on significant differences they present compared to the silanamine both on the chemical structure (free OH groups) and on certain physicochemical parameters. More specifically:

- Surface chemistry: RAC believes that the surface chemistry of the hydrophilic and the hydrophobic forms of SAS differ substantially, as in the former case the surface consists of Si-OH (silanol) groups and in the latter of $-SiO(Me)_2$ and $-Si(Me)_3$ units. Moreover, there is no data to compare and prove that the surface chemistry of the hydrophilic and the hydrophobic polymorphs of SAS is similar.
- Hydrophobicity: Surface treatments converting hydrophilic into hydrophobic silica can only be expected to decrease the solubility of the materials. Hydrophobicity can influence agglomeration and sorption, as well as 'dispersibility in biological media' and dustiness. In the two SAS polymorphs the hydrophobicity is very different since the Si-OH, $-SiO(Me)_2$ and $-Si(Me)_3$ surface groups affect the behaviour of the two SAS forms. Moreover, this is the purpose of the surface modification of SAS, to alter the surface behaviour of SAS from hydrophilic to hydrophobic.
- Solubility: Rate of dissolution / Equilibrium solubility:

  The rate of dissolution depends on factors including, but not limited to the chemical composition, particle size, coating, surface treatment, stability, manufacturing process, and biological environment. The rate of dissolution gives information on how many ions/molecules are released from the particle over time. The ion(s)/ molecule(s) released may also dictate the toxicity of the nanoforms, which will be an important aspect of the CLH evaluation. In EPA (2011) hydrophobic SASs are reported as practically insoluble in water at room temperature, which is not the case with hydrophilic SASs. The surface-treated, hydrophobic silica in general had a lower solubility compared to the hydrophilic SASs, due to its hydrophobic surface and consequent reduced wetting of its surface in aqueous systems. Although in the SCCS 2019 report, it is stated that temperature plays an important role in the solubility behaviour of hydrophobic and hydrophilic SASs and that at 37°C in a medium mimicking biological fluids, hydrophobic and hydrophilic SASs present comparable solubility, still the hydrophobic SASs have almost 40% lower solubility. At ambient conditions, though, hydrophobic SASs solubility is negligible ($< 10^{-4}$ mg/L, EPA 2011). Therefore, RAC believes that hydrophilic SASs will always have higher solubility than hydrophobic SASs (the higher the temperature the lower the difference in solubility) and the dissolution rate will be different between hydrophilic

and hydrophobic forms of SAS. As a consequence hydrophilic SASs are not considered suitable for read across at least for the environmental endpoints, while for human health endpoints it could possibly lead to over-classification. Hence the read across from hydrophilic SASs was not considered supported in the opinion.

- Dispersibility:

  This parameter can influence the degree of environmental transport and (environmental) exposure. Furthermore, this parameter may influence the degree of internal exposure (particularly by the oral route; however particle dispersibility also affects nanomaterial mobility within the lung and hence its potential for systemic uptake). Dispersibility, is one of the fundamental differences between hydrophilic and hydrophobic SAS, especially in aqueous media.

In conclusion, although some physicochemical parameters between hydrophilic and hydrophobic SASs may be similar (i.e. particle size, surface area and shape), due to the significant differences between the two SAS polymorphs (hydrophilic and hydrophobic) described above, and especially the chemical differences (i.e. free OH in hydrophilic SASs), which could render hydrophobic SASs different in its biological and environmental reactivity and fate compared to hydrophilic SASs and the lack of relevant references to support and justify possible read across between the hydrophilic and hydrophobic forms of SAS, RAC has used only the hydrophobic polymorph for classification purposes (Table 1, above).

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.04.2019	Netherlands		MemberState	7
Comment received				
No information was provided on the carcinogenicity after inhalation exposure. There is a concern for carcinogenicity after inhalation seen the increase in 8-OH-guanine DNA adducts in the lung. In addition, the provided oral study has several limitations. Therefore, it should be made clear that the conclusion for no classification is based on absence of data. This is also applicable to several other endpoints.				
Dossier Submitter's Response				
Indeed, the provided oral study has several limitations, however, it has been considered that since silicon dioxide is a worldwide food additive, it was not considered as a carcinogen after oral exposure. Regarding long term inhalation exposure, no information was provided. We agree to include in the document that for inhalation route of exposure, the conclusion for no classification is based on absence of data.				
RAC's response				
RAC agrees with the comment above (#7) and believes that silanamine should not be classified for carcinogenicity, or for mutagenicity or reproductivity toxicity (fertility, developmental and lactation) due to inadequate, insufficient or inconclusive data or lack of data. See also RAC's response to comment #8 from Sweden.				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	8

Comment received

We would like to emphasize that the data do not allow to make a conclusion on the carcinogenic potential of Aerosil R 812 S and Aerosil R 812 based on available data. We prefer that it is stated in the CLH-report and/or RAC-opinion that classification is not warranted due to insufficient data.

Dossier Submitter's Response

The provided oral study has several limitations, however, it has been considered that since silicon dioxide is a worldwide food additive, it was not considered as a carcinogen after oral exposure.
Regarding long term inhalation exposure, no information was provided.
We agree to include in the document that for inhalation route of exposure, the conclusion for no classification is based on absence of data.

RAC's response

In the oral feed carcinogenicity study (IIA6.7), where the treated animals were inconspicuous and showed no clinical effects (the slight effect seen in the adrenals was of no toxicological significance), there were major deficiencies. There were only 20 animals/sex used and only one dose and no statistical test (lack of control group and comparison with historical controls). The dose, 100 mg/kg bw/d, was rather low since in a 6 months repeated oral dose toxicity study (IIA.6.4.1), with 500 mg/kg bw/d of SAS-DDS (Aerosil R972) no effects with toxicological significance were observed. According to the guidance for dose selection in repeated dose toxicological studies and carcinogenicity studies the highest dose level should be chosen to identify toxic effects including the principal target organs while avoiding severe toxicity, morbidity, or death of the animals. It is clear that the dose selected for this study did not fulfil the specification (Guidance on the Application of the CLP Criteria, Version 5.0 July 2017; OECD Draft Guidance Document N° 116).

The epidemiological study (IIA6.12) has the limitation that the exposure is mainly to hydrophilic SASs which are outside the scope of this evaluation. The exposure levels, the duration of exposure and the possible use of PPE are also unknown. Additionally, it has the general uncertainties associated with epidemiological studies, such as the exposure assessment and the limited sensitivity and statistical power to confirm the carcinogenic properties of a substance.

In conclusion, based on the limitations mentioned above and the lack of an inhalation carcinogenicity study although there is a concern, since there was an increase in 8-OH-guanine DNA adducts seen in the lung in an *in vivo* genotoxicity and gene mutation assay (no repair mechanisms taken into consideration), RAC agrees with comment #8 and concludes that **no classification due to insufficient data should be attributed to silanamine.**

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.04.2019	Netherlands		MemberState	9
Comment received				
An increase in 8-OH-guanine DNA adducts was observed in lung cells after intratracheal installation. Even though this change may be only temporarily, it is a change of the structure of the DNA. Therefore, it fulfils the definition for genotoxicity ((Paragraph 3.5.1.3). Therefore, it cannot be concluded that all studies were negative. However, an increase in genotoxicity in somatic cells in the absence of positive mutagenicity tests in vivo or in vitro is insufficient for classification.				
Dossier Submitter's Response				
Noted.				
RAC's response				
There is a series of *in vitro* tests (gene mutation test in bacteria, chromosomal aberration test and mouse lymphoma assay ($tk^{+/-}$ locus)) from the literature and the CLH report which are all reported as negative, although some of them with deficiencies (especially the bacteria tests, inappropriate for nanomaterials). In addition, in the Ames test summarised in the CLH report, where the actual data could be retrieved from the CAR, a weak mutagenic effect was reported in presence of S9 mix especially for the *S. typhimurium* TA 100 strain at the highest test concentrations. According to Ames *et al.* (1975), a compound is considered negative if when tested up to 500 µg/plate the number of colonies are not doubled compared to control. Doubling of the number of revertant colonies was only seen at the highest tested dose of 5000 µg/plate and it could be argued that this criterion was not fulfilled, although a dose-response in the increase of revertant colonies is noted. There is also an *in vivo* mechanistic study with equivocal results, which could indicate mutagenic properties for SAS-HMDS (no data on repairing mechanisms available) and there is no *in vivo* test in somatic cells to complete the integrated testing strategy for mutagenicity (Guidance on the Application of the CLP Criteria, Version 5.0 July 2017). Therefore, RAC believes that required studies are missing for a scientifically sound evaluation of the mutagenic properties of SAS-HMDS, and thus **no classification for mutagenicity due to insufficient/ inconclusive data is warranted for silanamine.**				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	10
Comment received				
We would like to emphasize that the data do not allow to make a conclusion on the mutagenic potential of Aerosil R 812 S and Aerosil R 812 based on available data. We prefer that it is stated in the CLH-report and/or RAC-opinion that classification is not warranted due to insufficient data.				
Dossier Submitter's Response				
Noted.				
RAC's response				
See RAC's response to the comment #9.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.04.2019	Netherlands		MemberState	11
Comment received				
An increase in missing sternebrae was reported for the developmental study in mice at the highest dose but considered not adverse for development. In our opinion missing sternebrea should be considered adverse and would warrant classification. However, also maternal mortality was reported at this dose level. Therefore, it could be argued that the developmental effect is secondary to the maternal toxicity. However, this requires additional information on the maternal toxicity such as the number of death mice and a justification. Regarding the read-across from non-surface treated SiO2 particles to surface treated SiO2 particles, see the general comments. In addition, the lower bioavailability of surface treated SiO2 particles should be better explained, as more hydrophobic substances (i.e. surface treated SiO2) usually tend to display a higher level of bioaccumulation.				
Dossier Submitter's Response				
The information regarding the number of death mice is not available. This study is from the ECETOC JACC Report No. 51 and no further detail is available. Regarding read-across for human toxicity endpoints, there is no available information regarding the behaviour of the coating when the particules are taken up by lysosomes of macrophages. This point has not been investigated further. Silicon dioxide is a worldwide food additive and no nigh level of bioaccumulation is expected. A potential of bioaccumulation has been expected after inhalation exposure leading to a proposal for classification.				
RAC's response				
See RAC's response to comments #6 and #12.				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	12
Comment received				
Adverse effects on sexual function and fertility There is only one poorly described one-generation screening reproductive toxicity study available of Aerosil R 972. Since there were severe limitations of this study (e.g. no test guideline, no GLP, few parameters investigated, only one dose, only 2 males, mating ratio 1:5, mating period 14 days) the negative results are considered to be of limited value and hence not sufficient for concluding on the potential of Aerosil R 812 S and Aerosil R 812 to cause adverse effects on sexual function and fertility. Adverse effects on the development of the offspring Since there is no information on the characterisation of the (hydrophilic) tested material amorphous non surface-treated silica (Syloid, silica gel) it is difficult to judge the relevance of the four developmental toxicity studies included in the CLH proposal for the (hydrophobic) surface treated amorphous silicon dioxide (Aerosil R 812 S and Aerosil R 812). Moreover, since only examination of external gross abnormalities and no histophathology				

were done on the pups in the one-generation reproduction toxicity study we cannot support the DS conclusion that there were no malformations in rat pups in this study. Overall, the available data do not allow making a conclusion on the potential of Aerosil R 812 S and Aerosil R 812 to cause developmental toxicity.
Dossier Submitter's Response
Noted.
RAC's response
Regarding toxicity to fertility, the key screening study of the CLH report with SAS-DDS (test material accepted for read-across by RAC) has major deficiencies. In addition, studies in the CLH report with the hydrophilic SASs show no effects on fertility, but have major deficiencies, too. In addition, hydrophilic SASs as testing materials are not accepted for read-across. There is some evidence from the supporting studies (subchronic studies, the oral chronic/carcinogenicity study and the studies from the Becker *et al.*, 2013) that the hydrophobic polymorphs of silica do not actually induce any effects on reproduction. However, RAC believes that an appropriate key study is missing and the data available is of poor quality. Thus, **RAC believes no classification for fertility due to inadequate and insufficient data is warranted**. There was lack of data for developmental toxicity on the hydrophobic SASs, both in the CLH report and in the open literature. The read across from hydrophilic SASs to the hydrophobic SAS polymorphs (silanamine is hydrophobic) is not accepted by the RAC. Nonetheless, the data presented are equivocal but give an indication that the hydrophilic SAS does not possess teratogenicity properties. The effects, which are not negligible, were only observed in the mouse (incomplete ossification/ missing sternebrae) out of the four species tested, under mild maternal toxicity conditions (not adverse) and the studies had several deficiencies. Based on all of the above, **RAC believes no classification for developmental effects due to lack of data is warranted**.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
29.04.2019	Netherlands		MemberState	13
Comment received				
STOT SE It is stated that there are no studies available for STOT SE. However, acute studies are available after oral and inhalation exposure. We suggest comparing the effects observed in these studies with the STOT SE criteria. STOT RE The classification proposal is partly based on a read across with other surface treated, synthetic amorphous, nano surface treated silica. The current proposed classification STOT RE 2, H373 (lungs, inhalation) by the submitter is based on a read across from the results of a 90-d inhalation rat study with Aerosil R 974, in which slight to moderate significant increase of the lung collagen content with signs of focal interstitial fibrosis, on the granuloma-like lesions and on septal cellularity (still present at 52 weeks of recovery) after inhalation exposure to 35 mg/m3 for 6h/day Aerosil R 974 was seen. This finding is				

used in order to classify the substance with STOT RE 2 according to the threshold by effects observed at a dose between 20 – 200 mg/m3 during 6h/day. We agree that the results of this study justify classification in category 2. However, this study does not exclude classification in category 1 because no group is available with exposure below 35 mg/m3. Therefore, information from the 14 day range-finding study should be taken into account. For a 14-day study, the guidance value for STOT RE 1 is 120 mg/m3 when applying Haber's rule according to paragraph 3.9.2.9.5. At the dose level of 80 mg/m3, several adverse effects on the lung where observed. In addition, an increase in RBC was observed. This is a compensatory effect showing that the lung function was severely affected. Therefore, the effects observed at 80 mg/m3 warrant classification as STOT RE 1.

Dossier Submitter's Response

STOT SE

The acute toxicity after oral and inhalation exposure are from the ECETOC JACC Report No. 51 (September 2006). In this document, there is only details on mortality occurring during these studies but no detail is given regarding potential effect on target organs. Therefore, it is not possible to use the results of these studies to fulfil the criteria for STOT SE classification.

STOT RE

Regarding the proposal to take into account the results of the range finding dose study, we propose to discuss this approach at the RAC level. Indeed, the use of the 90-d study is already challenged due to the biais observed in the study and using the range finding dose study performed prior the 90-d may increase the uncertainty. Details on effects observed during this study are not always reported.

RAC's response

See RAC's responses to comments #1, #2, #3, #4.

Date	Country	Organisation	Type of Organisation	Comment number
26.04.2019	United Kingdom		Individual	14

Comment received

see attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BCP Opinion - Len Levy 26thApril 2019.docx

Dossier Submitter's Response

The study from Weber *et al*. has been published in November 2018 and therefore was not available when the CLH report of silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide has been provided by FR. Moreover, the CLH report is in line with the Assessment Report endorsed at EU level in November 2016 in the frame of the approval of the active substance under Regulation 528/2012.
Moreover, as stated in the document, the epidemiological data available were not considered fully reliable to be taken into account.

RAC's response

See RAC's responses to comments #1, #2, #3, #4.

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Sweden		MemberState	15
Comment received				
We agree that a classification in STOT RE 2, H373 (lung) for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide is warranted based on findings in a 90-day inhalation repeated dose toxicity study of Aerosil R 974 in rat: slight to moderate significant increase of the lung collagen content with signs of focal interstitial fibrosis, granuloma-like lesions and septal cellularity (still present at 52 weeks of recovery) at 35 mg/m3. These findings are in agreement with effects considered to support classification for Category 1 and 2 as in listed in 3.8.2.1.7.3 (b) and (e). Moreover, we agree that the results from the available epidemiological study cannot be used as evidence of no effect and cannot rule out the pulmonary effect reported in rats.				
Dossier Submitter's Response				
Noted.				
RAC's response				
See RAC's responses to comments #1, #2, #3, #4.				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Japan	Japan Business Machine and Information System Industries Association	Industry or trade association	16
Comment received				
Japan Business Machine and Information System Industries Association (JBMIA) appreciates the opportunity to give our comments on the proposal for Harmonized Classification and Labelling for silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide. In the CLH report for silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide, classification of the substance as STOT RE 2 is proposed. The classification of the substance as STOT RE 2 is proposed based on the results of the 90-d inhalation rat study for Aerosil R 974 which is an analogous substance (IIIA6.4.3_01). However, in the same report it is also stated that "all the observed effect were characteristic of an inflammation and were reversible" and "the effect could be mainly related to a pulmonary overload and no dose-response relationship could be established" for the study. These effects are not intrinsic to the substance but are considered to be common to PSLT. Classification of substance in the CLP Regulations should not be given based on these results.				

About JBMIA
Japan Business Machine and Information System Industries Association (JBMIA) is the industry organization which aims to contribute the development of the Japanese economy and the improvement of the office environment through the comprehensive development of the Japanese business machine and information system industries and rationalization thereof.
The advancement of information technology has brought about sophistication of the age of digitalization and networking and resulted in significant changes in the office environment accordingly. In response to the shift of business emphasis from the hardware to total business solutions including products, JBMIA carries out active committee/group activities regarding important issues that the industries are confronting in and outside Japan by conducting investigations and researches regarding the policy proposals, international cooperation, prevention of warming, environment preservation, standardization, product safety, etc., by deepening the association with the sales and software-related companies, as well as the manufacturers.

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Dossier Submitter's Response

It has been considered that these effects were directly related to the nature of the active substance since these are the direct consequences of SiO_2 inhalation after a 90-d exposure period.
We agree that this kind of effect is not specific to silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

RAC's response

See RAC's responses to comments #1, #2, #3, #4.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	Belgium		MemberState	17

Comment received

BE CA thanks ANSES for this CLH proposal but has following remarks:
- Tests were performed with the substances Aerosil R 972 and Aerosil R 974. Aerosil R972 and R 974 are somewhat less hydrophobic than Aerosil R 812 S due to the lower density of superficial methyl groups. However no values are given for the water solubility of R972 and R974.

- For poorly soluble substances with no toxicity recorded at levels in excess of the water solubility the LC50 may be considered to be > than the water solubility on the condition that the maximum dissolved concentrations are achieved (validated by measuring the concentrations) [CLP guidance, I.4.2.]. However in none of the available studies for the 3 trophic levels the actual exposure concentrations was determined (no analytical monitoring performed).
Furthermore, substance loss from the water cannot be excluded :
* Studies were all performed under static regime

* Notwithstanding that the substance is considered highly stable, it is however no guarantee for maintaining the concentration in the water as other factors can contribute to loss of test substance. Under conditions of normal handling and use, it is considered that the substance forms aggregates. The aggregates can form agglomerates. Furthermore the substance is expected to combine with soil or sediment organic matter and adopt the same behaviour as natural silica (strong adsorption). The formed agglomerates and particulates can lead to precipitation and rapid loss of the substance in the water. Except for the algae study where the suspensions were filtered, no information is given in the other studies whether particulate matter was present in the water nor information was given on possible precipitation.
* Furthermore it should be kept in mind that the substance is produced and used as nanoparticles. In particular, ECHA's Guidance on information requirements and chemical safety assessment (R7b and appendix R7-1) clearly indicates that ecotoxicity testing of nanomaterials needs to be carried out with accompanying analytics to monitor the exposure concentration.

Moreover for ecotoxicity testing of nanomaterials other aspects should be kept in mind/taken into consideration, amongst others:
o Low solubility does not automatically result in limited exposure of nanomaterials in the aquatic environment
o in most cases the dissolution rate (in the relevant test media) should be considered instead of solubility for nanomaterials.
o If acute toxicity testing is chosen, the conditions and test settings must be assessed in order to prove that the exposure concentration is adequate and duration is long enough to capture potential toxic effects
o if the substance is poorly water soluble or for nanoforms with low dissolution rate in the relevant test media (daphnia, fish) long-term testing shall be considered

Seen the above, we question the reliability of the available aquatic toxicity studies and are of the opinion that the studies are inadequate and invalid for classification purpose of this nanomaterial.

Dossier Submitter's Response

We confirm that no solubility data are provided for Aerosil R 972 and R974. Nevertheless, like Aerosil R812 and Aerosil R812s, they are also considered insoluble. Dissolution rate could have supported the low solubility however no data is available.

Studies were carried out before the recommandations to test the nanomataerials were available. At present no additional tests are provided. Besides structural data indicate that when used, 95% particles in Aerosil R812 S and R 972 are over 2 µm. However, applying a high shear force on Aerosil R 812S, R972 and R974 lead to lower size particulate. Nonetheless, 50% volume fraction is measured over 120 nm for Aerosil R 974, over 179 nm for Aerosil R972, and over 150 nm for Aerosil R 812S. These data support that used and tested substances are not nano sized material in the environment.

However, at present only acute studies with no monitoring of the test substances were available whereas chronic studies are recommended for low water soluble substances, even when they are not nanomaterials.

RAC's response

RAC agrees with comment # 17 and recognizes that there are several and significant deficiencies in the studies regarding the evaluation of the environmental hazards.

- There are no studies with SAS-HMDS, only with the read across substances which have a slightly different surface coating. However, the read across justification is explained in the respective section of the opinion.
- The actual exposure concentrations of the substances were not measured in the available studies for the three trophic levels. However, it is noted that the nominal concentration of > 10000 mg/L is considerably higher than the value for triggering classification and much higher than the solubility of the material in water. The test media remained turbid throughout the test, indicating that the limit of solubility of the product was exceeded. The analytical monitoring and other test conditions were not protocol-compliant. Moreover, the protocol for poorly soluble substances was not followed.
- Although hydrophobic SASs are produced as nanomaterials, the protocol for nanomaterial testing was not followed. Low solubility versus dissolution rates, acute versus chronic testing are key aspects which are not discussed in the CLH dossier and data is not available. However, RAC is of the opinion that the structure of the substances, their similarity with the naturally occurring silica, their rather low toxicity profile and the available studies give evidence that hydrophobic SASs probably do not have environmental toxicity properties.

In addition, RAC agrees with the DS' analysis regarding, hydrolysis, photolysis in water and air and bioaccumulation. In relation to degradation, RAC adds that the organic coating of the hydrophobic SASs could make these substances more susceptible to both biotic and abiotic degradation as compared with the non-treated SASs, but still there is no data to support this hypothesis.

Regarding the mode of action, RAC supports the analysis from the CAR. Sorptive dusts primarily act through adsorption to the exoskeleton of the insects and absorption of lipid contained in the outmost layer of the epicuticula, while abrasive dusts act through mechanical grinding and abrasion of the insects´ wax layer. In either case, the insects get deprived of their functional water barrier. Based on experimental evidence (CAR), water adsorption by silica dusts appears to be of minor importance especially for the hydrophobic ones. The key process behind the desiccation effect on insects is the functional impairment or destruction of the lipid-wax layer cuticula, which renders the animal unprotected from water loss. In experiments with hydrophobic silica dusts which cannot adsorb water, the efficacy of the biocidal activity was higher than with silica dusts which can adsorb water. Lipids of the wax layer of the insect´s cuticle become enriched on the silica dust during treatment, while the wax layer becomes reduced. As a result, the interaction of the silica with the lipids of the insect´s cuticula is considered the key factor, whereby the hydrophobic character of the silica intensifies adsorption to the insect´s surface. Destruction of the lipid layer deprives the animal of its essential protective outer skeleton and thus causes desiccation.

In conclusion, the hydrophobic surface modified amorphous silica are, nearly insoluble in ambient temperature (<1 mg/L) and difficult to test according to the standard ecotoxicity guidelines. The studies carried out with higher concentrations than the solubility limit had significant deficiencies and the protocol for nanomaterials was not followed. Thus, as explained above, although it is rather unlikely that SAS-HMDS would pause an acute hazard to aquatic organisms, based on the available studies the CLP criteria cannot be applied and RAC proposes no classification for aquatic acute hazard due to insufficient data.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON SILANAMINE, 1,1,1-TRIMETHYL-N-(TRIMETHYLSILYL)-, HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2019	United Kingdom		MemberState	18

Comment received

Comments on silanamine (CAS: 68909-20-6)
We are unsure how relevant the bioaccumulation assessment and related CLP criteria are to inorganic nanoparticles and whether these need to be considered differently and separately from non-nano forms of substances. Guidance is currently lacking on this under CLP - although proposals have been made under GHS (including by France) to consider nanomaterials separately. Whilst we do not envisage silicon dioxide to present a bioaccumulation hazard under normal circumstances, the bioavailability and uptake of these nanoparticles (which have been intentionally surface modified to affect their hydrophobicity) might well be different or operate through different mechanisms and timescales. It may be that due to this uncertainty at least a Chronic 4 'safety net' classification, as could be required for a potentially bioaccumulative substance, is warranted.

Again, whilst silicon dioxide would normally be expected to be inert and the available acute ecotoxicological data do indicate this, the biocidal products concerned are specifically formulated to have biological activity (to control 'fowl-infesting ectoparasites' in poultry houses). From the Biocides CA Report, the mode of action includes adsorption to and disruption of arthropod exoskeletons and potentially cell walls - so affecting water retention. This might not occur in the same way with aquatic organisms (although it does occur at 100% humidity). However, longer term toxicity, e.g. accumulation/uptake via fish gills and by filter feeders has not been investigated. We feel this activity and the potential mode of action on terrestrial vs. aquatic organisms need to be elaborated in more detail to determine whether it might also be relevant to any aquatic life over longer timescales. We note that testing specific to nanoparticles has not been conducted, although OECD test guidelines are in development. We are generally uncomfortable with substances manufactured to be biologically active, such as biocides and pesticides, not even having a 'safety net' environmental classification - and the uncertainties surrounding the available testing and biological activity may be sufficient to warrant this. We propose this be discussed further by the Dossier Submitter and the RAC.

Dossier Submitter's Response

We agree that bioaccumulation assessment are not well developed for nanomaterials. Other mecanisms than lipophilic bioaccumulation could occur, however this methodological issue is still under discussion. As the surface treatment lead to a higher hydrophobility of the substance, available particules could sorb on membrane of aquatic organisms as they do on the wax of insects. However, it is not clear if particules would be available for pelagic organisms. Similarly, adsorption to organic matter of sediment could strongly limit the availability and the reactivity of particules for benthic organisms.
Please note that in the study of the mode of action, humidity is the relative humidity of air. Moreover, for several tested insects, the efficacy decreased when the relative humidity increased.
See also our answer to the comment 17 regarding the identification of the nano definition of the substance.

RAC's response

Please refer to RAC's response to comment #17.

Regarding the safety net classification aquatic chronic category 4, RAC recognizes that the mode of action (sorptive or abrasive) of silanamine is based on the functional impairment or destruction of the lipid-wax layer cuticula, which renders the animal unprotected from water loss and as a result could affect both aquatic and terrestrial organisms after chronic exposure.
However, according to the CLP regulation, the safety net classification, chronic hazard category 4, is appropriate in cases when data do not allow classification based on the CLP criteria but there are nevertheless some grounds for concern. This includes, for example, poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility, and which are not rapidly degradable and have an experimentally determined BCF ≥ 500 (or, if absent, a log Kow ≥ 4), indicating a potential to bioaccumulate. These substances will be classified in this category unless other scientific evidence exists showing classification to be unnecessary.
Silanamine is a poorly soluble compound for which no acute toxicity is recorded (although with insufficient data), not rapidly degradable (although probably more degradable than hydrophilic SASs) but also not bioaccumulative and thus it fulfils only two out of the three above criteria. In addition, adsorption to organic matter of sediment could limit the availability and reactivity of silanamine particles for aquatic and benthic organisms.
Thus, considering the biocidal activity of SAS-HMDS, its mode of action and the criteria for aquatic chronic 4 classification, in a weight of evidence approach, RAC concludes that a safety net classification for SAS-HMDS is not warranted.

PUBLIC ATTACHMENTS
1. ASASP1090a-CLH surface treated SAS PBS.pdf [Please refer to comment No. 2]
2. BCP Opinion - Len Levy 26thApril 2019.docx [Please refer to comment No. 14]

CONFIDENTIAL ATTACHMENTS
1. SAS-CL-March-2019-ECHA.pdf [Please refer to comment No. 3]