CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Chemical name:

Silica, amorphous, fumed, cryst.-free; Pyrogenic, synthetic amorphous silica, nano [1]

Silica gel, pptd., cryst.-free; Precipitated silica, silica gel, colloidal silica, amorphous, nano [2]

EC Number: -

CAS Number: 112945-52-5 [1] / 112926-00-8 [2]

Index Number:

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CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the pyrogenic silica

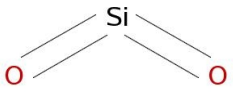
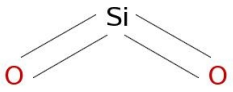
Name(s) in the IUPAC nomenclature or other international chemical name(s)	Dioxosilane
Other names (usual name, trade name, abbreviation)	Silica, amorphous, fumed, cryst.-free; Pyrogenic, synthetic amorphous silica, nano, pyrogenic silica, pyrogenic SiO_2, fumed silica, fumed SiO_2 Trade names include AEROSIL®, CAB-O-SIL®, HDK (see Annex I for trade names reported in the registration dossiers)
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	-
EC name (if available and appropriate)	Amorphous silica
CAS number (if available)	112945-52-5
Other identity code (if available)	
Molecular formula	SiO_2
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	60.08
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

Table 2: Substance identity and information related to molecular and structural formula of precipitated silica, silica gel and colloidal silica

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Dioxosilane
Other names (usual name, trade name, abbreviation)	Silica gel, pptd., cryst.-free; Precipitated silica, silica gel, colloidal silica, amorphous, nano, precipitated silica, silica gel, colloidal silica, hydrated silica Trade names include SIPERNAT®, LEVASIL®, ZEOSIL®, SYLOID®, LUDOX® (see Annex I for trade names reported in the registration dossiers)
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	-
EC name (if available and appropriate)	Silicon dioxide
CAS number (if available)	112926-00-8
Other identity code (if available)	
Molecular formula	SiO_2
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	60.08
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

The substance covered by this CLH proposal is synthetic amorphous silica (SAS), without surface modification.

SAS is a specific type of silicon dioxide. Other types of silicon dioxide are crystalline silica (e.g. quartz), natural amorphous silica (e.g kieselguhr), and by-products (e.g. silica fume). It is noted that the CAS number 7631-86-9 refers to all of these different types of silicon dioxide and does not refer specifically to SAS.

SAS can be produced via a thermal production process (pyrogenic silica) or a wet production process (precipitated silica, silica gel, colloidal silica). These different types of SAS are all registered in one REACH dossier. Each type of SAS can differ in physicochemical properties such as particle size, specific surface area, density, depending on the manufacturing, which results in many forms of SAS per SAS type (see Table 3). Despite this variation, the currently available evidence suggests toxicological properties are similar and the different forms of SAS only vary in potency.

Table 3: Compilation of physical and chemical properties of different SAS types (ECETOC 2006; Fruijtier-Pölloth 2012; OECD SIDS 2004)

Property (units)	Pyrogenic	Precipitated	Colloidal	Gel
SiO_2 content (% wt)	≥ 99.8	> 95	≥ 99.5	> 95 (dry)
Loss on drying (%)	< 2.5	5-7	50-85	2-6
Density (g/cm^3)	2.2	1.9-2.2	1.9-2.2	1.8-2.2
Water solubility (saturation), (mg/L) at 37°C and pH 7.1-7.4	144-151	141	Colloidal dispersion in water	127-141
pH (1:1 water:ethanol)	3.6-4.5	5-9	3.5-4.4 (4% w/v aqueous dispersion)	3-8
Specific surface area, B.E.T. (m^2/g)	50-500	30-800	50-380	250-1000
Primary particle size (nm)	5-50	5-100	1-10	1-10
Aggregate size in bulk (µm)	0.1-1	0.1-1	0.1-1	1-20
Agglomerate size in bulk (µm)	1-250	1-250	1-250	1-250

Exclusions from this proposal:

- SAS with surface modification. SAS can be modified at the surfaces, for example with silanes or siloxanes. One modified SAS has been evaluated by RAC, which is Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica. The surface modification may result in a different reactivity and potential differences in toxicological properties.
- Silicon dioxides other than SAS, such as quartz, kieselguhr, or silica fume. The structure and/or composition of those materials differs substantially from SAS, for example due to their crystalline structure or contamination with (heavy) metals.

Within this CLH proposal, the word SAS is used for synthetic amorphous silica without surface treatment and without specification of type. For specific types of SAS, the following terms are used: pyrogenic silica, precipitated silica, silica gel, colloidal silica.

1.2 Composition of the substance

Table 4: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
Silicon dioxide (CAS 112945-52-5; CAS 112926-00-8)	>= 99 - <= 100 %	None	None

Table 5: Impurities (non-confidential information) if relevant for the classification of the substance

No relevant impurities are present.

Table 6: Additives (non-confidential information) if relevant for the classification of the substance

No relevant additives are present.

Table 7: Test substances (non-confidential information) (this table is optional)

Not applicable.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 8:

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	Silica, amorphous, fumed, cryst.-free; Pyrogenic, synthetic amorphous silica, nano [1] Silica gel, pptd., cryst.-free; Precipitated silica, silica gel, colloidal silica, amorphous, nano [2]		112945-52-5 [1] 112926-00-8 [2]	STOT RE 1	H372 (respiratory tract) (inhalation)	GHS08 Dgr	H372 (respiratory tract) (inhalation)			

Table 9: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	hazard class not assessed in this dossier	No
Reproductive toxicity	hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	harmonised classification proposed	Yes
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

No previous or current classification is available for SAS, without surface modification.

In December 2019, RAC agreed that Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica, a SAS with surface modification, should be classified under CLP for category 2 specific target organ toxicity (STOT RE 2) for the lungs. In May 2022, STOT RE 2 was adopted in the 18th adaptation to technical progress (ATP) to CLP.

In December 2019, RAC also agreed on category 2 acute toxicity, via inhalation, however, this opinion was reconsidered in the RAC-65 meeting in June 2023. In that meeting, RAC agreed on no classification for acute toxicity due to inconclusive data.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

At present there is no harmonised classification for SAS without surface modification. There is a concern on repeated dose toxicity via the inhalation route of exposure. The concern was founded on the outcome of various repeated dose inhalation studies. In a recent substance evaluation, a (modified) 90-day inhalation study was requested (Fraunhofer, 2019). This study provided information on repeated dose inhalation toxicity, including insight in the effects induced, the influence of surface area on toxicity, and (ir)reversibility of the effects. Based on the adverse effects observed in this and previous studies, it was concluded that there is sufficient ground that SAS fulfills the criteria for classification as STOT RE. However, SAS is currently not self-classified for STOT RE. The dossier submitter disagrees with the current self-classification by the notifiers and/or registrants. Therefore, it is considered justified to draft a proposal for harmonised classification and labelling (CLH) for the endpoint repeated dose toxicity via inhalation.

5 IDENTIFIED USES

SAS has a wide dispersive use with a large variety of applications. It is used at industrial sites, by professional workers and by consumers.

SAS types are used amongst others in paints, lacquers, rubber products, cosmetics, metal surface treatment products, manufacturing of textiles, in adhesives and sealants. It is also used in biocidal products (e.g. disinfectants, pest control) and plant protection products. Processes that involve these uses include spraying, mixing and blending, and humans can be exposed via inhalation during manufacturing or use of the products.

6 DATA SOURCES

In the drafting of this CLH dossier information was used from the registration dossier of Silicon dioxide (EC Number 231-545-4, CAS Number 7631-86-9), scientific literature, the ECETOC report (2006), and the study report of Fraunhofer ITEM (2019).

7 PHYSICOCHEMICAL PROPERTIES

Table 10: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101.3 kPa	Solid	ECHA, dissemination website	
Melting/freezing point	> 526.9°C	ECHA, dissemination website	
Boiling point	Not relevant	ECHA, dissemination website	The study does not need to be conducted because the substance is a solid which melts above 300°C

Property	Value	Reference	Comment (e.g. measured or estimated)
Density*	2.2-2.4 g/cm^3	ECHA, dissemination website	
Vapour pressure	Not relevant	ECHA, dissemination website	The study does not need to be conducted because the substance is a solid which melts above 300°C
Surface tension	Not relevant	ECHA, dissemination website	Based on structure, surface activity is not expected or cannot be predicted. Not sufficiently soluble in water to assess.
Water solubility at 37°C, pH 7.1-7.4	Pyrogenic silica: 144–151 mg/L Precipitated silica: 141 mg/L Silica gel: 127–141 mg/L	Fruijtier-Pölloth, 2012	Colloidal silica: colloidal dispersions with water
Water solubility at 20°C, pH 5.5-6.6	Pyrogenic silica: 15–68 mg/L	Fruijtier-Pölloth, 2012	
Water solubility	All non surface-treated SAS types (silica gel, colloidal, precipitated and pyrogenic SAS): 100 mg/L or higher	ECHA, dissemination website	
Partition coefficient n-octanol/water	Not relevant	ECHA, dissemination website	Substance is inorganic. It is not soluble in octanol and water.
Flash point	Not relevant	ECHA, dissemination website	The substance is an inorganic solid that has a high melting point
Flammability	Not flammable	ECHA, dissemination website	
Explosive properties	Not explosive	ECHA, dissemination website	
Self-ignition temperature	No self-iginition	ECHA, dissemination website	
Oxidising properties	No oxidizing properties	ECHA, dissemination website	
Granulometry – primary particles size*	Pyrogenic silica: 5-50 nm Precipitated silica: 5-100 nm Silica gel: 1-10 nm Colloidal silica: 7-50 nm	Fruijtier-Pölloth, 2012	
Granulometry – aggregate size	0.1-1 µm	Fruijtier-Pölloth, 2012	

Property	Value	Reference	Comment (e.g. measured or estimated)
Granulometry – agglomerate size	1-250 µm	Fruijtier-Pölloth, 2012	
Stability in organic solvents and identity of relevant degradation products	Not relevant	ECHA, dissemination website	Inorganic substance, does not dissolve in organic solvent
Viscosity	Not relevant	ECHA, dissemination website	The substance is a solid

*Note that these values are slightly different compared to those reported by ECETOC and included in Table 3.

The solubilities reported fall within the range of values mentioned in the SCCS opinion on the solubility of SAS (SCCS/1606/19, 2019). SCCS concluded in this opinion that: "In regard to the nanomaterial definition in the Cosmetic Regulation, none of the SAS materials (hydrophilic or hydrophobic) included in the dossier can be regarded as soluble."

8 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Toxicokinetics data are limited to SiO_2 deposition in lungs and mediastinal lymph nodes, determined in animal experiments Table 11.

Data from pyrogenic and precipitated silica indicate that increased Si levels or SiO_2 particles could be detected in lungs and lymph nodes after exposure by inhalation. Some studies show that Si could not be detected 2-3 months after exposure, while others present that Si or SiO_2 particles were found even three months after end of exposure, indicating slow clearance.

Table 11 Summary of Si and SiO_2 measurements in lungs and mediastinal lymph nodes.

Method	Results	Remarks	Reference
Publications			
13-wk inhalation study rats; 6 h/day, 5 days/wk; nose-only. 1, 2.5 and 5 mg/m^3 SiO_2 particles detected with TEM and chemical analysis Test substance: precipitated silica (NM-200) Particle size not measured.	**Lungs** <u>1 day post-exposure</u>: 91, 172, and 307 µg (for 1, 2.5 and 5 mg/m^3 respectively) <u>1 and 3 months post-exposure</u>: calculated actual half-times of 30, 32, and 28 days respectively in the low, mid and high dose groups Statistically significant increases in silicon levels in the lungs were detectable on days 1, 30, and 90 post-exposure (all dose groups). Silica particles were found in the cytoplasm of intraalveolar macrophages in the lung and the cytoplasm of macrophages in the lung associated lymph node. **Lung-associated lymph nodes** TEM analysis confirmed the presence of SiO_2 particles up to day 90 post-exposure.	Particles were not detectable in the selected organs (nasal epithelium, trachea, larynx, liver, spleen, kidney, and mesenteric lymph node). Clearance was partly due to dissolution.	Anonymous 2014, reviewed by Creutzenberg et al., 2022
5-day inhalation study rats; 6	**Lungs**	Silicon levels in	Anonymous,

Method	Results	Remarks	Reference
h/day; nose only 1, 5, and 25 mg/m^3 Si measured in lungs and mediastinal lymph nodes using inductively coupled plasma atomic emission spectrometry (ICP-AES). Detection limits: 25-30 µg for ZEOSIL, 15 µg for SYLOID and CAB-O-SIL. Test substance: - Precipitated silica: ZEOSIL® 45 - Silica gel: SYLOID® 74 - Pyrogenic silica: CAB-O-SIL® M-5 MMAD ZEOSIL 45: 2.83, 3.23 and 3.27 µm at 1, 5 and 25 mg/m^3 respectively. MMAD SYLOID 74: 1 mg/m^3: 1.71 ± 0.16* 5 mg/m^3: 1.60 ± 0.14 25 mg/m^3: 1.57 ± 0.15 µm. MMAD CAB-O-SIL M5: 1 mg/m^3: 1.86 ± 1.10[a] 5 mg/m^3: 1.94 ± 0.95 25 mg/m^3: 1.70 ± 0.58 µm	<u>Levels at 1 day post-exposure - 25 mg/m^3</u> - ZEOSIL: 30-40 µg Si (64-86 µg SiO_2) - SYLOID: 76 µg Si (163 µg SiO_2) - CAB-O-SIL: 43 µg Si (92 µg SiO_2) <u>Levels at 1 month post-exposure - 25 mg/m^3</u> Below detection limit, with the exception of one male exposed to CAB-O-SIL with a level of 17 µg. <u>Levels at 3 months post-exposure - 25 mg/m^3</u> - ZEOSIL: 60-90 µg Si - SYLOID and CAB-O-SIL: below detection limit	lungs of animals exposed to the lower concentrations and in mediastinal lymph nodes of all exposed animals were below the detection limit at all time points.	2003c An Published by Arts et al., 2007
13-wk inhalation study rats; 6 h/day, 5 days/wk' whole body exposure Si content determined by flame absorption spectrometry. Test substance: - AEROSIL 200: 1.3, 5.9 or 31 mg/m^3 - SIPERNAT 22S: 35 mg/m^3 The range of the geometric agglomerate/aggregate size distribution was 1 to about 120 µm with maxima at about 10 and 100 µm. The aerodynamic agglomerate/aggregate size distribution was not possible to determine in the test atmospheres.	**Lungs** End of exposure: - Aerosil 200, 30 mg/m3: 0.1-0.3 mg - Aerosil 200, 6 mg/m3: 0.1 mg - Aerosil 200, 30 mg/m3: 0.2 mg - SIPERNAT 22S, 30 g/m^3: 0.5 mg <u>Recovery period</u> - AEROSIL: not detected during recovery period. - SIPERNAT: detected up to 26 weeks post-exposure, decreasing in time. No SIPERNAT was detected at 39 and 52 weeks post-exposure.	No quantitative Si levels provided.	Reuzel et al, 1991
13-wk inhalation study rats; 6 h/day, 5 days/wk; whole body exposure 50 mg/m^3	**Lungs** End of exposure: 883 µg 3-months post-exposure: 156 µg		Johnston et al., 2000

Method	Results	Remarks	Reference
Si analysis by emission spectroscopy. Test substance: Pyrogenic silica (AEROSIL 200) MMAD: 0.81 µm			
6-12 month inhalation study rats; 8 h/day, 5 days/wk 53 mg/m^3; whole body exposure Exp. I: continuous exposure up to 12 months. Rats were killed for study during the course of the exposure. Exp II: 6 month exposure, followed by a recovery period (normal air) up to 12 months Si analysis by chemical analysis Test substance: pyrogenic silica (DOW silica, AEROSIL) No MMAD or GSD	**Lungs – Exp I** 3 months exposure: 1.5 mg SiO_2 6 months exposure: 1.3 mg SiO_2 9 months exposure: 1.6 mg SiO_2 **Lungs – Exp II:** - 6 months exposure + 3 months post-exposure: 0.5 mg SiO_2 - 6 months exposure + 6 months post-exposure: 0.5 mg SiO_2 - 6 months exposure + 9 months post-exposure: 0.3 mg SiO_2 - 6 months exposure + 12 months post-exposure: 0.3 mg SiO_2	8h exposure per day. During the remaining 16 hours, the dust was allowed to settle, but a small amount remained suspended in the atmosphere of the room.	Schepers et al., 1957a
12-month inhalation study guinea pigs; 8 h/d, 5 days/wk 53 mg/m^3 ; whole body exposure Si analysis by chemical analysis Test substance: pyrogenic silica (DOW silica, AEROSIL) No MMAD or GSD	**Lungs** End of 12 month exposure: 2.5 mg 1-3 day post-exposure: 1.5 mg SiO_2 14 days post-exposure: 1.3 mg SiO_2 30 days post-exposure: 0.8 mg SiO_2	8h exposure per day. During the remaining 16 hours, the dust was allowed to settle, but a small amount remained suspended in the atmosphere of the room.	Schepers et al., 1957b
Only summaries available			
12-month inhalation study rats; 5 h/day, 5 days/wk 50 to 55 mg/m^3 total dust; 30 mg/m^3 respirable particles Test substance: pyrogenic silica (HDK® V15)	**Lungs** 3 days: 0.25 mg SiO_2 6 wks: 0.5 mg SiO_2 18 wks: 1.2 mg SiO_2 12 months: 1.37 mg SiO_2 5 months post-exposure: 0.16 mg SiO_2 **Mediastinal lymph nodes** 6 wks: 0.02 mg SiO_2 18 wks: 0.11 mg SiO_2 12 months: 0.13 mg SiO_2 5 months post-exposure: 0.047 mg SiO_2	No details available on exposure, measurement of SiO_2, or particle size	Anonymous, 1969 Only summaries available, from ECHA website, OECD SIDS (2004) and ECETOC (2006)
120-day inhalation study rats; 4 h/day, 5 days/wk Lower unspecified exposure for 40 days, 40-50 mg/m^3 for subsequent 80 days Test substance: pyrogenic silica (AEROSIL 150)	**Lung** End of exposure: 300 µg **Mediastinal lymph node** End of exposure: 135 µg	No further details available	Klosterkotter 1963 Only summaries available, from OECD SIDS (2004) and ECETOC (2006)
3-day inhalation study rats; 5h/day	**Lungs** 3 days exposure: 0.25 mg SiO_2	No further details available	Klosterkotter, 1969

Method	Results	Remarks	Reference
50 mg/m^3 Test substance: pyrogenic silica (HDK® V15)	1 month post-exposure: 0.105 mg SiO_2 3 months post-exposure: 0.018 mg SiO_2 **Mediastinal lymph node** 20h post-exposure: not detected 1 month post-exposure: 0.018 mg SiO_2 3 months post-exposure: 0.008 mg SiO_2		Summarized on ECHA website
12-month inhalation study rats; 5 h/day, 5 days/wk 112 mg/m^3 Test substance: pyrogenic silica (OX50)	**Lungs** 20h: 0.130 mg SiO_2 4 months: 1.578 mg SiO_2 12 months: 1.820 mg SiO_2 4 months post-exposure: 0.92 mg SiO_2 **Mediastinal lymph nodes** 4 months: 0.151 mg SiO_2 12 months: 0.430 mg SiO_2 4 months post-exposure: 0.814 mg SiO_2	BET: 55 m^2/g	Klosterkotter, 1968a Summarized in ECETOC (2006)
12 month inhalation study rats; 5 h/day, 5 days/wk 55 mg/m^3 Test substance: precipitated silica (FK700)	**Lungs** 20h: 0.138 mg SiO_2 4 months: 1.022 mg SiO_2 12 months: 3.443 mg SiO_2 5 months post-exposure: 0.457 mg SiO_2 **Mediastinal lymph nodes** 4 months: 0.033 mg SiO_2 12 months: 0.069 mg SiO_2 5 months post-exposure: 0.052 mg SiO_2	No MMAD. BET: 700 m^2/g	Klosterkotter, 1968b Summarized in ECETOC 2006
6-day inhalation study rats; 4h/day Concentration not reported Test substance: pyrogenic and precipitated silicas	**Lungs** 3 months: 73.8% eliminated from the lungs **Mediastinal lymph nodes** 3 months: small amounts present: - 0.6 - 3.5% of silica eliminated from lungs - 0.2 - 2.8% of total retained.	No further details available	Klosterkötter and Bünemann, 1961, 1962 Only summary available, from ECETOC (2006)
3-day inhalation study rats; 5 h/day 30 mg/m^3 Test substance: precipitated silica (TK 800 and Ultrasil VN3)	**Lungs** <u>TK800</u> 20h post-exposure: 0.31 mg SiO_2 1 month post-exposure: 0.11 mg SiO_2 3 months post-exposure: 0.06 mg SiO_2 <u>VN3</u> 20h post-exposure: 0.21 mg SiO_2 1 month post-exposure: 0.07 mg SiO_2 3 months post-exposure: 0.06 mg SiO_2 **Mediastinal lymph nodes** <u>TK800</u> 3 months post-exposure: 0.009-0.012 mg SiO_2		Klosterkotter, 1970 Summarized in ECETOC (2006)

Method	Results	Remarks	Reference
	VN3 1 month post-exposure: 0.005 mg SiO_2 3 months post-exposure: 0.013 mg SiO_2		

[a] MMADs during the last two exposure days were between 2.2 and 3.5 lm whereas these were about 1.2–1.3 lm during the first 3 days. The discrepancy between these measurement days was due to accumulations of test material in the flexible tubing connected to the APS. Using shorter tubing with less chance of accumulation resulted in larger MMADs because sedimentation preferentially affected the larger particles. Because of these results, particle size measurements were also repeated with Syloid 74 (*), resulting in almost twice as high MMADs, viz. 2.8–2.9 lm.

8.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

The data indicate that increased Si levels or SiO_2 particles could be detected in lungs and lymph nodes after exposure by inhalation and that clearance may be slow, taking months.

9 EVALUATION OF HEALTH HAZARDS

It is noted that the results are the interpretation of the dossier submitter and may differ from what is reported by the registrants. In Table 12, an overview is given of all uncoated SAS types and forms that have been used as test materials in the inhalation toxicity studies discussed.

Table 12: Comparative table of SAS types and forms included in the opinion

Name	Type	Specific surface area (BET) [m^2/g]	Purity
AEROSIL OX50	Pyrogenic	40-50	> 99.8%
Cab-O-Sil	Pyrogenic	400	> 99.8%
AEROSIL 200	Pyrogenic	200	> 99.8%
Cab-O-Sil M5	Pyrogenic	200	> 99.7%
VA-Kieselsäure LGS	Pyrogenic		
SIPERNAT 22S	Precipitated	190	98%
NM-200	Precipitated	190-220	
Kieselsäure FK 700/ SIPERNAT 700	Precipitated	700	
SYLOID 74	Silica gel	200	> 99.5%
ZEOSIL 45	Precipitated	250	> 97.3%
LUDOX	Colloidal	130	Colloidal silica particle dispersed in water
SiO_2 naked	Colloidal	-	-

9.1 Specific target organ toxicity-repeated exposure

Not included are three studies of which the reporting was too limited to be used, for example due to absent substance information or (almost) no description of the results. These studies were given Klimisch reliability score 4 (not assignable) by the registrants. This applies to the following studies:

- Non-guideline study from 1984 with HDK N20
- Non-guideline study from 1984 with HDK H2000
- Non-guideline study from 1984 with BS 111

Table 13: Summary table of repeated dose toxicity animal studies with pyrogenic silica

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
OECD 413 GLP According to ECHA substance evaluation decision: skipped the endpoints clinical pathology and ophthalmology. Gross pathology and histopathology was conducted on the lungs, trachea, lymph nodes, naso-pharyngeal tissues, nasal-associated lymphoid tissue (NALT) and larynx; other organs and tissues were excluded from examination. As an addition, collagen was analysed in lung tissue. Male and female Wistar rats [strain Crl:WI (Han)] 10/10 exp +1 d 5/5 exp + 90/180/360 d	AEROSIL Cab-O-Sil (SAS1) and OX50 (SAS2) (high and low surface area resp.) nose-only inhalation 0.5 mg/m^3, 1 mg/m^3, 2.5 mg/m^3 and 5 mg/m^3 (nominal) Mean MMAD (µm): SAS1 2.08-3.04 SAS2 1.30-2.20 Mean gsd: SAS1 2.16-3.53 SAS 2 2.90-3.53 90-d 6h/d, 5d/wk recovery periods of 0, 90, 180, 360 d	Effects induced by both SAS materials include interstitial inflammation, granuloma, fibrogenesis, and fibrosis of the lungs and lymph nodes. There was a clear link between surface area and the severity and persistence of the effects, with higher incidence, severity and duration associated with low BET particles. More details are provided in the text and tables below. LOAEC SAS 1 (high surface area): 1 mg/m^3 LOAEC SAS 2 (low surface area): 0.5 mg/m^3 Values according to the study report: LOAEC SAS 1: 2.5 mg/m^3 LOAEC SAS 2: 0.5 mg/m^3	Fraunhofer ITEM, 2019 (Two separate studies reported in one report)
Comparable to OECD 413 GLP Male and female Wistar rats, [strain Cpb: WU Wistar random] 20/20 exp	Aerosi1 200 1, 6, 30 mg/m^3 (nominal) MMAD could not be determined 13 wks 6h/d, 5d/wk	Dose dependent increases in accumulation of alveolar macrophages, cellular debris, intra-alveolar polymorphonuclear leucocytic infiltration,	Reuzel et al., 1991 and Weber et al., 2018

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
10/10 exp + 13/26/39 wk 20/20 exp + 52 wk	recovery periods of 0, 13, 26, 39, 52 wks	increased septal cellularity, alveolar bronchiolization, focal interstitial fibrosis, cholesterol clefts Fibrosis incidence increased with increasing duration of the recovery period LOAEC all effects: 1 mg/m³ LOAEC fibrosis: 30 mg/m³ Value according to the registration dossier: NOAEC: 1.3 mg/m³ (nominal: 1 mg/m³) In a re-evaluation of the slides of 10 males/dose no fibrosis was detected according to a newer scoring system, but only macrophage aggregations and granulomas, which appeared reversible within 13-52 weeks.	
OECD 413 Fischer 344 rats 4 male rats per time point focussed on pulmonary effects in comparison with crystalline silica	AEROSIL 200 50.4 mg/m³ air (analytical) whole body inhalation MMAD (µm): 0.81 13 wks 6h/d, 5d/wk Recovery 0, 12 and 32 wks	Reversible changes in all bronchoalveolar lavage (BAL) parameters. Elevated numbers of neutrophils and macrophages and some fibrosis in the alveolar septa of lungs. LOAEL (only one dose tested): 50.4 mg/m³ air (analytical)	Johnston et al., 2000
No guideline 18 months exposure SD rats, guinea pigs, and Cynomolgus monkeys 80 rats, 20 guinea pigs, 10 monkeys per group	Pyrogenic silica, not further specified 15 mg/m³, whole body inhalation Geometric mean (µm): 0.17 5.5-6h/d, 5d/wk	Strongest effects were seen in monkeys. There was deposition of large quantities of amorphous silica in macrophages in the lungs and tracheal lymph nodes of	Groth et al., 1981

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Unintentional additional exposure to mica and kaolin of some monkeys, this did not seem to influence the outcome	No recovery period	monkeys. Early nodular fibrosis was seen in the lungs of 6 out of 9 exposed monkeys. Also pulmonary function parameters were significantly different	
OECD 412 Adapted as 5 d study GLP Wistar albino rats 10 males/dose/time point	Cab-O-Sil M5 1, 5, 25 mg/m³ (nominal), nose only MMAD (µm): 1.70-1.94 gsd: 1.70-1.79 5d 6h/d 0, 4 and 13 wks recovery	Increased lung weight and increase in inflammatory markers at mid and high dose. Changes were reversible after 3 months. LOAEC: 5 mg/m³ Value reported in publication: NOAEC is 1 mg/m³	Anonymous et al., 2003a. Published by Arts et al., 2007
OECD 412 Adapted as 5 d study GLP Wistar rats 10 males/dose/time point	VA-Kieselsäure LGS/VA-silica LGS 1, 5, 25 mg/m³ (nominal), nose only MMAD (µm): 1.57-2.07 gsd: 2.10-2.34 5d 6h/d 0, 4 and 13 wks recovery	At the high dose intraepithelial and peribronchial infiltration of polymorphonuclear inflammatory cells, accompanied by slight hypertrophy and/or hyperplasia of the bronchiolar epithelium. LOAEC: 25 mg/m³	Anonymous et al., 2009

Table 14: Summary table of repeated dose toxicity animal studies with precipitated silica/silica gel/colloidal silica

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Comparable to OECD 413 GLP 20/20 exp 10/10 exp + 13/26/39 wk 20/20 exp + 52 wk	SIPERNAT 22S 30 mg/m^3 MMAD could not be determined 13 wks 6h/d, 5d/wk recovery periods of 0, 13, 26, 39, 52 wks	Accumulation of alveolar macrophages in the lung, reversible after 39 weeks	Reuzel et al., 1991
OECD 413 with additional endpoints (bronchoalveolar lavage, cell proliferation, immunological parameters, oxidative stress analysis, electron microscope analysis, toxicokinetics) Male Wistar rat 55 animals/dose Histopath on 10 rats/dose/time point	NM-200 1, 2.5, 5 mg/m^3 (nominal), nose only MMAD: - low dose: 2.16 µm, GSD: 0.09 - mid dose: 2.94 µm, GSD: 0.2 - high dose: 3.12 µm, GSD: 0.06 13 wks 6h/d, 5d/wk Recovery periods 0, 90 d	Increased lung weights (mid and high dose), persistent inflammatory responses in the nasal cavity in all dose groups and transient inflammatory effects in the lungs in mid and high dose groups. LOAEC: 1 mg/m^3	Anonymous, 2014a, reviewed by Creutzenberg et al., 2022
No guideline 18 months exposure SD rats, guinea pigs, and Cynomolgus monkeys 80 rats, 20 guinea pigs, 10 monkeys per group	Silica gel and precipitated silica not further specified 15 mg/m^3, whole body inhalation MMAD (µm): 0.27 (gel) and 0.38 (prec) 5.5-6h/d, 5d/wk No recovery period	Strongest effects were seen in monkeys. There was deposition of large quantities of amorphous silica in macrophages in the lungs and tracheal lymph nodes of exposed monkeys. Monkeys exposed to precipitated silica demonstrated significantly lower lung volumes compared with controls, while monkeys exposed to silica gel had significant changes in ventilatory performance and mechanical properties	Groth et al., 1981
No guideline 1 y exposure Rats 110 females Very limited reporting	Kieselsäure FK 700 (SIPERNAT 700) 55 mg/m^3 (analytical), whole body inhalation MMAD unknown	Some bronchial effects were shown after 1 year of exposure, but they mostly subsided after 5 months of recovery. No fibrosis was detected.	Klosterkotter, 1968b

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
	6h/d, 5d/wk 1 yr exp 5 m recovery with 16 rats		
Short term rep dose study Crj: CD(SD) rats 25 males/dose 10 exp 5 exp + 10 d 10 exp +3 m	LUDOX CL-X 10, 50, 150 mg/m³, whole body MMAD (µm): 2.9-3.7 gsd 1.9-2.3 4 wks 3 m recovery	At mid and high dose reversible increase in lung weights, alveolar macrophage response, polymorphonuclear leukocytic infiltration, and Type II pneumocyte hyperplasia in alveolar duct regions. LOAEC: 50 mg/m³ Value reported in publication: NOEL = 10 mg/m³	Anonymous, 1990 Lee and Kelly, 1992 Warheit, 1991
OECD 412 with additional endpoints Male Wistar rat 35 animals/dose	NM-200 1, 5, 25 mg/m³ (nominal), nose only MMAD: - low dose: 0.69 µm, GSD: 6.95 - mid dose: 2.87 µm, GSD: 1.97 - high dose: 3.16 µm, GSD: 1.77 14 d 6h/d, 5d/wk 14 d recovery	Slight to moderate mucous (goblet) cell hyperplasia (5 of 5 males of the high-dose group) and dose dependent epithelial eosinophilic droplets in the nasal cavity; in the high dose group, the epithelial eosinophilic droplets were associated with (multi)focal subepithelial inflammatory cell infiltration. A significant increase of alveolar/interstitial macrophage infiltration and of (multi)focal very slight alveolar granulocyte infiltration in the lungs of the high dose group. Multifocal 'granuloma-like' foci of macrophages (histiocytosis) in the lung associated lymph nodes of 3/5 high dose rats LOAEC: 5 mg/m³	Anonymous, 2014b
5-day range finding study Male Wistar rat 5 animals/dose	NM-200 1, 5, 25 mg/m³ (nominal), nose only MMAD: - low dose: 2.12 µm, GSD: 3.15 - mid dose: 3.47 µm, GSD: 2.31 - high dose: 2.29 µm, GSD: 3.44	Dose-dependent mucous cell hyperplasia in the respiratory epithelial lining of the nasal septum and nasal meatus, very slight bronchiolo-alveolar hyperplasia and very slight to slight bronchial mucous cell hyperplasia in the lungs	Anonymous, 2014c

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
	5 d	at the top dose LOAEC: 5 mg/m³	
OECD 412 Adapted as 5 d study GLP Wistar albino rats 10 males/dose/time point	SYLOID 74 1, 5, 25 mg/m³ (nominal), nose only MMAD (µm): 1.57-1.71 GSD: 1.51-1.60 5d 6h/d 4 and 13 wks recovery	The high dose induced changes in differential cell count and biochemical parameters in BAL fluid, increased weights of lungs and tracheobronchial lymph nodes, and histopathological changes, reversible after one month except a light increase in lung collagen content after three months. At the mid dose, there was a slight but significant increase in the percentage of neutrophils in BAL fluid LOAEC: 5 mg/m³ Value reported in publication: NOAEC is 1 mg/m³	Anonymous, 2003b. Published by Arts et al., 2007
OECD 412 Adapted as 5 d study GLP Wistar albino rats 10 males/dose/time point	ZEOSIL 45 1, 5, 25 mg/m³ (nominal), nose only MMAD (µm): 2.83-3.27 GSD: 1.75-1.90 5d 6h/d 4 and 13 wks recovery	The high dose induced changes in differential cell count and biochemical parameters in BAL fluid, increased weights of lungs and tracheobronchial lymph nodes, and histopathological changes, reversible after one month. At the mid dose there was a slight increase in relative neutrophil count in BAL fluid. LOAEC: 5 mg/m³ Value reported in publication: NOAEC is 1 mg/m³	Anonymous, 2003c Published by Arts et al., 2007
Short-term inhalation study protocol by NanoSafe2 (www.nanosafe. org) Han Wistar rats 5 males/dose	Colloidal uncoated amorphous silica (SiO_2 naked) 0.5, 2.5, 10, 50 mg/m³ MMAD (µm): 1.0-2.2 gsd 2.2-3.4 5d 6h/d 3 wks recovery	Multifocal macrophage aggregates were observed in the lung shortly after exposure. This finding exacerbated towards a slight multifocal pulmonary inflammation by the end of the 3-week exposure free period. LOAEC: 10 mg/m³	Landsiedel et al., 2014

Table 15: Summary table of human data on STOT RE

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
Cross-sectional study Workers at five German production plants (n= 462)	SAS, pyrogenic and precipitated	Inhalation Full-time employees, who worked at least 1 month at the plant were eligible to participate. Evaluation of the effect of cumulative exposure to inhalable SAS dust on symptoms, spirometry (pulmonary function test), and chest films Two exposure scenarios: - Expert assessment only - Expert assessment + personal SAS measurement data	Symptoms: 11% had chronic bronchitis. Inconsistent results on relation with exposure. Chest films: no evidence for pneumoconiosis. Spirometry: reduced FVC in one scenario. No effect on FEV_1 or FEV_1/FVC ratio.	Morfeld et al., 2014; Taeger et al., 2016 Yong et al., 2022
Cross-sectional study Workers at a chemical plant engaged in synthesis of amino acids and vitamins (n=41)	SAS, precipitated	Inhalation. Exposed group (n=41): mean duration of exposure was 8 years (range: 1-18 years). Control group (n=90): workers in same plant, not exposed Chest X-ray, pulmonary function, blood gas analysis	Blood gas analysis and X-ray: no effects observed. Lung function: significantly decreased values in the exposed group compared to the control group. Respiratory symptoms: higher % of workers with usual cough, dyspnea and asthma in the exposed group.	Choudat et al., 1990
Cohort study Workers at a metallurgical company (n=40)	SAS, pyrogenic. Dust particles ranged from 0.05-0.75 µm.	Inhalation. Employees started working between 1954 and 1956. They worked at the company for 11-18 years. Examination of X-rays. Spirometry in three selected workers (all smokers); biopsy in 2/3 of the selected workers.	X-rays: abnormalities in 11 employees. In 3 selected workers: pulmonary disease with nodules and reticular pattern observed in 1966-1968. Spirometry and biopsy (in 1974): reduced FEV_1 and reduced diffusing capacity for CO in 2/3 selected workers. Both showed subpleural peribronchial and perivascular fibrosis, pigment in connective tissues, intraalveloar macorphages and emphysema. On a dry basis, 6.7% silica (not specified) was found in lung tissue.	Vitums et al., 1977

Assessment of health records 78 men employed in the manufacture of SAS.	Precipitated silica (Hi-Sil) and hydrated calcium silicate (Silene)	Inhalation. Examination of yearly X-rays and reported symptoms.	No indications of silicosis or other pulmonary diseases.	Plunkett and DeWitt, 1962
Evaluation chest X-rays 215 workers in production of SAS, in Germany	Pyrogenic silica	Inhalation. Examination of regular (every half year) X-rays. Observation period: 1947-1959. Dust concentrations available for the last year. SAS concentrations during the exposure period are unknown.	No indications of silicosis.	Volk, 1960
Assessment medical records 165 workers involved in manufacturing of SAS, in two industrial facilities.	Precipitated silica	Inhalation. At least one full year of exposure to SAS. Review of spirograms (FVC, FEV_1, FEV_1/FVC), respiratory questionnaires and chest radiographs.	No association between SAS exposure and pulmonary function.	Wilson et al., 1979

9.1.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Human data

A cross-sectional study was performed in 484 male workers from five German SAS-producing plants (Morfeld et al., 2014; Taeger et al., 2016). All current (1997) full-time employees, who worked at least 1 month at the plant were eligible to participate (duration of employment varied between 0.2 and 41.8 years; median is 12.4 years). Cumulative exposure estimates based on all 484 workers were on average 31.8 mg/m^3·years (range 0.1 – 419) based on expert assessment and 56.9 mg/m^3·years (range 0.4 - 480) based on personal measurements + expert assessment. Based on an accumulative exposure of e.g. 80 mg/m^3·years, a mean dust concentration of 2 mg/m^3 over 40 years would be estimated. The effect of cumulative exposure to inhalable SAS dust on symptoms, spirometry (pulmonary function test), and chest films was evaluated. Two exposure scenarios were used: the first was based on expert assessments only, the second on expert assessment + personal SAS measurement data. A reduction in forced vital capacity (FVC) was observed in one of the scenarios, but had no effect on forced expiratory volume in 1 second (FEV1) or FEV1/FVC. Monte Carlo analysis indicated a decline in FVC of -11 mL per 10 mg/m-years exposure (-6 to -0.4). Chest films showed no evidence of pneumoconiosis. Of all workers, 52 reported chronic bronchitis (11%). Although some significant effects were observed for bronchitis, results between the two exposure scenarios were not consistent and prevent firm conclusions. An extended analysis of the data, performed by Yong et al. (2022), to investigate the effect of cumulative

exposure to *respirable* SAS dust did not indicate any adverse effect on FEV_1 and FEV_1/FVC, but did show a reduction in FVC as a result of exposure to respirable SAS.

A group of 41 workers at a chemical plant were compared with a control group (n=90) for symptoms, x-ray examination, lung function and blood gas analysis (Choudat et al., 1990). No differences in blood gas analysis and x-rays were found between the two groups. Lung function values were decreased in the exposed group, compared to the controls. The decreased parameters included FEV_1/FVC and forced expiratory flow between 25% and 75% of the pulmonary volume (FEF_{25-75}), FEF_{50} and FEF_{75}. The mean values of all three FEF values were lower among the smokers and exposed workers than among the non-smoking non-exposed workers (only significant between smoking-exposed and non-smoking non-exposed). The percentage of smokers was comparable between the two groups (46% exposed group, 42% control group).

Employees of a metallurgical plant producing SAS (by vaporizing crystalline silica) were examined by X-rays, lung function and lung biopsy. Employees started working at the plant in 1954-1956 and worked there for 11-18 years. X-ray examination showed lung abnormalities in 11 workers. Three of these workers were selected for further investigation by spirometry and biopsy. Lung function tests showed a moderate to severe decrease in FEV_1 and mild to moderate reduction in diffusing capacity for carbon monoxide in worker 1 and 3. Biopsies of worker 1 and 2 showed subpleural peribronchial and perivascular fibrosis, pigment in connective tissues, intraalveloar macorphages and emphysema (milder changes in worker 2). A review of an pathology institute pointed ut that the fibrohistiocytic nodules have some similarity with descriptions of experimental pneumoconiosis with amorphous silica. It is noted that the three selected workers all smoked (Vitums et al., 1977).

Company health records were reviewed for 78 men employed in the manufacture of precipitated silica (Hi-Sil) and hydrated calcium silicate (Silene) in the USA. Duration of employment ranged from 1 year to 16 years and 7 months (average of 4.75 years). The percentage of time/employee exposed to SAS varied from less than 30% (7 employees), 50 to 90% (31 employees) to up to 100% (40 employees). Total SAS levels ranged from 0.3 to 204 mg SiO_2/m^3. Symptoms included mechanical irritation of (unprotected) skin, eyes, nose and throat from dry dust contact and thermal burns of skin and eyes from wet slurry. The incidence and type of injury was not different from any other group of workers in the factory. The workers did not exhibit silicosis or any other pulmonary disease based on annual X-ray examination (Plunkett and DeWitt, 1962).

The chest X-rays of 215 workers involved in the production of pyrogenic AEROSIL (substance not further specified) in Germany were evaluated. X-ray data were collected from 1947 to 1959. The average duration of exposure was not calculated, but only 9 of the employees had been employed for more than 10 years. Airborne SAS concentrations measured in 1959 in the bagging room and production room ranged from 2 to 7 mg SiO_2/m^3. Levels were considerably higher at the filling nozzle (15 - 100 mg/m^3), but it is unclear if these exposures occurred in the breathing zone of the workers. None of the X-rays showed any evidence of lung pathology, indicative of silicosis (Volk, 1960).

The medical records of 165 workers involved in the manufacturing of precipitated silica (Hi-Sil and Silene) in two industrial facilities in the USA were reviewed with regard to their annual spirometry, chest X-ray, and most recent respiratory questionnaire. Workers were exposed for 1 to 35 years with mean exposure duration of 8.6 years. Linear regression analysis of yearly change of all pulmonary function variables showed no correlation with the either the dose of SAS or total years of exposure. Eleven workers had minimal radiographic evidence of pneumoconiosis, but they also had prior occupational exposure in limestone mines or soda ash plants using limestone, which the authors noted contained crystalline silica. Of 143 workers with serial radiographs and exposure to only SAS, none had radiographic pneumoconiosis (Wilson et al, 1979, 1981).

Animal data

Repeated dose inhalation studies have been performed with several forms of SAS, as summarized in Tables 13 and 14. The most informative studies were considered to be those with at least 28-days

exposure, multiple dose groups and at least 10 animals/sex/dose (including recovery groups). The outcome of these studies is discussed in more detail below.

Recently a 90-day nose-only inhalation study was performed in rats with recovery periods of 0, 3, 6, and 12 months (Fraunhofer ITEM, 2019). Two forms of SAS were tested, both pyrogenic silica, but different in surface area. SAS 1 has a high surface area of approximately 400 m^2/g and SAS 2 a low surface area of 40-50 m^2/g. The doses included clean air control, SAS 1/SAS 2 0.5 mg/m^3 (very low), 1 mg/m^3 (low), 2.5 mg/m^3 (mid) and 5 mg/m^3 (high). The number of animals allocated to each group was 10 rats/sex/dose for the groups sacrificed at the end of the exposure period and 5 rats/sex/dose for the recovery groups. Analyses included gross pathology of all organs, histopathology of the respiratory organs including lymph nodes, bronchoalveolar lavage (BAL) and collagen analysis of the lung tissue.

Two animals died during the study and two were killed in moribund condition. They were from different exposure groups and the deaths were not treatment related.

There were no statistically significant changes in body weight or food consumption in any of the treated groups. In gross pathology, enlarged lung-associated lymph nodes (LALN) were observed in the SAS 1 mid and high dose groups and in all SAS 2-treated groups. SAS 1 induced a statistically significant increase of the absolute and relative lung wet weights in the female high dose group at 1 day post-exposure only. At 3 months post-exposure, this effect had disappeared. SAS 2 induced statistically significant increases of the absolute and relative lung wet weights in the low, mid and high dose groups at 1 day post-exposure (both sexes). Lung weights recovered at 3 months post-exposure in the low and mid dose groups; the high dose group only showed a persistent statistically significant increase at 6 and 12 months post-exposure.

BAL measurements showed at day 1 post-exposure statistically significant increases of polymorphonuclear neutrophils (PMN) in the SAS 1 mid and high dose groups of both sexes. In both dose groups a full recovery was detected at 3 months post-exposure. At day 1 post-exposure statistically significant increases of PMN were detected in all SAS 2 dose groups of both sexes. Full recovery was detected in the very low dose group at 3 months, in the low dose group at 6 months and in the mid and high dose groups at 12 months post-exposure. For lactate dehydrogenase (LDH), ß-glucuronidase (GLU) and total protein (TP) no statistically significant increases were detected in all SAS 1 groups at all four sacrifice dates (but for total protein in the female SAS 1 high dose group at day 1). In the SAS 2 mid and high dose groups, statistically significant increases of LDH, GLU and TP were observed at 1 and 3 months post-exposure; these effects returned to normalisation mostly at 6 and 12 months post-exposure.

Hydroxyproline as an indicator of collagen in lungs was statistically significantly increased in the high dose males of the SAS 2 group after 12 months recovery.

In the histopathological evaluation, treatment-related findings were noted in nasal cavities, lungs, and lung associated lymph nodes (see also Table 16).

In nasal cavities, the major lesions consisted of:

- Slight mucosal degeneration in the high dose groups at the end of treatment
- Goblet cell proliferation in levels 1 and 2 and nasopharyngeal duct at the end of treatment and after 3 months recovery in all SAS 1 and SAS 2 groups.
- Hyaline inclusions in olfactory mucosa at higher incidences and severity than in the controls with increased incidences during the course of the study in all exposed groups.
- Chitinase-positive crystals in olfactory mucosa in nasal cavity levels 2-4, observed up to 6 months recovery without any further injury in olfactory mucosa, mainly in the high dose SAS 1 treated animals.

In lungs, the findings consisted of:

- End of treatment: discoloration or discolored foci in lungs from animals treated at ≥1.0 mg/m3 SAS 2 associated with inflammatory lesions that increased in incidence and/or severity in a dose-dependent manner in the test item-treated groups and was not reversible.

- Increased perivascular infiltration in SAS 1 groups ≥ 1.0 mg/m3 and all SAS 2-treated groups. This effect was reversible in the SAS 1 groups (already at 3 months recovery) and mostly reversible after 12 months in the SAS 2 groups.

- Dose dependent increase of alveolar macrophages and macrophage aggregations starting at the lowest dose, as well as macrophage type II hyperplasia for SAS 1 and SAS 2 associated with interstitial inflammation, granulomas at the bronchio-alveolar junctions. Granulomatous inflammation at a minor severity was noted in single animals from the very low and low dose (SAS 1), and in most animals from mid and high dose groups (SAS 1) and all dose groups of SAS 2. The effect was mostly reversible, except in animals exposed to ≥ 1.0 mg/m^3 SAS 2 (see Table 16 for details).

- Bronchio-alveolar hyperplasia in single animals from SAS 1 groups ≥ 1.0 mg/m^3 and all SAS 2 groups.

- Hyperplasia in the BALT (Bronchus Associated Lymphoid Tissue) in one SAS 2 0.5 mg/m^3 male and one group 2.5 mg/m^3 SAS 2 female.

- Minimal macrophage agglomeration in the BALT of a few animals at ≥ 1.0 mg/m^3 SAS 1 but almost all animals at 5.0 mg/m^3 SAS 1, as well as in almost all animals treated with SAS 2. Granulomatous inflammation in the BALT in animals treated with SAS 2.

- BALT fibrogenesis in single animals at 0.5 and 1.0 mg/m^3 SAS 1, at an increased incidence at higher doses of SAS 1, and in all doses of SAS 2 with increasing incidence. At the end of the 12 month recovery period there was fibrogenesis in the lungs at increased incidence in both sexes ≥2.5 mg/m^3 SAS 2 likely due to still ongoing inflammatory processes, and minimal interstitial fibrosis in one animal at 5.0 mg/m^3.

In lymph nodes, the findings consisted of:

- Granulomas in lymph nodes ≥ 1 mg/m^3 SAS 1 and in all SAS 2 groups, which were reversible after 6 months in the SAS 1 groups.

- Related granulomatous inflammation at a minor severity in single males ≥ 2.5 mg/m^3 SAS 1, and in a high number of animals from all groups treated with SAS 2

- Lymphoid hyperplasia in most lymph nodes

- Fibrogenesis in the lymph nodes from several animals from all SAS 2-treated groups, and fibrosis in one female at 0.5 mg/m^3 SAS 2, and in both sexes at ≥1.0 mg/m^3 SAS 2. At the end of the 12 month recovery period there was fibrogenesis or fibrosis in a few animals of all SAS 2 groups, with high incidence at 5 mg/m^3. See Annex II for the summary tables of the histopathological evaluation of the lymph nodes.

In summary, the most serious effects induced by both SAS materials were interstitial inflammation, granuloma and fibrogenesis of the lungs and granulomas, granulomatous inflammation, hyperplasia in the lymph nodes. In addition, SAS 2 induced fibrosis in the lungs of one high dose animal and fibrogenesis and fibrosis in the lymph nodes at all dose levels. The severity of the effects and the kinetic of the recovery differ for both materials, with an observed higher incidence and severity and a lower recovery kinetic for the low surface area material (SAS 2). The LOAEC of SAS 1 was 1 mg/m^3, while SAS 2 induced effects at all tested doses, the lowest of which was 0.5 mg/m^3.

Table 16: Granuloma and fibrogenesis observed in the lung, expressed in number of animals affected / mean severity from 0-4. Groups are separated in males (left) and females (right)

Dose	Air		SAS 1 0.5 mg/m³		SAS 1 1.0 mg/m³		SAS 1 2.5 mg/m³		SAS 1 5.0 mg/m³		SAS 2 0.5 mg/m³		SAS 2 1.0 mg/m³		SAS 2 2.5 mg/m³		SAS 2 5.0 mg/m³	
After 3 months inhalation (K0) (10 animals/sex/dose)																		
Granuloma (junct.)	0	0	0	0	2/1.0	0	4/1.0	0	9/1.0	9/1.0	9/1.2	5/1.6	6/1.7	6/1.5	9/1.2	6/1.5	9/1.2	5/1.2
Masson T.: Fibrogenesis	2/1.0	1/1.0	0	1/1.0	3/1.0	1/1.0	6/1.0	5/1.0	8/1.0	7/1.0	7/1.0	9/1.0	6/1.0	7/1.0	7/1.0	9/1.0	10/1.0	7/1.0
After 3 months recovery (R1) (5 animals/sex/dose)																		
Granuloma (junct.)	0	0	0	1/2.0	0	0	1/1.0	1/1.0	1/1.0	1/1.0	4/1.5	5/1.2	5/1.4	4/1.3	3/1.0	5/1.4	1/1.0	3/1.7
Masson T.: Fibrogenesis	0	0	1/1.0	1/1.0	0	0	0	1/1.0	0	0	4/1.3	4/1.0	5/1.2	4/1.0	3/1.0	5/1.0	4/1.0	5/1.0
After 6 months recovery (R2) (5 animals/sex/dose)																		
Granuloma (junct.)	0	0	0	0	0	0	0	0	0	1/1.0	0	3/1.0	2/1.0	4/1.0	4/1.0	5/1.2	5/1.2	5/1.0
Masson T.: Fibrogenesis	0	0	0	0	0	0	0	0	0	0	3/1.3	1/1.0	4/1.8	2/1.0	5/1.2	0	5/1.4	5/1.4
After 12 months recovery (R3) (5 animals/sex/dose)																		
Granuloma (junct.)	0	0	0	0	0	0	0	0	1/1.0	0	0	2/1.0	0	0	1/1.0	1/1.0	3/1.3	2/1.0
Masson T.: Fibrogenesis*	2/1.0	0	2/1.0	0	0	0	0	0	0	0	0	2/1.0	0	1/1.0	4/1.0	4/1.8	5/2.0	4/2.0

*Masson trichrome staining for collagen fibers

Reuzel et al. (1991) performed a 13-week inhalation study with three different SAS types (untreated pyrogenic silica, i.e. AEROSIL 200, surface-treated pyrogenic silica, i.e. AEROSIL R 974, and precipitated silica, i.e. SIPERNAT 22S). Rats were exposed to 1, 6 or 30 mg/m^3 AEROSIL 200, to 30 mg/m^3 SIPERNAT 22S or to 30 mg/m^3 surface-treated AEROSIL R 974 (nominal concentrations). Separate exposure groups were included for recovery periods of 13, 26, 39 and 52 weeks. As surface treated SAS is not included in this proposal, these results are omitted here.

In the AEROSIL 200 exposure groups higher incidences of fibrosis were observed (seen as amorphous eosinophilic, collagen-containing thickenings of the septa) which were very consistent, showed a clear concentration-response relationship and were still observed after 52 weeks recovery (see Table 17 for details). A low incidence of fibrosis was observed 13 weeks post-exposure in rats exposed to SIPERNAT 22S; at 26 weeks post-exposure fibrosis was not observed.

The lung collagen content at the end of exposure was higher in all treatment groups compared with the control group. The increase was most pronounced in rats exposed to 30 mg/m^3 pyrogenic silica and showed a dose-dependent increase which was more pronounced in males. The lung collagen content gradually decreased during the duration of the recovery period, but at 6 and 30 mg/m^3 it did not return to control levels, indicating that the observed effect is not completely reversible within the 52 week recovery period.

Accumulation of alveolar macrophages was observed in all SAS treated groups in all animals at the end of treatment. Although the incidence decreased during the recovery period, it was still present at 52 weeks recovery, especially in the mid and high dose AEROSIL 200 treated animals.

Other effects induced by AEROSIL 200 in both sexes included intra-alveolar polymorphonuclear leucocytic infiltration (IPLI) (reversible) and increased septal cellularity (still observed at 52 weeks recovery). Alveolar bronchiolisation was only observed in males and reversible after 39 weeks.

Table 17: Summary of focal interstitial fibrosis induced by AEROSIL 200 (pyrogenic silica) from Reuzel et al. (1991).

Dose (mg/m^3)	**End of treatment**		**13 weeks recovery**		**26 weeks recovery**		**39 weeks recovery**		**52 weeks recovery**	
	M	F	M	F	M	F	M	F	M	F
0	0/10	0/10	0/5	0/5	0/5	0/5	0/5	0/5	0/10	0/10
1	0/10	0/10	0/5	1/5	0/5	1/5	0/5	0/5	0/10	1/10
6	0/10	0/10	1/5	3/5	2/5	3/5	1/5	1/5	2/10	1/10
30	0/10	0/10	5/5**	4/5*	4/5*	5/5**	5/5**	4/5*	9/10**	10/10**

Values are for the number of rats shown, and those marked with asterisks differ significantly (Fisher's exact probability test) from the corresponding control value (*P < 0.05; **P < 0.01). M= males; F = females.

Table 18: Summary of effects other than fibrosis induced by AEROSIL 200 (pyrogenic silica) in number of animals affected, from Reuzel et al. (1991)

		Males					Females				
	Time after exposure (wk)	Control	1 mg/m³ AEROSIL 200	6 mg/m³ AEROSIL 200	30 mg/m³ AEROSIL 200	30 mg/m³ Sipernat 22S	Control	1 mg/m³ AEROSIL 200	6 mg/m³ AEROSIL 200	30 mg/m³ AEROSIL 200	30 mg/m³ Sipernat 22S
Accumulation alveolar macrophages	0	4	10	10	10	10	1	10	10	10	10
	52	1	1	1	10	4	0	1	4	8	0
IPLI[a]	0	1	10	10	10	2	0	8	10	10	0
	52	0	0	0	0	0	0	0	0	0	0
Increased septal cellularity	0	1	10	10	10	2	1	9	9	10	6
	52	1	1	2	7	4	0	0	3	7	0
Alveolar bronchiolization	0	0	0	5	10	0	0	0	0	1	0
	52	1	2	0	1	1	0	1	0	2	0

[a] intra-alveolar polymorphonuclear leucocytic infiltration

The pathology slides of Reuzel et al. (1991) have been re-stained with hematoxylin-eosin (HE) staining and re-evaluated almost 30 years later, the result of which was published by Weber et al. (2018). Only slides of males at time points 0, 13 weeks and 52 weeks recovery were still available. The diagnostic criteria and terminology used throughout the study were based upon recognised texts and current scientific literature, that is, according to International Nomenclature and Harmonization of Diagnostic Criteria (INHAND) nomenclatures. Fibrogenesis is defined by Weber et al. in this re-evaluation as "Increases in septal or interstitial thickness resulting from edema or inflammation without substantial fibre cross-linking. In the present study associate with minimal inflammatory infiltration considered to be fully reversible". Fibrosis is defined by Weber et al. as "Observable increase in amount or abnormal location of collagen in lung parenchyma, resulting in disruption of the normal lung architecture. Occurrence in alveolar septa, interstitium, and pleura. Formation of distinct collagen bands".

In this re-evaluation, Weber et al. (2018) concluded that only single incidences of minimal focal fibrosis were observed, without relation to the concentration, and a slight increase in fibrogenesis at the high dose males (2/10). There was also an increase in inflammation indicators, comparable with the other effects noted by Reuzel et al. (1991). In light of this assessment and in particular regarding the interpretation of the Reuzel study and its re-evaluation by Weber et al., the recent RAC opinion of silanamine should also be mentioned (RAC, 2019). In the CLH evaluation of silanamine a read-across with AEROSIL R 974 (surface-treated pyrogenic silica modified with Dimethyldichlorosilane (DDS)) was used, which is structurally similar to silanamine and shares physical, chemical and toxicological properties. RAC noted several issues with Weber et al.:

- the re-evaluation did not concern all animals, and only one lung section per animal;
- the almost 30-year old slides were de-cover-slipped, re-stained (with standard hematoxylin and eosin staining) and then cover-slipped again, whereby the de-cover slipping may potentially have damaged the original tissue samples;
- the specific Van Gieson stain for the detection of collagen was not used in the re-evaluation nor was hydroxyproline measured;
- the claimed recovery pertains to unusually long recovery periods for a 13-week rat study (13-52 weeks). Moreover, it was noted by RAC that although exposure-related fibrogenesis and structural remodelling of the lung tissue may be reversible, they cannot be excluded as an adverse effect that could progress to fibrosis, if exposure persists and in the presence of another detrimental pathology, such as infection. In all cases, histopathological findings like these could account for clinical symptoms of respiratory distress and were considered relevant.

A 90-day study with precipitated silica was performed by Anonymous (2014), reviewed by Creutzenberg et al. (2022). The study was performed in rats exposed to 1, 2.5 and 5 mg/m^3 NM-200 (55 males/dose) via nose only inhalation, with a 90-day recovery period. The absolute lung weights were increased in the high dose group 1 day after end of exposure and after 3 months of recovery (mid and high dose group). The relative lung weights were statistically significantly increased 1 day after exposure end (mid and high dose group). Most histopathological effects occurred in the nose and were not or only slightly reversible (see Table 19). A significant increase of alveolar infiltration of granulocytes in lungs was detected in the mid and high dose groups. Interstitial macrophage infiltration and (multi)focal very slight alveolar granulocyte infiltration were increased in the lungs of the high dose group animals. Histopathological examination 3 months after end of exposure revealed a full recovery of all treatment-related effects in lungs.

A 28-day study was published in two papers that investigated the inhalatory effects of colloidal silica (Lee and Kelly (1992) and Warheit et al., (1991)). The study exposed male rats to 10, 50, and 150 mg/m^3 LUDOX-CL-X. After 4 weeks exposure to 50 mg/m^3 LUDOX CL-X, a slight alveolar macrophage response, polymorphonuclear leukocytic infiltration, and Type II pneumocyte hyperplasia in alveolar duct regions were present. After 3 months post-exposure, these pulmonary lesions had almost disappeared with removal of most dust-laden alveolar macrophages (AMs). The pulmonary response to 150 mg/m^3 LUDOX CL-X was similar in character but increased in magnitude from that

seen at 50 mg/m^3. At 3 months PE, most particle laden AMs had disappeared and the remaining AMs were aggregated and sharply demarcated (see Table 20).

Table 19: Nasal effects from Anonymous (2014) in rats exposed to precipitated silica NM-200

	End of treatment				End of recovery			
	Control	1 mg/m^3	2.5 mg/m^3	5 mg/m^3	Control	1 mg/m^3	2.5 mg/m^3	5 mg/m^3
Mucous cell hyperplasia (very slight)						3/10		
Mucous cell hyperplasia (slight)	1/10	10/10	8/10	2/9	3/10	3/10	10/10	6/10
Mucous cell hyperplasia (moderate)			2/10	7/9		2/10		3/10
Mucous cell hyperplasia (severe)								1/10
Hyperplasia of the respiratory epithelium (very slight)						1/10	2/10	4/10
Hyperplasia of the respiratory epithelium (slight)		2/10	5/10	9/9		5/10	5/10	6/10
Epithelial hyaline droplets (very slight)	3/10				7/10			
Epithelial hyaline droplets (slight)	1/10	10/10	9/10			9/10	10/10	2/10
Epithelial hyaline droplets (moderate)			1/10	9/9		1/10		7/10
Epithelial hyaline droplets (severe)								1/10
Multifocal epithelial (mixed) inflammatory cell infiltration (very slight)	1/10	10/10	6/10	2/9	2/10	6/10	8/10	8/10
Multifocal epithelial (mixed) inflammatory cell infiltration (slight)			4/10	7/9		2/10	1/10	2/10
Multifocal (chronic) inflammation of the nasal submucosal glands (slight)								1/10

Table 20: Overview of main pulmonary lesions after exposure to colloidal silica from Lee and Kelly, 1992

	4 weeks exposure				**10 days post-exposure**				**3 months post-exposure**			
Exposure concentration (mg/m^3)	0	10	50	150	0	10	50	150	0	10	50	150
Number of rats	10	10	10	10	5	5	5	5	10	10	10	10
Dust-laden alveolar macrophages (AM)	-	-	10 (++)	10 (+++)	-	-	5 (++)	5 (++)	-	-	10 (+)	10 (+)
Type II pneumocyte hyperplasia, alveoli	-	-	10 (+)	10 (++)	-	-	1 (+)	-	-	-	-	-
Neutrophilic infiltration, alveoli	-	-	10 (+)	10 (++)	-	-	-	-	-	-	-	-
Fibroblast proliferation, alveoli	-	-	9 (+)	10 (++)	-	-	2 (+)	5 (+)	-	-	1 (+)	-
Silicotic nodular-like lesions, alveoli	-	-	-	-	-	-	-	-	-	-	1 (+)	3 (+)
Nodular AM aggregates, alveolar walls	-	-	-	-	-	-	-	-	-	-	1 (+)	9 (+)
Translocated dust particles, histiocytes, tracheobronchial lymph nodes	-	-	7 (++)	9 (+++)	-	-	5 (++)	5 (+++)	-	-	10 (+++)	10 (++++)

Severity of lesions: -, no lesions; +, minimum; ++, slight; +++, moderate; ++++, marked

There are also studies that exposed rats for 5 days, usually followed by a recovery period of one to three months. The studies published together by Arts et al. (2007) were the most notable of these studies, because they included pyrogenic silica, precipitated silica and silica gel. Rats were exposed to 1, 5, and 25 mg/m^3 for 5 days with recovery periods up to three months. Exposure to all three SAS at 5 mg/m^3 induced histopathological changes in the lungs and changes in BAL fluid. With all three SAS these effects were transient and, with the exception of slight histopathological lung changes at the higher exposure levels, were reversible during the 3-month recovery period. This was compared with quartz that showed almost an opposite pattern, with hardly any effects directly after exposure but clear changes after 3 months.

Overview of results of the different types of SAS

As stated at the beginning of this report, the two types of SAS discussed here share one REACH dossier and are generally considered to have no significant differences in toxicity by the registrants.

Although there are a few comparative studies, they unfortunately all have considerable weaknesses that hamper a solid comparison between the types. These problems include very short exposure duration (Arts et al., 2007), only single doses (Reuzel et al., 1991, Groth et al., 1981), or very limited reporting of the results (Groth et al., 1981). Based on the studies that are available, the dossier submitter concludes that the nature of effects induced after inhalation of SAS is similar over the different SAS types. Pyrogenic SAS induced the clearest adverse effects and at the lowest concentrations, however the difference is not such as to invalidate a single CLH entry based on the current knowledge.

In Table 21 an overview is presented of the main effects that are relevant for classification for STOT RE. This overview is limited to studies of sufficient quality, with exposure times of at least 28-days and multiple doses.

Table 21: Overview of results for classification of SAS

Study reference and exposure duration	Effective dose (mg/L/6h/day, 5 days/week) and type of effects	Extrapolated effective dose when extrapolated to 90-day exposure	SAS type	Classification supported by the study (inhalation, dust, mg/m^3)
Fraunhofer ITEM, 2019 13-w	LOAEC SAS 1 (high surface area): 1 mg/m^3 LOAEC SAS 2 (low surface area): 0.5 mg/m^3 SAS 1: interstitial inflammation, granuloma and fibrogenesis of the lungs and granulomas, granulomatous inflammation, hyperplasia in the lymph nodes SAS 2: same as SAS 1 + fibrogenesis of the lungs and fibrosis of the lymph nodes	-	Pyrogenic SAS	Category 1 C ≤ 20 (90-day)
Reuzel et al., 1991 13-w	LOAEC: 1 mg/m^3 Dose dependent increases in accumulation of alveolar macrophages, cellular debris, intra-alveolar polymorphonuclear leucocytic infiltration, increased septal cellularity, alveolar	-	Pyrogenic SAS	Category 1 C ≤ 20 (90-day)

Study reference and exposure duration	Effective dose (mg/L/6h/day, 5 days/week) and type of effects	Extrapolated effective dose when extrapolated to 90-day exposure	SAS type	Classification supported by the study (inhalation, dust, mg/m³)
	bronchiolization, focal interstitial fibrosis, cholesterol clefts			
Anonymous (2014), reviewed by Creutzenberg et al. (2022) 13-w	LOAEC: 1 mg/m³, effects relevant for classification from 2.5 mg/m³ Increased lung weights (2.5 and 5 mg/m³), persistent inflammatory responses in the nasal cavity in all dose groups with a dose dependent increase in severity and transient inflammatory effects in the lungs in 2.5 and 5 mg/m³	-	Precipitated SAS	Category 1 C ≤ 20 (90-day)
Anonymous, 1990 Lee and Kelly, 1992 Warheit, 1991 4-w	LOAEC: 50 mg/m³ At 50 and 150 mg/m³ dose reversible increase in lung weights, alveolar macrophage response, polymorphonuclear leukocytic infiltration, and Type II pneumocyte hyperplasia in alveolar duct regions.	17 mg/m³	Colloidal SAS	Category 1 C ≤ 20 (90-day)

9.1.2 Comparison with the CLP criteria

Substances are classified in Category 1 for STOT RE when they have produced significant toxicity in humans or, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included. This can be determined with reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. The guidance value for dusts/mists/fumes after six hours/day exposure of rats in a 90-day repeated dose inhalation study is <20 mg/m³ for Cat 1 and 20-200 mg/m³ for Cat 2.

There are some reports on effects in workers exposed to SAS described by Morfeld et al. (2014), Taeger et al. (2016) and Yong et al. (2022) that found no significant effects. It is noted that former workers that are retired or have quitted their work due to health problems are not included in the study group. Therefore, it could be speculated that, seen the progression of the toxicity in animals over time after exposure, the most important people may not have been taken into account. Further, the duration of employment varies between 0.2 and 41.8 years, but more details on the distribution were not provided. In case of cumulative exposure, the exposure levels per worker can vary majorly depending on their employment years. Hence, the available human data have limited value and cannot be used to either support or refute classification of SAS.

The main findings in animal studies (all performed in rats) were inflammatory responses in the lungs, lymph nodes and in some cases the nose. Typical findings include alveolar macrophage response, polymorphonuclear leukocytic infiltration, pneumocyte hyperplasia, increased inflammatory markers in

BALf measurements and lung/lymph node weight increases. The studies by Fraunhofer ITEM (2019) and Anonymous (2014) also found inflammatory effects in the nose including hyperplasia and epithelial hyaline droplets formation after exposure to respectively pyrogenic and precipitated silica. These effects started at the lowest dose of 0.5 and 1.0 mg/m^3 and increased in frequency and severity in a dose dependent manner. Histopathology of the nose was not always performed (for example not in Reuzel et al. 1991 or Arts et al. 2007), which seems to be an important reason these effects were reported more incidentally than those in the lungs.

The recent 90-day study by Fraunhofer ITEM (2019) was the only study that included two different surface areas of pyrogenic silica, one of which (SAS 2) had clearly lower surface area (hence larger) particles than any of the other forms tested (BET 40/50 m^2/g). Although both SAS forms induced inflammatory effects, the incidence, severity and persistency was clearly higher after exposure to low BET particles. The most severe effects induced by both SAS materials were interstitial inflammation, granuloma and fibrogenesis of the lungs and granulomas, granulomatous inflammation, hyperplasia in the lymph nodes. In addition, SAS 2 induced fibrosis in the lungs of one high dose animal and fibrogenesis and fibrosis in the lymph nodes at all dose levels. Effects persisted through the 52-week recovery period in all SAS 2 groups, with high incidences at 2.5 and 5 mg/m^3 (up to 80/90% males/females). The LOAEC of SAS 1 was 1 mg/m^3 and of SAS 2 it was 0.5 mg/m^3.

It should be noted that in the study by Reuzel et al. (1991) fibrosis was also found after exposure to smaller SAS particles (BET 200 m^2/g), starting already at 1 mg/m^3 and reaching statistical significance at 30 mg/m^3.

The untreated SAS forms discussed in this dossier can be divided into two main types of SAS, that differ in production method. Pyrogenic silica is produced via a thermal process, while precipitated silica, silica gel and colloidal silica are produced via a wet process. All these types of SAS are nanostructured materials comparable in chemical identity and purity and non-crystalline in structure. Also other physicochemical properties, such as density and water solubility, are in a similar range (see Table 3).

The clearest effects were observed after exposure to pyrogenic silica. However, the amount of data available with precipitated silica is more limited and the available findings are in line with data from pyrogenic silica. Regarding silica gel and colloidal silica, very limited information is available. However, these types are closely related to precipitated silica and in fact share the same CAS number. As the toxicity of SAS is considered to be mainly attributed to the particle size and surface characteristics of the particles, it can be assumed that the unmodified types of SAS under the scope of this proposal are similar and effects observed can be extrapolated to the non-tested types and forms of SAS. It is noted that this evaluation only includes inhalation exposure to SAS in the form of dusts/mists/fumes, which generally excludes silica gel and colloidal silica dispersions in liquids that are not inhalable. A note could be considered such as: ”This classification applies only to mixtures that may lead to exposure of the end-user’s lungs by inhalation.”

In summary, multiple studies in rats showed inflammatory effects and fibrogenesis/fibrosis in the respiratory organs and/or lymph nodes after inhalation exposure to various types and forms of SAS. While some of the inflammatory effects were reversible, it took often more than 3 months and fibrogenesis/fibrosis was not reversible 1 year after exposure to SAS particles with a low surface area. In the CLH criteria ‘multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity’ are specifically mentioned as effects relevant for classification. However, these are non-exhaustive examples of functional impairments that are not just adaptive. The inflammatory reactions occurring at doses far below the guidance values such as seen in Fraunhofer ITEM (2019), Anonymous (2014), Reuzel et al. (1991) and Anonymous (1998) are also considered supportive for classification.

Due to differences in the applied concentration levels, exposure length and parameters analysed, it is very difficult to draw any conclusion on the relative toxicity of different SAS types and forms. However, the lowest effect concentrations reported in the 90-day studies that included lower concentration levels were all in the 0.5-2 mg/m^3 range for both pyrogenic and precipitated silica

(Fraunhofer ITEM 2019, Reuzel et al., 1991, Anonymous, 1998, Anonymous, 2014), which lies (far) below the guidance value of STOT RE Cat 1 of 20 mg/m^3 for inhalation of dust.

9.1.3 Conclusion on classification and labelling for STOT RE

Based on the observed effects in rats in various repeated dose inhalation studies, a classification is proposed of **STOT RE 1, H372 (respiratory tract) (inhalation)**.

Based on the effects in the Fraunhofer ITEM (2019) study at 0.5 and 1.0 mg/m^3 SAS 2, a specific concentration limit might be justified. However, this would be based mainly on a SAS form with a lower surface area than usual. For other SAS forms, the severity of the effects at concentrations below 2 mg/m^3 is insufficient to warrant a specific concentration limit.

No evaluation was performed of the effects after repeated oral and dermal exposure. However, the effects after inhalation were all local effects related to the presence of SAS particles and no systemic effects were observed. Due to the different physiological properties of the organs and the nature of the effects after inhalation, no local effects to the skin and the intestinal tract are expected. Therefore, the proposed classification is limited to the inhalation route.

The lung effects after inhalation are only expected for particles small enough to reach the alveoli (i.e. respirable). However, the aggregate particle size range of these forms of SAS are in the respirable range and expected to reach the alveoli. Therefore, no limitation on the particle size is required for the proposed classification.

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11 ANNEX I TRADE NAMES ACCORDING TO THE REGISTRATION DOSSIER

ABSIL -100

ABSIL-HC

AC6120 carrier

AEROPERL

AEROSIL [Silica, fumed, pyrogenic]

ARSIL

ART Hydroprocessing catalysts

ART Hydroprocessing catalysts

Acematt [Silica, precipitated]

Acematt [Silica, precipitated]

Admafine Silica

Aeroperl [Silica, fumed, pyrogenic]

Aerosil [Silica, fumed, pyrogenic]

Airlica

Alusilica

ApART™ System, ApART™ Catalyst System

BARIACE

BARIFINE

BECOSORB

Britesorb

CAB-O-SIL® fumed silica

CAB-O-SIL™ Colloidal silica

CAB-O-SIL™ silica

CAB-O-SPERSE® silica dispersion

CHIFFONSIL

CP

Cabot aerogel

Caldic Silica

Caldic Silica 02

Caldic Silica 02GR

Caldic Silica 04

Caldic Silica 04GR

Caldic Silica 05

Caldic Silica 05 MP

Caldic Silica 05GR

Caldic Silica 06

Caldic Silica 06GR

Caldic Silica 07

Caldic Silica 07GR

Caldic Silica 08MP

Caldic Silica 08T

Caldic Silica 09

Caldic Silica 09GR

Carplex [Silica, precipitated]

Catalyst KD CAT

Chameleon Gel

Compression Pack™

DARACLAR®

DAVISIL®

DX® Catalyst Platform, DX® Catalyst Technology

Denka Fused Silica (DF)

EBROSIL

EQ-Pak

EXP [Silica, precipitated]

Egesil [Silica, precipitated]

Enova® aerogel

Envirogel

FLOWING AGENT TP88

Fumed Silica

GRADE

GR® catalysts, technology

Gasil

HOLLOWY-N15

HOP Catalyst

High Stability Low Sediment (HSLS), HSLS™ Catalyst Technology

IBERSIL

ICR Catalyst

Indicator Gel

Insil [Silica, precipitated]

JR-800

KONASIL

Kovasil

Köstropur®

Köstrosolid®

Köstrosol®

Köstrosorb®

LC FINING technology, LC FINING™ Catalyst

LEVILITE

LS™ Catalyst Platform, LS™ Catalyst Technology

LUDOX®

Lucilite

Lumira® aerogel

MATREX®

MEBU™ Pilot Plant, Mini Ebullating Bed Unit (MEBU)

MFIL- 150(G)

MFIL- 200(S)

MFIL-125

MFIL-125(S)

MFIL-P (S)

MFIL-P(U)

MICROD

MIZUKASIL P-73

MT-500SA

Microsil

N-IDS carrier

Neosil

Neosyl

NiSAT carrier

OCR® Catalysts

Orange Gel

PE

PHOENIX™ catalyst, PHOENIX Process

Precipitated silica

QUARTRON PL

REMASOL®

ReforMax carrier

Reolosil

Rescor castable ceramic binders, Resbond adhesive, Thermeez Ceramic Putty

Rubingel

SATINIER

SHIELDEX®

SILICA A

SILICA GEL

SILICA GEL CARRIER SG

SILICA GEL CAT LITTER

SILICA LC

SILICA MICRO BEAD

SILICA PERAL

SILICON DIOXIDE

SILIGEL

SIOGEL® white

SP

SPHERICA

SPHERON L-1500

SS-SIL

SSP

STR

SYLOBEAD®

SYLOBLANC™

SYLOBLOC®

SYLODENT®

SYLOID®

SYLOJET®

SYLOX®

Several Catalyst grades including synthetic amorphous silica, e.g. SYLOPOL®, P.O. CAT CARRIER XPO, Ziegler Natta Catalyst grades

SiO_2

SiO_2-Sootstaub

Sident [Silica, precipitated]

Sident [Silica, precipitated]

Silcron

Silfil

Silica

Silica Gel

Silicagel

Silicon Dioxide

Silicon dioxide (SD-B)

Silicon dioxide as used in different catalyst mixtures

Silicon dioxide in different catalyst mixtures

Silizium Dioxid

Siliziumdioxid

Sipernat [Silica, precipitated]

Sipernat [Silica, precipitated]

SmART Catalyst System® series, SmART System

Sodium dihydrogenorthophosphate

Sorb-it

Sorbosil

Sorbsil

StART™ System, StART™ Catalyst System

T-Lite

TAFOSIL

TAVERSIL

TIXOSIL

TP88

TREADSIL

TRISYL®

TYSIL

Thermal Wrap™

Tokusil

Tolled trading goods

ULS

ULTRABOND™ fumed silica

Ultrasil [Silica, precipitated]

Ultrasil [Silica, precipitated]

WL [Silica, precipitated]

Wet Gel

Wetgel

White Carbon HCSIL

White Gel

XWP GEL

YH [Silica, precipitated]

ZEODENT®

ZEOFLO®

ZEOFOAM®

ZEOFREE®

ZEOPOL®

ZEOSIL

ZEOSYL®

ZEOTHIX®

ZEO®

ZS

Zeobead

Zeoprep

Zeosphere

carbon-white

fumed silica

silica gel

silicon dioxide

white carbon black

12 ANNEX II – SUMMARY HISTOPATHOLOGICAL EVALUATION OF THE LYMPH NODES (CONFIDENTIAL)