CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

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

Index Number: -

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CLH REPORT FOR SILANAMINE, 1,1,1-TRIMETHYL-N-(TRIMETHYLSILYL)-, HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

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CLH REPORT FOR SILANAMINE, 1,1,1-TRIMETHYL-N-(TRIMETHYLSILYL)-, HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

1 IDENTITY OF THE SUBSTANCE

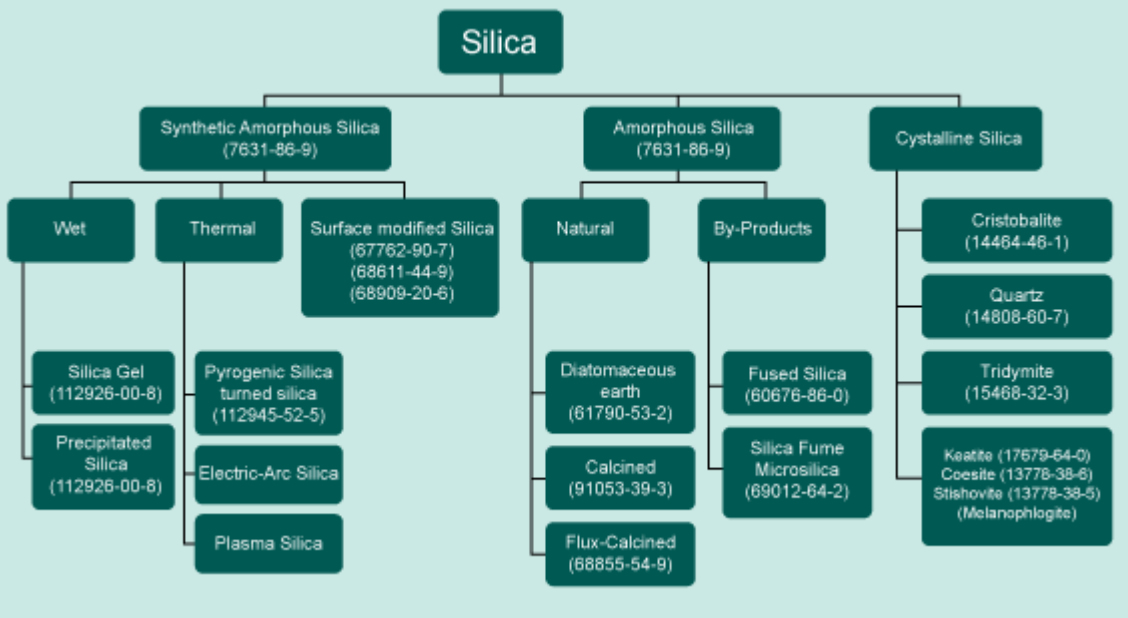
1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide
Other names (usual name, trade name, abbreviation)	surface treated synthetic amorphous silica, surface treated amorphous silicon dioxide Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica Reaction products of 1,1,1-trimethyl-N-(trimethylsilyl)-silanamine with silica
Common name (if available and appropriate)	Pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide
EC number (if available and appropriate)	272-697-1
EC name (if available and appropriate)	silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica
CAS number (if available)	68909-20-6
Other identity code (if available)	Aerosil R 812 S Aerosil R 812
Molecular formula	$[SiO_2]_n$-$[OSi(CH_3)_3]_m$ with n>m m corresponds to the surface treatment of silica with methyl groups.
Structural formula	See figure below figure 2
SMILES notation (if available)	Not relevant
Molecular weight or molecular weight range	Approx 60.08 g/mol (which is the molecular weight of one unit of SiO_2) The surface modification does not significantly affect the molecular weight of the substance which is slightly higher than the SiO2 molecular weight (carbon content actually only represents from 0.6 to 4% w/w).
Information on optical activity and typical ratio of (stereo) isomers (if applicable	Not relevant

and appropriate)	
Description of the manufacturing process and identity of the source (for UVCB substances only)	surface treatment of pyrogenic synthetic amorphous silica (nano) with 1,1,1-trimethyl-N-(trimethylsilyl)-silanamine)
Degree of purity (%) (if relevant for the entry in Annex VI)	Purity of silica : ≥ 99.8 % (w/w) for pyrogenic (fumed) silica before and after the surface modification
Primary particle size (TEM)	Experimental data : 6.9-8.6 nm Range covered by this dossier: 6.9-8.6 nm
Shape of primary particles (TEM)	spherical

Figure 1: Polymorphs of silica covering crystalline as well as non-crystalline (amorphous) forms. CAS RN of the different forms are shown in square brakets. The specific surface-treated silica under this CLH proposal is derived from synthetic amorphous silica (SAS) (surface treated silica, CAS RN 68909-20-6).



Source: European Industrial Minerals Association

As shown in Table 1 above, the substance covered by this CLH proposal is "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) and a molecular formula as [SiO2]n-[OSi(CH3)3]m where n > m. The m corresponds to the surface treatment of silica with methyl (alkyl) groups. This description fit with two surface treated silica in this proposal: Aerosil R 812 and R 812 S.

The main difference between Aerosil R 812 and R 812 S is the density of superficial methyl groups which is slightly higher in Aerosil R 812 S (2-3% for R812 and 3.0-4.0 for R 812 S). The specific surface area (260 m²/g for R812 and 220 m²/g for R812S) is also a data which differentiates the Aerosils R 812 and R 812 S, but those two values remain in the same range. Aerosil R 812 and R 812S have been obtained by surface modification of the hydrophilic silica

with 1,1,1-trimethyl-N-(trimethylsilyl)silanamine [CAS No. 999-97-3], that results in a trimethylsilyl-surface modified silica.

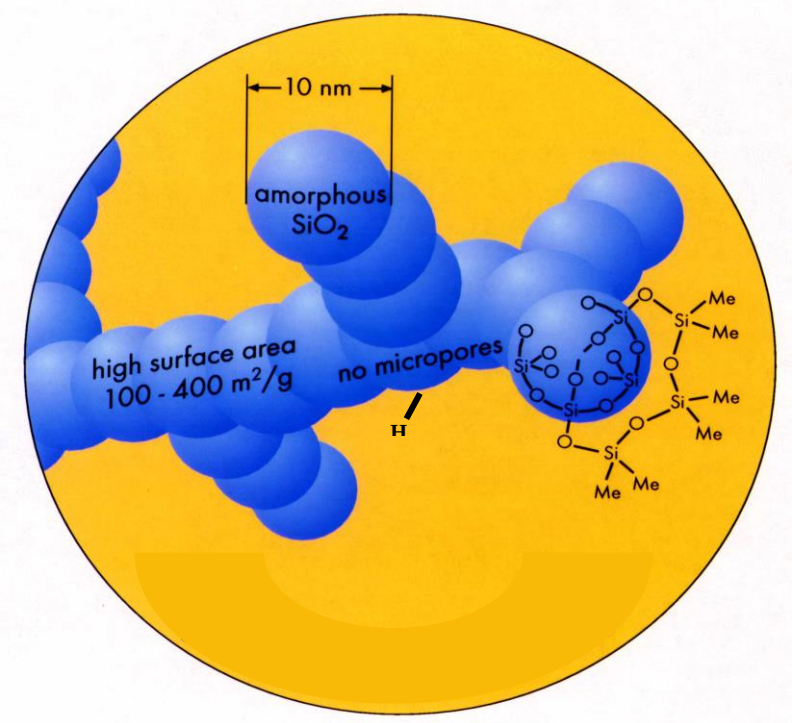
The surface modification of the hydrophilic silica with dichlorodimethylsilane [CAS No. 75-78-5] results in a dimethylsilyl-surface modified silica (Aerosil R 972, R 974, R 976) [CAS No. 68611-44-9], which are somewhat less hydrophobic than Aerosil R 812 S due to the lower density of superficial methyl groups.

Other surface treated silica are presented in this CLH proposal: Aerosil R 972, Aerosil R 974 and Aerosil R 976.

The difference between Aerosil R 972, Aerosil R 974 and Aerosil R 976, used in toxicology and ecotoxicology, and the Aerosils R 812 and R 812 S presented in this dossier is the molecule used for functionalisation of silica : Dichlorodimethylsilane for Aerosil R 972, Aerosil R 974 and Aerosil R 976 and 1,1,1-trimethyl-N-(trimethylsilyl)silanamine for Aerosils R 812 and R 812 S.

As a consequence, the density of superficial methyl groups in Aerosil R 972, Aerosil R 974 and Aerosil R 976 are slightly lower than the Aerosils R 812 and R 812 S .

Figure 2. Treated hydrophobic amorphous silica: here with dichlorodimethylsilane (HPV consortia 2003)



1.2 Composition of the substance

Table 2: 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 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Purity of silica	≥ 99.8 % (w/w) for pyrogenic (fumed) silica before and after the surface modification	none	Skin Irrit. 2 – H315 Eye Irrit. 2 – H319 Acute Tox 4 – H332 STOT RE 2 – H373

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Crystalline silica	<0.1%	None	STOT RE 1 – H372 (lung) (inhalation) STOT RE 2 – H373 Eye Irrit.2 – H319 Acute Tox 4 – H332	No

Crystalline silica is classified in group 1 (carcinogenic to humans) by IARC.

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
-					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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 existing entry in Annex VI										
Dossier submitters proposal	To be determined	silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide	272-697-1	68909-20-6	STOT RE 2	H373 (lungs; inhalation)	GHS08 Wng	H373 (lungs; inhalation)	EUH066		
Resulting Annex VI entry if agreed by RAC and COM	To be determined	silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica; pyrogenic, synthetic	272-697-1	68909-20-6	STOT RE 2	H373 (lungs; inhalation)	GHS08 Wng	H373 (lungs; inhalation)	EUH066		

		amorphous, nano, surface treated silicon dioxide									

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	**Reason for no classification**	**Within the scope of public consultation**
Explosives	data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Not relevant	No
Oxidising gases	Not relevant	No
Gases under pressure	Not relevant	No
Flammable liquids	Not relevant	No
Flammable solids	data conclusive but not sufficient for classification	Yes
Self-reactive substances	data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Not relevant	No
Pyrophoric solids	data conclusive but not sufficient for classification	Yes
Self-heating substances	data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	data conclusive but not sufficient for classification	Yes
Oxidising liquids	Not relevant	No
Oxidising solids	data conclusive but not sufficient for classification	Yes
Organic peroxides	not relevant	No
Corrosive to metals	data conclusive but not sufficient for classification	Yes
Acute toxicity via oral route	data conclusive but not sufficient for classification	Yes
Acute toxicity via dermal route	data lacking	No
Acute toxicity via inhalation route	data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	data conclusive but not sufficient for classification	Yes
Serious eye damage/eye irritation	data conclusive but not sufficient for classification	Yes
Respiratory sensitisation	data lacking	No
Skin sensitisation	data conclusive but not sufficient for classification	Yes

Hazard class	Reason for no classification	Within the scope of public consultation
Germ cell mutagenicity	data conclusive but not sufficient for classification	Yes
Carcinogenicity	data conclusive but not sufficient for classification	Yes
Reproductive toxicity	data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	data lacking	No
Specific target organ toxicity-repeated exposure	A classification STOT RE 2 – H373 is proposed	Yes
Aspiration hazard	data lacking	No
Hazardous to the aquatic environment	Conclusive but not sufficient for classification	Yes
Hazardous to the ozone layer	data lacking	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

No previous or current classification is available for the Pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Large-scale production and use of amorphous silica nanoparticles (SiNPs) have increased the risk of human exposure to SiNPs, while their health effects remain unclear. STOT RE is proposed by industrial minerals producers (see their website at https://www.crystallinesilica.eu/content/classification-and-labelling-rcs). Action is proposed in view of the divergences in notifications from the C&L inventory where 99% of the notifiers (n=1841) do not classify.

5 IDENTIFIED USES

Under regulation (EU) 528/2012, "pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide" is approved as an existing active substance for use in biocidal products of product-type 18 (Insecticides, Acaricides and Products to Control Other Arthropods):

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0795&from=EN

The main intended use assessed is the the control of fowl-infesting ectoparasites in poultry houses, by professional operators.

6 DATA SOURCES

The information from the Competent Authority Report of the pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide are included in the dossier.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid / form: powder	Degussa SDS 2005b-e, 2006i	
Melting/freezing point	Not relevant, as the substance is an inorganic solid of mineral character with extreme melting point (of SiO2).	Degussa SDS 2005b-e, 2006i	
Boiling point	Not relevant, as the substance is an inorganic solid of mineral character with extreme melting point (of SiO2).	Degussa SDS 2005b-e, 2006i	
Relative density	Density of Bulk material: approx. 50 – 70 g/L density of particles: approx. 2 (20°C)	Degussa SDS 2005b-e, 2006i	measured
Vapour pressure	Not measurable	Degussa SDS 2005b-e, 2006i	
Surface tension	Not applicable / inorganic solid with mineral character	-	
Water solubility	Silica particles are not soluble. They form a suspension of particles in water. Due to the fonctionalisation of the surface it is expected that functionalised Aerosil is not susceptible to hydrolyse in monosilicic acid.	Expert assessment	Statement
Partition coefficient n-octanol/water	Not applicable as the substance is insoluble in water and octanol.	-	
Flash point	Not relevant	-	
Flammability	Not flammable	AQura 2007c	
Explosive properties	The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no structural alerts for ignition (silica derivative).	-	
Self-ignition temperature	Not relevant, as the substance is an inorganic solid of mineral character with extreme melting point (of SiO2).	-	
Oxidising properties	The substance is an inorganic, inert solid with mineral character and no oxidising, reactive chemical structures (silica	-	

Property	Value	Reference	Comment (e.g. measured or estimated)
	derivative).		
Granulometry	See below the table		
Stability in organic solvents and identity of relevant degradation products	No data		
Dissociation constant	Not applicable	-	
Viscosity	Not applicable	-	

Particle size distribution:

Silica is produced as very small particles called primary particles that have potential to aggregate. Aggregate are particle comprising of strongly bound or fused particles. Under conditions of normal handling and use, it is considered that aggregates are the smallest stable particles. These aggregates can form agglomerates.

Different studies were submitted on different shear forces to characterize the active substances. The curves are submitted but raw data are not submitted on each volume fraction implying blanks in tables below:

Table 8: particle size distribution of silicon dioxide surface treated under different condition

Volume fraction %	d_{10}	d_{50}	d_{90}	Proportion <10µm
AEROSIL® R812S (Dynamic light scattering)				
20101222-001-6 , Perlet 2011 *high shear force in ethanol, 1 batch*	95 nm	150 nm	190 nm	100%
A060009416 AQura 2006 *Dispersion in ethanol, 1 batch*	3.7 µm	11.2 µm	25.7 µm	45%
AN-ASB 0638, anonymous 2014 *In air stream, 5 batches*	5.1 µm	13.6 µm	32 µm	38%
Indispron® D110 (Dynamic light scattering)				
in 50/50 ethanol/water dispersion	15.9 µm	53.6 µm	93 µm	7%

It will be consider that the aQura 2006 and test report AN-ASB 0638 (2014) studies measure agglomerate form (d_{50} around 10-15 µm) while Perlet 2011 measure aggregate form (d50 around 150 nm) of aerosil R812S. This last value can be confirmed by TEM pictures demonstrating packs of 100-200 nm aggregates linked together with small chains of primary particles.

When the active substance is formulated in Indispron D110, the measured size of particles increases. Additional microscopy data are submitted to confirm the particle size distribution in

Indispron D110. No data is submitted on particle size distribution of biocidal product under shear force to clarify if this particle size distribution changes when the biocidal product is sprayed.

Specific surface area:

Specific surface area was tested on aerosol R812S using BET method.

The range on 5 batches was found in the range of 217-225 m^2/g.

These values can be converted to volume specific surface area using absolute density of Silicon dioxide 2.229 as given in Handbook of chemistry and physics (D. R. Lide 2005-2006):
Range of volume specific surface area on 5 batches: 483-501 m^2/m^3.

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no structural alerts for explosivity (silica derivative).

8.2 Flammable gases (including chemically unstable gases)

Not relevant

8.3 Oxidising gases

Not relevant

8.4 Gases under pressure

Not relevant

8.5 Flammable liquids

Not relevant

8.6 Flammable solids

The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no structural alerts for flammability (silica derivative).

8.7 Self-reactive substances

The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no structural alerts for self-reactive behaviour (silica derivative).

8.8 Pyrophoric liquids

Not relevant

8.9 Pyrophoric solids

The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no structural alerts for pyrophoric properties (silica derivative).

8.10 Self-heating substances

The substance is an inorganic, inert solid with mineral character, with high melting point.

No self-heating behaviour expected.

8.11 Substances which in contact with water emit flammable gases

The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no flammable gases is expected to be emitted with contact with water.

8.12 Oxidising liquids

Not relevant

8.13 Oxidising solids

The substance is an inorganic, inert solid with mineral character, almost fully oxidised, therefore, no structural alerts for oxidising properties (silica derivative).

8.14 Organic peroxides

Not relevant

8.15 Corrosive to metals

Not relevant

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

There is no toxicokinetics data specifically related to the substance covered by this dossier. The lack of systemic effects reported in the toxicity studies can be due to a lack of systemic absorption.

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

No information is available regarding the toxicokinetic profile of the substance.
No systemic effect has been observed.

10 EVALUATION OF HEALTH HAZARDS

Read-across between the different types of amorphous silica

The substance under consideration in the Biocidal Product Dossier and relevant for the claimed application consists of reaction product of synthetic amorphous silica treated with hexamethylsilazane (leading to a silica characterised by CAS No 68909-20-6 and marketed as Aerosil R 812 and Aerosil R 812S). This does not apply to other silica, as amorphous non surface-treated silica or crystalline silica. In this dossier, an X-ray analysis showed that Aerosil R 812 and R 812S have a content of crystalline silica < 0.1%.

Several toxicological studies (acute inhalation study, repeated dose toxicity studies by oral route and inhalation, carcinogenicity study by oral route and one-generation study by oral route) were performed with Aerosil R 972 or Aerosil R 974 which are reaction products of dichlorodimethyl-silane with silica characterised by CAS No 68611-44-9.

For repeated oral toxicity endpoints, the studies were performed with Aerosil R 972. The difference between Aerosil R 972 and Aerosil R 812/812S is the nature of the surface-treatment (hexamethylsilazane for CAS 68909-20-6 (HMDZ) and dichlorodimethylsilane for CAS 68611-44-9). The chemical groups added by the reaction have no particular activity by themselves impacting the repeated toxicity of both Aerosil.

Based on Substane Evaluation Reports avialbel for HMDZ and dichlorodimethylsilane (2015), concerns were specifically related to environnement. Classification described in the reports suggest that both substances shere similar toxicological properties (irritant properties) without any sufficient hazards triggering a classification STOT RE.

Similar physico-chemical properties such as non solubility in water and stability to hydrolysis are reported between these two types of silica. Therefore, no impact on systemic toxicity after oral exposure is expected.

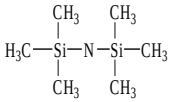
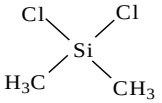
Table 10.1. Identity of the tested materials

Common name, Synonyms	**Pyrogenic, Synthetic Amorphous Silicon dioxide, nano, surface treated silicon dioxide** Synthetic amorphous silica, Amorphous surface treated silicon dioxide	
CAS-No.	68909-20-6	68611-44-9
EINECS-No.	272-697-1	271-893-4
Other No. (CIPAC, ELINCS)	/	/
IUPAC Name	Reaction products of 1,1,1-trimethyl-N-(trimethylsilyl)-silanamine with silica	Reaction products of dichlorodimethyl-silane with silica
Chemical name	Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica	Silane, dichlorodimethyl-, reaction products with silica

Trade names used	Aerosil R 812 S * Aerosil R 812	Aerosil R 972 Aerosil R 974 Aerosil R 976
Molecular formula	$[SiO_2]_n$-$[OSi(CH_3)_3]_m$ with n>m	$[SiO_2]_n$-$[OSi(CH_3)_2]_m$ WITH N>M
	m corresponds to the surface treatment of silica with methyl groups. thus, depending on aerosils notified n can be from more than 10 times higher than m.	
Structure	Random arrangement of SiO_4 tetrahedron (base unit of the structure of the macromolecular network). The surface treated silica notified are synthetic amorphous silica with surface treatment Shape of primary particles: spherical	
Molecular weight (g/mol)	Approx 60.08 g/mol (which is the molecular weight of one unit of SiO_2) The surface modification does not significantly affect a lot the molecular weight of the substance which is slightly higher (carbon content actually only represents from 0.6 to 4% w/w).	
Primary particle size (TEM)	Experimental data : 6.9-8.6 nm Specifications: 6.9-8.6 nm	No experimental data Specifications: 12-16 nm
Shape of primary particles (TEM)	spherical	spherical

Table 10.2. Production process: (Degussa 2003a: Technical Bulletin Fine Particles)

Synthetic amorphous *hydrophobic* silica are produced by surface treatment of the synthetic amorphous *hydrophilic* silica:

Step of production process	Aerosil R 812 and Aerosil R 812 S [CAS No. 68909-20-6]	Aerosil R 972, R 974, R 976 [CAS No. 68611-44-9]
1. Silica production, pyrogenic, hydrophilic [CAS 112945-52-5]	The raw material $SiCl_4$ (tetrachlorosilane) or as a mixture with other chlorosilanes of alkylchlorosilane is mixed at gaseous stage with air and hydrogen and is burned in a flame at about 1000 °C ("flame hydrolysis"), according to the following equation (pyrogenic process): $SiCl_4 + 2\ H_2 + O_2 \rightarrow SiO_2$ (polymer, hydrophilic, amorphous) + 4 HCl	
2. Chemical after-treatment of the hydrophilic amorphous silica: The surface-attached free hydroxyl groups (silanol groups) are irreversibly replaced by organic residues such as methyl groups	Surface modification with hexamethylsilazane [CAS No. 999-97-3]  This results in a trimethylsilyl-surface modified silica which is highly hydrophobic. The main difference between Aerosil R 812 and R 812 S is the density of superficial methyl groups which is slightly higher in Aerosil R 812 S (2-3% for R812 and 3.0-4.0 for R812S). The specific surface area (260 m²/g for R812 and 220 m²/g for R812S) is also a data which differentiates the Aerosils R 812 and R 812 S, but those two values remain in the same range.	Surface modification with dichlorodimethylsilane [CAS No. 75-78-5]  This results in a dimethylsilyl-surface modified silica, which are somewhat less hydrophobic than Aerosil R 812 S due to the lower density of superficial methyl groups. The difference between Aerosil R 972, Aerosil R 974 and Aerosil R 976 is the density of superficial methyl groups which is slightly lower than the Aerosils R 812 and R 812 S and the specific surface area

For the specific concern of inhalation, the studies were performed with Aerosil R 974. In this case, the main relevant physico-chemical parameter influencing absorption is the particle size. Under conditions of normal handling and use, primary particle of surface-treated silica is not expected and the aggregates are considered as the smallest stable particles. In this context, the particle size distributions of aggregates of Aerosil R 812/R 812S and Aerosil R 974 were compared in high shear forces conditions. The values are in the same order of magnitude (peak and shapes of curves). This suggests that results from inhalation tests on Aerosil R 974 can be extrapolated to Aerosil R 812/R 812S.

Table 10.3: Comparative table between the different AEROSIL presented in the dossier

	Synthetic amorphous silica, surface treated				
	CAS No. 68909-20-6		**CAS No. 68611-44-9**		
	R 812 S	**R 812**	**R 972**	**R 974**	**R 976**
Specific surface area (BET) [m^2/g]	220 ±25	260 ±30	110 ±20	170 ±50	250 ±25
Average primary particle size					
Specification	7 nm	7 nm	16 nm	12 nm	No data
experimental data	7 -8 nm	5 nm	No data	No data	No data
Particle size **high shear force → aggregates**					
range (d5-d95)	88-240 nm	No data	120-240 nm	50-300 nm	No data
median (d50)	150 nm	No data	179 nm	120 nm	No data
Particle size **low shear force in ethanol → agglomerates**					
range (d5-d95)	2-32 µm	No data	2-23 µm	No data	No data
median (d50)	11.2 µm	No data	4.4 µm	No data	No data
Particle size **powder**					
range (d5-d95)	6-90 µm	7-130 µm	No data	No data	No data
median (d50)	23µm	30 µm	No data	No data	No data

Teratogenicity studies performed with a synthetic amorphous non surface-treated silica gel were also submitted. The aim of the surface modification is to block the silanol group in order to reduce the affinity of silica for water. Therefore, it is expected that surface-treated silica would not be better absorbed by oral route than non surface-treated silica. Furthermore, the lack of systemic effects of both surface treated silica and non surface-treated silica in oral toxicity studies (based on data submitted in this dossier for the first and on literature for the latter) supports a read-across for systemic toxicity. However, for local pulmonary endpoints, it was agreed at Biocidal Technical Meeting II 2011 that no read-across between surface-treated and non surface-treated silica should be considered since it could not be concluded that these types of silica are technically equivalent.

It has to be noted the substance is a nanoparticle, however the available studies are not designed to assess specifically the toxicity linked to this property.

10.1 Acute toxicity - oral route

Table 10.1.1: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
OECD 401 (1981)	Rat, Wistar, 5 m, 5 f	Aerosil R 812	2 000 mg/kg bw, single dose	> 2 000 mg/kg bw	IIIA6.1.1

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Acute oral exposure to Aerosil R 812 is void of acute toxic adverse effects (LD_{50} > 2000 mg/kg bw). No signs of intoxication were noticed after 14 days of observation.

10.1.2 Comparison with the CLP criteria

The LD_{50} in rats is higher than 2000 mg/kg bw.
This value is out of the range for classification under regulation (EC) 1272/2008.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results of the acute oral toxicity study, no classification is proposed for the active substance.

10.2 Acute toxicity - dermal route

No study was provided for acute toxicity by dermal route.

Information from the skin irritation study performed with Aerosil R 812 (see section below) could suggest a low dermal toxicity of Pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide since no mortality was observed at the dose of 0.5 g per animal.

10.3 Acute toxicity - inhalation route

Table 10.3.1: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
No data on the method	Rat, Wistar, 5 m, 5 f	Aerosil R974 56% of the particles had	477 mg/m^3 [analytical,] 4 h	> 477 mg/m^3	IIIA6.1.3

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
		an aerodynamic diameter <5µm (respirable)			

Table 10.3.2: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Mechanistic study on local effects, inflammation reaction model, no GLP	Aerosil R 812 S	Rat, Wistar, 10 f/dose Intra-tracheal application 0.15, 0.30, 0.60, and 1.2 mg dust/lung single dose with an observation period of 3, 21, and 90d	All doses: Acute-phase reaction (3 d): reversible increase in inflammation markers from bronchoalveolar lavage	IIIA6.10

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

Inhalation of respirable Aerosil R 974 provokes an inflammatory tissue reaction.
Similar inflammatory reactions have been described for other dusts (LC_{50} > 477 mg/m^3 [maximum attainable concentration]).

After a single *intratracheal* application of Aerosil R 812S, inflammation was assessed in the bronchoalveolar lavage, by counts of neutrophils, macrophages, total cells, and the expression of specific proliferation proteins and TNF-alpha.
At day 3, a significant transient increase of inflammatory markers was observed from the lowest tested dose (0.15 mg dust/lung) with a severity clearly dose-dependent.
At the dose of 0.6 mg dust/lung, the intensity was somewhat lower, but comparable to that of quartz at the same dose. Return to normal levels was reached within 21 days for all doses of Aerosil R 812S (highest dose 1.2 mg/lung), in contrast to quartz that induced a progressively chronic inflammation, not reversible within 90 days of observation. Furthermore, after a single exposure to Aerosil R 812S, no sign of fibrosis was evident in the lungs at 90 days post-exposure.

10.3.2 Comparison with the CLP criteria

The Lc_{50} in rats is higher than 477 mg/m^3 (corresponding to 0.48 mg/L).

The design of the study did not allow to determine a LC_{50}. Therefore, it is not possible to conclude whether the substance is acutely toxic by inhalation under regulation (EC) 1272/2008.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the results of the acute inhalation toxicity study, no classification is proposed for the active substance.

10.4 Skin corrosion/irritation

Table 10.4.1: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
OECD 404 (1981), GLP	New Zealand white Rabbit 3 m, 3 f	Aerosil R 812	(0.5 g) in polypropylene glycol/water (1:1) 4 hours of exposure on an intact (9cm^2) and an abraded (6.25 cm^2) shaved dorsal skin area.	No erythema was seen, neither on intact nor on abraded skin. The mean score for erythema was 0. No edema was seen, neither on intact nor on abraded skin. The mean score for edema was 0. Neither mortality nor symptoms of toxicity were seen. Body weight gain was inconspicuous. No test substance-related skin discoloration was seen within the application areas.	IIIA6.1.4

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

Rabbits received Aerosil R812 moistened with polypropylene glycol and physiological saline (1:1) on intact and abraded skin in a study performed according to OECD guideline 404.
No skin reaction was observed.

10.4.2 Comparison with the CLP criteria

Scores for erythema and edema are 0.
This score value is out of the range for classification under regulation (EC) 1272/2008.

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Based on the results of the skin irritation study, no classification is proposed for the active substance.

10.5 Serious eye damage/eye irritation

Table 10.5.18: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results** **- Observations and time point of onset** **- Mean scores/animal** **- Reversibility**	**Reference**
OECD 405 (1981), GLP	New Zealand white Rabbit 3 m, 3 f	Aerosil R 812	The test substance was applied undiluted 0.1 g <u>First group of animals (3 males)</u>: eyes remained untreated following instillation of the test substance. <u>Second group of animals (3 females)</u>: eyes were rinsed for one minute with physiological saline after 30 seconds following the instillation of the test substance.	Examination time points: 60min, 24h, 48h and 72h following instillation of the test substance. Neither mortality nor symptoms of toxicity were seen. The body weight gain was similar for all animals and inconspicuous. For both, rinsed and non-rinsed treated eyes, no corneal opacity was seen; an average score of 0 was reported for all examination time points and all animals. For both, rinsed and non-rinsed treated eyes, the iris remained inconspicuous; an average score of 0 was reported for all examination time points and all animals. At examination time point 60 minutes, all animals with non-rinsed treated eyes as well as one animal of the "rinsed"-group displayed redness of the conjunctiva (scored 1 for each animal). This effect disappeared in all concerned animals within 24 hours, indicating reversibility. At all further examination time pints (24, 48 and 72h), no more redness of the conjunctiva was seen (score = 0). No chemosis was seen. No test substance-related discoloration of the cornea and/or conjunctiva was seen.	IIIA6.1.4

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

10.5.2 Comparison with the CLP criteria

After instillation of 0.1g of Aerosil R812 in rabbits, an irritation score of 0.25 was reported when the treated eyes were not rinsed. Following rinsing, the irritation score was lowered to 0.08. These slight signs of irritation were reversible and disappeared within 24 hours.

These score values are out of the range for classification under regulation (EC) 1272/2008.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Based on the results of the eye irritation study, no classification is proposed for the active substance.

10.6 Respiratory sensitisation

No data on the potential of pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide to induce respiratory sensitisation are available.

10.7 Skin sensitisation

Table 10.7.1: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
OECD 406 (1981), GLP (Maurer optimization test)	Dunkin-Hartley albino Guinea pigs 24 m and 24 f	Aerosil R 812 A separate test was conducted with di-nitro-chloro benzene and was positive.	Induction: 0.1% Challenge: 0.1 % (first challenge) and 30% (second challenge)	At 24h: negative control: 0/24 treated: 0/24 At 48h: negative control: 0/24 treated: 0/24 Neither mortality nor clinical symptoms of toxicity were reported. The animals were inconspicuous and their body weight gains were not affected by the experiment.	IIIA6.1.5

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

For induction, 0.1 ml of a 0.1% dilution of test substance in physiological saline and propylene glycol (1:1) has been applied.
A first challenge was conducted 13 days after the last treatment of the third induction. A second challenge was conducted 13 days after the first one.
For the first challenge, 0.1 ml of a 0.1% dilution of test substance in physiological saline and propylene glycol (1:1) has been used.
For the second challenge; 30% of test substance in Vaseline has been applied.

None of the treated animals showed a positive reaction 24h and 48h after challenge.
Neither mortality nor clinical symptoms of toxicity were reported. All animals were inconspicuous and their body weight gains were not affected by the experiment.

10.7.2 Comparison with the CLP criteria

None of the treated animals showed a positive reaction 24h and 48h after challenge. Thus, no classification under regulation (EC) 1272/2008 is required.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the results of the skin sensitization study, no classification is proposed for the active substance.

10.8 Germ cell mutagenicity

Table 10.8.1: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
Similar to OECD 471 and 472, no GLP	Toluene-extract of Aerosil R 812 (values related to original amount of Aerosil).	*S. typhimurium*: TA 1537, TA 98, TA 100 *E. coli*: WP2 uvr A 0, 5, 15.8, 50, 158, 500, 1 580 and 5 000 µg/plate	Slight cytotoxicity from 1 580 to 5 000 µg/plate in the absence of S9 mix. The results for the negative and positive control plates were as expected. **Results:** Negative with S9 mix Negative without S9 mix	IIIA6.6.1
Guideline-like, acc. to Evans 1976, no GLP	Tested silica: Cab-O-Sil TS-610 [CAS 68611-44-9] (amorphous, surface-treated silica)	Chinese hamster Ovary (CHO) cells 0, 63, 125, 250, and 500 µg/ml	The test article was insoluble in the solvent (DMSO) at a stock concentration of 50 mg/ml and insoluble in treatment medium at a concentration of 500 µg/ml, it was soluble at all other concentrations tested.	IIIA6.6.2

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
			Cytotoxicity observed at 500 µg/ml: ~37 % (-S9) ~28 % (+S9) The positive and negative controls fulfilled the requirements for a valid test. **Results:** Negative with S9 mix Negative without S9 mix	
OECD 476, GLP	Aerosil R 812 S	Mouse Lymphoma L5178Y cells (TK+/-) 0, 2.34, 4.69, 9.38, 18.8, 37.5 µg/ml (+/- S9 mix), and 150 µg/ml (-S9 mix)	Precipitation: ≥ 37.5 µg/ml (± S9 mix) Cytotoxicity: In the main tests, no significant impact on relative survival was noted in any test combination. Expected results were obtained with solvent and positive controls. **Results:** Negative with S9 mix Negative without S9 mix	IIIA6.6.3

Table 10.7.2: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Bronchiolar Lavage: Radical-induced 8-OH-Guanine (8-OH-G) content in alveolar cells no GLP	Aerosil R 812 S	Rat Wistar 5 f/group Administration route: intra-tracheal (single exposure) 0, 0.15, 0.30, 0.60, and 1.2 mg dust/lung Sampling times: 3 d, 21 d, and 90 d	Increase in 8-OH-G, reversible but no clear dose-response relationship - 3 days after exposure: At the application dose of 0.15 and 0.30 mg/lung, the content of 8-OH-G radical-induced in alveolar cells is ~2x control; At the application dose of 1.2 mg/lung, the content of 8-OH-G radical-induced in alveolar cells is ~3x control; - 21 days after the exposure:	IIIA.6.6.4

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		after the single exposure	A slight increase of the content of 8-OH-G radical-induced in alveolar cells (< 2 x control) is observed at the application dose of 1.2 mg/lung. - 90 days after the exposure: No increase of the content of 8-OH-G radical-induced in alveolar cells is observed.	
Bronchiolar Lavage: Mutated p53 protein no GLP	Aerosil R 812 S	Rat Wistar 5 f/group Administration route: intra-tracheal (single exposure) 0, 0.15, 0.30, 0.60, and 1.2 mg dust/lung Sampling times: 3 d, 21 d, and 90 d after the single exposure	No mutated p53 protein was detected by monoclonal antibodies raised against a specific epitope of the protein.	IIIA.6.6.4

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

***In vitro* studies**

Pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (Aerosil R 812, Cab-O-Sil TS-610) were tested in *in vitro* tests.

In an Ames test (Doc IIIA 6.6.1), Aerosil R 812, negative results are observed in *S. typhimurium* TA 1537, TA 98, TA 100 and E. coli WP2 uvr A at doses up to 5 000 µg/plate with and without S9 mix. Nevertheless, several deficiencies were noted in this study such as only 4 strains used and product tested as a toluene extract (only liposoluble fraction was therefore analysed) without data on the solubility in this solvent. At the highest dose, the extract formed a macroscopically visible precipitate on the test plates that was still present at the end of the experiment. The cytotoxicity test revealed a weak toxicity at the two highest tested concentrations of the toluene extract from Aerosil R 812 (i.e. at 1580 and 5000 µg/plate), in the absence of S9 mix. An increase of number of revertant colonies was reported only at the highest tested dose with TA 100, in the presence of S9 mix (weak equivocal mutagenic effect).

A chromosome aberration test was performed with Cab-O-Sil TS-610, a synthetic pyrogenic amorphous surface-treated silica, in CHO cells (Doc IIIA 6.6.2) and gave negative results. Nevertheless, deviations from the guideline were noted, such as the lack of a second continuous experiment without S9 mix, since the first experiment gave negative results and the number of analyzed cells was half the OECD recommendations.

An *in vitro* gene mutation assay in mouse lymphoma L5178Y cells (TK+/-) run in compliance with the guideline OECD 476 (Doc IIIA 6.6.3) has been performed with Aerosil R 812S in order to cover the detection of gene mutations and chromosome aberrations.
In the absence of S9 mix, there was no evidence of mutagenic effect.
In the presence of S9 mix, there was no evidence of mutagenic effect even if in the second assay, a positive linear trend was present. However, the individual values were included in the range of values for the negative control and no statistically significant increases in mutant frequency were observed. Moreover, the IMF (induced mutation frequency) was lower than the GEF (global evaluation factor) and in the first experiment, this trend was not significant.

***In vivo* studies**

A mechanistic *in vivo* assay (Doc IIIA.6.6.4) has been provided and considered as supportive document. The study focused on observed lung damages and markers of toxicity after exposure of rats to amorphous Aerosil R 812 S, compared to the positive lung carcinogen, a crystalline silica (quartz) dust.

Aerosil R 812 S was given by a single intra-tracheal injection to rats and followed by a 90 day post-exposure period. The Aerosil R 812 S data were compared to the effect of a crystalline silica (quartz) dust which is a known toxic to lungs and carcinogenic. This test followed no guideline and was not conducted according to GLP. Four different parameters were evaluated in this mechanistic study: the measurement of DNA-adducts (8-OH-guanine), markers of inflammation, histological analysis and presence of mutant p53.

Concerning the mutagenicity issue, it was found that, following treatment with Aerosil R 812 S, the 8-OH-guanine level increased significantly in DNA during the first period of the post-exposure phase, and was not persistent thereafter, returned to background level after 90 days of recovery while the signs of acute inflammation were also decreasing.
On the contrary, the crystalline silica (quartz) induced a high and persistent reaction (although the increase of 8-OH guanine level was below the values after exposure to Aerosil R 812 S, this reaction persists over the time). These increases of primary DNA lesions could be explained by an inflammation response which was associated with the production of reactive oxygen species (ROS).
Additionally, the Ab-1 mutant-specific (Epitope aa 212-217) mouse monoclonal antibodies failed to detect the presence of mutant tumour suppressor protein p53 after exposure to Aerosil R 812 S, while the crystalline silica (quartz) caused a significant accumulation of mutated p53 protein over time.

10.8.2 Comparison with the CLP criteria

Negative results are observed in *in vitro* and *in vivo* tests with and without metabolic activation.

The criteria for classification as mutagenic under regulation (EC) 1272/2008 are not fulfilled.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

Based on the results of the *in vitro* and *in vivo* mutagenicity tests, no classification is proposed for the active substance.

10.9 Carcinogenicity

Table 10.9.1: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Oral, feed no guideline study Rat Wistar 20 m, 20 f The test substance was offered to the animals in feed balls. The animals received these balls in the morning prior to getting any other feed; particular attention was given to complete intake of these balls containing the test substance. The controls were fed with the same feed as treated animals but without test substance. The animals were examined for general state of health and clinical symptoms of toxicity.	Aerosil R 972 100 mg/kg bw/d 7 d/wk 24 months	At the end of the experimental period, the treated males weighed between 275 and 490. The treated females weighed between 205 and 445 g. Body weight increase was within the range of normal untreated male rats (control) and was therefore inconspicuous. No clinical effects was observed in males and females. One male displaying a visible tumor (benign fibrosis adenoma). In the animals showing signs of chronic bronchopneumonia, haematology revealed hyperleukocytosis with polynucleosis as well as hypergammaglobulinemia. The remaining animals showed no abnormalities and normal electrophoresis-values. No treatment-related development of tumor was observed. No subcutaneous sarcoma, no pituitary gland tumors and no tumors in testes were seen. A benign tumor (fibro–adenoma) was seen in one male; such tumors also occur in control Wistar rats. No signs of leucosis were seen.	IIIA6.7

Table 10.9.2: Summary table of human data on carcinogenicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Health survey (five German plants): 497 exposed workers, 206 not exposed Investigations performed between 1995 and 2000	Specificity of the substance not known (surface-treated or not)	Concentration unknown Chronically exposed (duration unknown)	No tumours. No evidence of long-term pulmonary effects.	IIIA6.12

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

The carcinogenic potency of pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (Aerosil R 972) has been evaluated through a 2-year oral carcinogenicity study in rats.

Only one dose was tested in this carcinogenicity study, 100 mg/kg bw/d and no adverse effect was identified. Although some deficiencies are observed, such as the single tested dose, the low number of tested animals, the lack of statistical test and the lack of control group (comparison with historical controls), this study provides some supportive evidence that these types of material are void of any significant carcinogenic potential by way of ingestion.

No study with a second species was available. Silicon dioxide is a worldwide accepted food additive for animals (US EPA…) and no systemic effect were observed in the available studies. Therefore, the oral route is of no concern. Furthermore, it is not expected that a study in a second species would demonstrate a highest sensitivity.

A published epidemiological study including workers exposed by inhalation to amorphous silicon dioxide is available (Table 17).

The aim of the study was to assess the health impacts of chronic exposure to synthetic amorphous silica (SAS). The study population consisted of 497 subjects exposed to synthetic pyrogenic or precipitated amorphous silica from five SAS producing plants in Germany and 206 non-exposed volunteers selected from white collar workers, health care, fire fighters, technicians, laboratory workers, plant security officers and others.

The prevalence of chronic bronchitis was within expected ranges but slightly higher in exposed subjects (8.7 % in controls vs 11.7% in exposed groups). Tests of pulmonary function showed that air flow values, median FVC (forced vital capacity) and FEV_1 (forced expiratory volume in one second), were somewhat lower in workers exposed to silica (except for plant 4) but there was no difference in the FEV_1/FVC ratio. Additionally, chest radiography showed no increased risk of pneumoconiosis of exposed subjects. In conclusion, this health survey gave no evidence of long-term pulmonary effects after exposure to synthetic amorphous silica.
Nevertheless, the specificity of the substance (surface-treated or not) was not known, no information has been provided regarding the characterisation of particles (particle size) and no data was available concerning the duration and the level of exposure of the workers. Therefore, due to this lack of data, this survey study should be considered with cautious and only in an informative way.

According to the IARC, amorphous silica is not classifiable as to its carcinogenicity in humans (Group 3)[1].

Moreove, the mutagenicity studies suggest negative results, despite some deviations from guidelines.

10.9.2 Comparison with the CLP criteria

No treatment-related development of tumor was observed.

The criteria for classification as carcinogenic under regulation (EC) 1272/2008 are not fulfilled.

10.9.3 Conclusion on classification and labelling for carcinogenicity

Based on the results of the oral carcinogenicity study, no classification is proposed for the active substance.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 10.10.1.1: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
One-generation Screening within a subchronic feeding study Oral, feed	Aerosil R 972 0, and 500 mg/kg/d Pre-mating: period: 8 wk before 1st mating and	The parental males showed no effects. The parental females showed no effects, and the fertility parameters were inconspicuous and within control range. Offspring showed no abnormalities and no differences were seen between treated and untreated groups.	IIIA6.8.2_02

[1] IARC Group 3 carcinogen: *not classifiable as to its carcinogenicity to humans*. « This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals. Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents that do not fall into any other group are also placed in this category. An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations » *(from http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf).*

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Rat Wistar 10 females; 2 males	17 wk before 2nd mating Post-mating period: from gestation to 4 wk post-natal		

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

No guideline fertility study was available. A "one-generation reproduction screening" study using Aerosil R 972 revealed no impairment of reproductive performance and foetal development. Furthermore, no adverse effects were observed in reproductive tissues from the sub-chronic studies and the oral chronic/carcinogenicity study.

10.10.3 Comparison with the CLP criteria

No impairment of reproductive performance and foetal development was observed.

Thus, no classification according to regulation (EC) 1272/2008 is required.

10.10.4 Adverse effects on development

Table 10.10.4.1: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
No data, national standards USA Mouse CD1 25 females/dose	Syloid (Silica gel) Oral, gavage Days 6-15 of gestation 0, 13.4, 62.3, 289 and 1340 mg/kg bw/d	At the highest dose, the skeletal findings observed in fetuses such as incomplete ossifications of sternebrae, of vertebrae of extremities or the sternebrae missing, are not considered as adverse for development. Moreover, dams' mortality occurs at this dose. NOAEL for embryotoxic/teratogenic effects = 1340 mg/kg bw/d; NOAEL for maternal toxicity = 289 mg/kg bw/d.	IIIA6.8.1_01

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
No data, national standards USA Rat Wistar 25 females/dose (24 in the highest dose treated group)	Syloid (Silica gel) Oral, gavage Days 6-15 of gestation 0, 13.5, 62.7, 292 and 1350 mg/kg bw/d	The treatment of pregnant rats with up to 1350 mg/kg bw test substance from day 6 to day 15 of gestation had no adverse effects on nidation and on maternal or fetal survival when compared to the control group. No effects indicative of teratogenicity were seen. NOAEL for embryotoxic/teratogenic effects = 1350 mg/kg bw/d; NOAEL for maternal toxicity = 1350 mg/kg bw/d.	IIIA6.8.1_02
No data, national standards USA Syrian hamster 23 females/dose (24 in the highest dose treated and the positive control groups)	Syloid (Silica gel) Oral, gavage Days 6-10 of gestation 0, 16.0, 74.3, 345 and 1600 mg/kg bw/d	The treatment of pregnant hamsters with up to 1600 mg/kg bw test substance from day 6 to day 10 of gestation had no adverse effects on nidation and on maternal or fetal survival when compared to the control group. No effects indicative of teratogenicity were seen. NOAEL for embryotoxic/teratogenic effects = 1600 mg/kg bw/d; NOAEL for maternal toxicity = 1600 mg/kg bw/d.	IIIA6.8.1_03
No data, national standards USA Rabbit (Dutch) 11-24 females/dose	Syloid (Silica gel) Oral, gavage Days 6-18 of gestation 0, 16.0, 74.3, 345.0 and 1600 mg/kg bw/d	The treatment of pregnant rabbits with up to 1600 mg/kg bw test substance from day 6 to day 18 of gestation had no adverse effects on nidation and on maternal or fetal survival when compared to the sham control group. No effects indicative of teratogenicity were seen. NOAEL for embryotoxic/teratogenic effects = 1600 mg/kg bw/d; NOAEL for maternal toxicity = 1600 mg/kg wb/d.	IIIA6.8.1_04

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

No study on the effects of pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide on teratogenicity is available.

Nevertheless, teratogenicity studies conducted in four different species (mouse, rat, hamster, and rabbit) with an amorphous non surface-treated silica gel (CAS No. 7631-86-9) could give some supportive information on the teratogenic potential of amorphous hydrophobic silica.

The aim of the surface modification is to block the silanol group in order to reduce the affinity of silica for water. Therefore, it is expected that pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide would not be better absorbed by oral route than non surface-treated silica. Furthermore, the lack of systemic effects of both surface treated silica and non surface-treated silica in oral toxicity studies (based on data submitted in this dossier for the first and on literature for the latter) supports a read-across for systemic toxicity.

No teratogenic effects were observed up to the highest doses (between 1340 and 1600 mg/kg bw/d, according to the species).

At the highest dose, skeletal findings were observed in mice fetuses such as incomplete ossifications of sternebrae, of vertebrae of extremities or the missing sternebrae (no statistical test in the report). As delays of ossification are fully reversible, these observations are not considered to be of adverse nature for the development.

Furthermore, based on the results, the FDA concluded that "*the number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated control*". This conclusion is also present in the ECETOC report[2] and in the SIDS[3] relative to amorphous silica and silicate.

Finally, given the fact that these effects were not found in rabbits, rats and hamsters, that the expected oral absorption is low and given the inherent physico-chemical properties of amorphous silica, there is no indication of a potential for reproductive developmental toxicity.

In conclusion, the amorphous non surface-treated silica gel has no teratogenic potential and this result could support the lack of teratogenic effects expected for the pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

Moreover, a screening study for reproductive effects (1-generation study) of Aerosil R 972 has been conducted (Doc IIIA 3.8.2), where no malformations were observed in rat pups at the only tested dose of 500 mg/kg bw/d.

10.10.6 Comparison with the CLP criteria

No teratogenic effects were observed up to the highest tested doses (between 1340 and 1600 mg/kg bw/d, according to the species).

Thus, no classification according to regulation (EC) 1272/2008 is required.

10.10.7 Adverse effects on or via lactation

No study available.

[2] Synthetic Amorphous Silica (CAS No. 7631-86-9), JACC No. 51, ECETOC, 2006.

[3] OECD SIDS for SIAM 19, concerning Synthetic amorphous silica and silicates, 2004

10.10.8 Conclusion on classification and labelling for reproductive toxicity

Based on the results of the reproductive toxicity studies, no classification is proposed for the pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

10.11 Specific target organ toxicity-single exposure

No study available.

10.12 Specific target organ toxicity-repeated exposure

Table 10.12.1: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**	**Reference**
No guideline study, it was performed in 1964 No GLP Rat, Wistar, 5 males and 5 females	Aerosil R 972 Oral, feed 5 weeks; 8 weeks (high-dose group) 7 d/wk 0, 500, 1 000 and 2 000 mg/kg bw/d) (the 2000 mg/kg bw/d successively increased to 16 000 mg/kg/d)	**Low dose:** no effects observed **Medium dose:** at 1000 mg/kg bw/d and above: liver atrophy (2/10 rats), loss of basophilic structure and diminution of the glycogen content in the hepatocytes. **High dose:** at 2000 mg/kg bw/d: shrunk and hyperchromatic nuclei of the hepatocytes **Higher** : at 16 000 mg/kg/d: loss of bodyweight gain, emaciation, cachexia, mortality	IIIA6.3.1

No guideline study, it was performed in 1964 No GLP Rat, Wistar, 20 males and 20 females	Aerosil R 972 Oral, feed 6 months 7 d/wk 0, 500 mg/kg/d	The treated animals were inconspicuous and showed no clinical effects. No statistically significant differences between the treated and the corresponding control groups were seen regarding mortality and mean body weight. Food consumption in the treated groups was similar to that in controls. The haematological parameters showed no treatment-related changes. No significant differences in organ weights between treated and corresponding control groups were seen. Neither gross- nor histopathological examination revealed treatment-related abnormalities. However, histopathology revealed a slight progressive change indicative of a chronic stress-reaction in the adrenals of treated animals. In females subjected to a post exposure period of 3 weeks, the effect seen in the adrenals turned back to normal, indicating reversibility. These effects were considered of no toxicological significance.	IIIA6.4.1

No guideline study, it was performed in 1969 No GLP Rat, Wistar, 20 males and 20 females	Aerosil R 972 Oral, feed 24 months 7 d/wk 0, 100 mg/kg/d	No mortality was observed. None of the treated animals showed clinical signs of toxicity. There were signs of chronic bronchopneumonia in 14 cases (7 males and 7 females). No signs of leukosis were seen. The changes reported for the lung and the kidney are known to occur with similar incidences in control animals and were therefore not treatment-related effects. The changes reported for the genital tract of the females (atresic follicles in the ovaries, hyperplasia of the interstitial glandular tissue and slight hyperplasia of the uterine mucosa) also occur in control animals and are therefore not treatment-related. Moreover, 3 males and 6 females showed important fat deposit; such deposit however are considered to be normal for the rat strain used. No treatment-related development of tumor could be observed.	IIIA6.5
No guideline study No GLP Rat, Wistar, 10 males and 10 females	Aerosil R 974 Inhalation 14 d (preliminary test) 6h/d 5 d/wk 0, 31, 87, and 209 mg/m^3 (analytical)	**Low dose:** Respiratory distress; Histological changes in lungs related to alveolar inflammatory response (bronchiolar mucous cell proliferation and increased cellularity, accumulation of alveolar macrophage, alveolar oedema and early granuloma); Increased lung weight **Medium dose:** Slight to moderate dyspnea; Haematological effects (increased red blood cell count, haemoglobin content and packed cell volume). **High dose:** Mortality 6/20 (4 m + 2 f)	IIIA6.3.3

No guideline mentioned, but comparable to guideline study (acc. to OECD Guide-line 413) GLP Rat Wistar 70 males and 70 females, sub-groups of 10 males and 10 females	Aerosil R 974 Inhalation 13 wks (recovery period: up to 52 wks) 6h/d 5 d/wk 0, 35 mg/m^3 (analytical), (total dust)	Increased lung weight; Inflammatory signs such as nasal irritation; Granuloma like lesions; Accumulation of alveolar macrophages; Leukocytosis; Signs of interstitial fibrosis with increase of the lung collagen content. Si deposit in lungs and in lymphatic mediastinal nodes. No mortality. No particular clinical signs. **Recovery**: septal cellularity still present at the end of the recovery period. The other changes appear reversible.	IIIA6.4.3_01

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

Repeated dose toxicity studies were available for Aerosil R 972 *via* oral route and for Aerosil R 974 *via* inhalation (Please refer to Doc IIIA for details).

Oral administration:

No concern arose from a sub-acute oral exposure.

Rats were exposed to 500, 1000 mg/kg/d of Aerosil R 972 for 5 weeks (Doc IIIA6.3.1). Another dose group was tested using an escalating method with a starting dose of 2000 mg/kg bw/d for 2 weeks. Because of good tolerance of the 2000 mg/kg bw dosing, this dose was increased after 2 weeks to 4000 mg/kg bw/d, after further 2 weeks to 8000 mg/kg bw/d and finally the dose was increased to 16000 mg/kg bw/d for 2 weeks. Therefore, the exposure period for this dose group was extended to 8 weeks. The experimental period of the control group also was extended to 8 weeks.

A loss of body weight gain was noted at 8000 mg/kg bw/d and above.

At 16000 mg/kg bw/d, animals died by emaciation and cachexia. The histological analysis showed hepatic effects at 1000 mg/kg bw/d and above (2/10 animals). These effects were characterised by an occasional atrophy of the liver epithelium, a loss of basophilic structure and a diminution of the glycogen content in the hepatocytes. These liver effects were considered to be related to starving and not being systemic effects provoked by the Aerosil R 972, at the dose of 16000 mg/kg bw/d.

At 1000 mg/kg bw/d (corresponding to 1.5 – 2 % in the feed), after 5 weeks, the link between these liver effects and the substance (systemic effect or starving) was not evident. Furthermore, silicon dioxide is a worldwide accepted food additive and no systemic effects were observed in the other submitted oral studies.

Finally, since several deficiencies were noted (no individual data, no control group and no statistical test), the study seemed to be irrelevant to conclude that the tested substance could have a liver systemic toxicity.

In a 6-month feeding study in rats receiving only one dose-level of Aerosil R 972 (500 mg/kg bw/d), there was no treatment-related findings (Doc IIIA6.4.1).

Aerosil R 972 was administered to rats in a 24-month feeding study at the only dose level of 100 mg/kg bw/d (Doc IIIA6.5).
Some effects observed in the lung, the kidney and in the genital tract of the females of treated groups were also observed in the control group and are therefore considered as not treatment-related.
Although several deficiencies such as the low number of tested animals, the absence of statistical test, the only one tested dose and the lack of control group (comparison with historical controls), the study was considered as supportive data for this endpoint.

No study with a second non-rodent species was available.
As already stated, silicon dioxide is a worldwide accepted food additive for animals (US EPA…) and no systemic effect were observed in the available studies. The low systemic toxicity of the pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide can be a result of its limited absorption or it relates real lack of toxicity. It is not expected that studies in a non-rodent species would demonstrate a higher sensitivity.

Dermal administration:

No data is available. However, considering the lack of local effects observed in irritation studies, only systemic effects may be expected.
Nevertheless, since no systemic effects were observed in oral studies (see above) and because of the low potential of dermal penetration, it is considered that no hazards are expected by dermal administration.

Administration by inhalation:

The 90-day inhalation study (doc IIIA6.4.3_1) compared the toxicity of three amorphous silica: Aerosil 200 (fumed silica), Aerosil R 974 (pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide) and Sipernat 22S (precipitated silica) with quartz dust.

Rats were exposed to 1, 6 or 30 $mg_{Aerosil\ 200}/m^3$, 35 $mg_{Aerosil\ R974}/m^3$, 35 $mg_{Sipernat\ 22S}/m^3$ or 60 mg_{quartz}/m^3 in inhalation chambers for 6 h/day, 5 days/week for 13 weeks. Only Aerosil R 974 was considered further for assessing the toxicity of the notified surface-treated silica.

The unique dose of 35 mg/m^3 (analytical value) of Aerosil R 974 was determined in a range finding study run during 14 days (doc IIIA6.3.3).
The study is comparable to guideline study and is GLP: the number of animals (10 animals/sex/ group), the duration of exposure (90 d, 6h/d, 5 d/week), the experimental conditions, the observation of clinical effects, the evaluation of haematological parameters, clinical chemical parameters, urinalysis and the examination at necropsy, all these assessment parameters are similar to the guideline. However, particle size determination in test atmospheres could not be performed due to electrostatic charge of the particles.

Rats were killed for observations after the exposure period and 13, 26, 39 and 52 weeks after exposure. Clinical signs, body weight, haematology, biochemistry, urinalyses, organ weights, retention of test material in the lungs and the regional lymph nodes, collagen content of the lungs and gross and microscopic pathology were determined.

Males exhibited statistically significantly lower body weights in weeks 6 to 9 only. Haematological changes (increased red blood cell counts, haemoglobin contents, packed cell volumes and prothrombin time) were observed in males at the end of the exposure period only. These changes can be probably considered as a compensative hyperaemia, result of the

impaired lung function. The following effects were observed in the lungs of rat exposed to 35 mg/m^3 of Aerosil R 974:

- increased lung weight noted at the end of the exposure period but normal after a recovery period of 3 months;
- swollen and/or spotted lungs and irregular surface of the lung in some animals at the end of exposure and after 13 weeks;
- accumulation of alveolar macrophages in most males and females after observation periods of 13, 26 and 39 weeks but not seen after 52 weeks of recovery;
- intra-alveolar accumulation of granular material, cellular debris and leucocytes infiltration observed at the end of the exposure period but not found anymore after 13 weeks of recovery;
- granuloma-like lesions seen in all animals at the end of the exposure period and after an observation period of 13 weeks. These lesions did not show fibroblastic activity and hyalinization in the granulomas. This lesion decreased in incidence and was not found anymore after an observation period of 52 weeks;
- increase in the lung collagen observed in males and females at the end of the exposure period. Although the differences gradually decreased during the recovery period, they remained statistically significant after observation periods of 13 and 39 weeks;
- some signs of focal interstitial fibrosis observed in 3/5 male rats after 13 weeks of the recovery period and in 1/5 male rat after 26 weeks of recovery period (not statistically significant);
- increased septal cellularity still present in a few animals after an observation period of 52 weeks (very slight degree);
- alveolar bronchiolisation in 2/10 males after the exposure period and in 1/5 at 13 week post-exposure (not statistically significant);
- high amount of silicon detected in the lungs and lymph nodes of males and females at the end of the exposure period and after observation periods of 13 and 26 weeks. Silicon was still present in lymph nodes of one male at the end of the observation period.

Nasal inflammatory signs such as nasal irritation, focal necrosis and rhinitis and slight degeneration of the olfactory epithelium, were also reported.

In conclusion, the lung was the major target organ after exposure to Aerosil R 974.
All the observed effects were characteristic of an inflammation and were reversible. They completely disappeared at the end of the one-year recovery period, except septal cellularity which was still present in 2 animals of each sex.

The effects could be mainly related to a pulmonary overload and no dose-response relationship could be established. Similar phenomenon in the generation of an alveolar inflammation was observed in preliminary 14-day study in rats (III6.3.3). This supports the conclusions that lung is the target organ after exposure to amorphous silica.

No study with a second non-rodent species was available. It is acknowledged that rats have a more protective upper respiratory surface area compared to human, the observed effects in rat lungs lead to consider that human lungs and especially alveolar part, could be more severely exposed to silica. Rat remains the most suitable species to predict lung toxicity.

Finally, in the mechanistic *in vivo* assay (Doc IIIA.6.6.4), Aerosil R 812 S was given by a single intra-tracheal injection to rats and followed by a 90 day post-exposure period. The study focused on observed lung damages and markers of toxicity after exposure of rats to

amorphous Aerosil R 812 S, compared to the positive lung carcinogen, a crystalline silica (quartz) dust.
An increase of the 8-OH-guanine level is observed, it could therefore be assumed that a chronic exposure to high level of Aerosil R 812 S could lead to a saturation of the DNA repair mechanism that could give rise to the occurrence of mutations.
Moreover, the fact that mutant protein p53 was not detected by a specific antibody does not ensure that no mutation was produced in DNA. Nevertheless, it was observed in the study that Aerosil R 812 S induced a response clearly different from that of quartz.

10.12.2 Comparison with the CLP criteria

A classification STOT RE 2 H373 (May cause damage to organs through prolonged or repeated exposure) according to the CLP regulation is proposed for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide ; based on the 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 Aerosil R 974.
Even if the majority of these effects were reversible during the one-year recovery period, it is considered that the time necessary for the reversibility is relatively important compared to the duration of the exposure.

According to the CLP regulation (1272/2008), these findings meet the following criteria for classification STOT RE 2: "*significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sens of smell)* (criteria b) *or multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity* (criteria e).
Classification is based on observed effects and not on potential expected effects. The threshold value is defined by the effects observed at a dose between 20 and 200 mg/m^3 in rats, during 6h/d, which is the case in this study.

Finally, even if there is no long-term respiratory health effect in the available epidemiological study in workers (section 10.9_Table 50), uncertainties are present in this publication (nature of the silica, duration and level of the exposure) leading to inadequate evidence. In this context, the epidemiological study cannot be used as a proof of no effect and cannot rule out the pulmonary effect reported in rats.

10.12.3 Conclusion on classification and labelling for STOT RE

Based on the results of the 90-d inhalation rat study, a classification STOT RE 2 – H373 is proposed for the active substance.

10.13 Aspiration hazard

No study available.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Silicon dioxide occurs ubiquitously in the environment. It accounts for approximately 27.6% of the earth's crust and is widely distributed in water, soils and plant and animal tissues. Silicon dioxide is regarded as inert in all but extreme conditions.

Initially, the applicant Degussa notified two CAS numbers for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (CAS n°68909-20-6 and 68611-44-9). These silicon dioxides are a part of the wider synthetic amorphous silica family (CAS n°7631-86-9). These surfaces modified silica are obtained by reaction with hexamethylsilazane (Aerosil R 812 and R 812 S) or dimethyldichlorosilane (Aerosil R 972, R 974, R 976) which induces the fixation of methyl group on the surface of the molecule. By this surface modification, synthetic amorphous silica, which are originally hydrophilic, are rendered physico-chemically hydrophobic. These hydrophobic amorphous silica are therefore inorganic compounds with an organic carbon content of 0.6 – 4.0 % (w/w). Nevertheless more than 95 % of the hydrophobic amorphous silica is comprised of polymerically bound silicon dioxide (SiO_2). The majority of hydroxyl groups on the particle surface are covalently bound to dimethylsilyl groups (Aerosil types of the 97 series) or trimethylsilyl groups (Aerosil R 812 and R 812 S). Methylation results in highly hydrophobic solids which are very stable, insoluble in water and non-volatile. Degradation is only possible by physical means: e.g. combustion would result in >99.5 % silicon dioxide, small amounts of water and carbon dioxide. When released into the environment, these forms are expected to combine with soil or sediment organic matter and adopt the same behaviour as natural silica.

For these reasons, a reduced set of data was accepted in the frame of biocide assessment.

Moreover, following Biocide Technical Meeting II 2011, it has been decided that only Aerosil R 812 and R 812 S will be kept for the assessment of the active substance. Nevertheless, France noted that all environmental studies are performed with Aerosil R 972 and R 974. However, based on physico-chemistry data (see section 1 – Identity of the substance), Aerosil R 972 and R 974 are considered similar to Aerosil R 812 and R 812 S.

It has to be noted the substance is a nanoparticle, however the available studies are not designed to assess specifically ecotoxicity linked to this property.

11.1 Rapid degradability of organic substances

Biodegradation study is not applicable. Hydrophobic amorphous silica are inorganic compounds with an organic carbon content of 0.6 – 4.0 % (w/w). More than 95 % of the hydrophobic amorphous silica is formed of polymerically bound silicon dioxide (SiO_2). The majority of hydroxyl groups on the particle surface are covalently bound to dimethylsilyl groups (Aerosil types of the 97 series) or trimethylsilyl groups (Aerosil R 812 and R 812 S). Methylation results in highly hydrophobic solids which are very stable and insoluble in water and not accessible to biological transformation. The chemical structure and composition of these silica particles is of inorganic rather than of organic nature. Therefore, biodegradation is not reasonably applicable to such inorganic substances and, considering its high stability and inertness, the study is not required.

Considering that the hydrophobic amorphous silica are inorganic compounds with an organic carbon content of only 0.6 – 4.0 % (w/w) and that more than 95 % of the hydrophobic amorphous silica is comprised of polymerically bound silicon dioxide (SiO_2), even if the organic part of the molecule was degraded, the metabolites formed would not exceed 4.0 %, which remains below the trigger of 10 %.

11.1.1 Ready biodegradability

Not relevant

11.1.2 BOD_5/COD

Not relevant

11.1.3 Hydrolysis

Hydrolysis study is not scientifically justified. Amorphous silica is rendered highly hydrophobic through blocking the polar superficial hydroxy groups by dimethylsilyl groups (Aerosil 972 or 974) or by trimethylsilyl groups (Aerosil 812 or 812S). This surface can be considered resistant to hydrolytic attack under environmental conditions and even under boiling in water at neutral pH. Therefore, based on the chemical nature (inorganic character, high chemical stability of the Si-O bond and very low solubility in water), no pH-dependent hydrolysis will occur in water at low and high temperatures.

11.1.4 Other convincing scientific evidence

No further available data

11.1.5 Field investigations and monitoring data (if relevant for C&L)

No available data

11.1.6 Inherent and enhanced ready biodegradability tests

Not relevant

11.1.7 Water, water-sediment and soil degradation data (including simulation studies)

No available data

11.1.8 Photochemical degradation

Photolysis in water and air

Photolysis studies in water and in air are not scientifically necessary.

Aerosils R 812, R 812 S, R 972, and R 974, typical representatives of pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide, are of inorganic nature and are insoluble in water. Furthermore, the compounds do not absorb light above 270 nm. Therefore, based on the physico-chemical nature (inorganic structure, chemical stability, i.e. high stability of the Si-O bond, absence of water solubility and lack of interference with light), no light-induced transformation is expected in water.

For the same reasons of physico-chemical nature of pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide, no photo degradation in air will occur. Moreover, the exposure via the atmospheric compartment is not considered relevant as the volatility of these compounds is negligible.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant

11.2.1 Summary of data/information on environmental transformation

Not relevant

11.3 Environmental fate and other relevant information

Hydrophobic amorphous silica are inorganic compounds with an organic carbon content of 0.6 – 4.0 % (w/w). More than 95 % of the hydrophobic amorphous silica is formed of polymerically bound silicon dioxide (SiO_2). Therefore, biodegradation is not reasonably applicable to such inorganic substances and, considering its high stability and inertness, the study is not required. Moreover, based on the chemical nature of the substance (inorganic character, high chemical stability of the Si-O bond and very low solubility in water), no pH-dependent hydrolysis will occur in water at low and high temperatures.

11.4 Bioaccumulation

The pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide is considered as inorganic substances composed by 95% of polymerically bound silicon dioxide (carbon organic content is less than 4%). These synthetic amorphous silica are practically insoluble in water and thus are barely bioavailable via the water phase.

Although highly hydrophobic, these synthetic amorphous silica do not dissolve in non-polar fluids or lipids in view of their stable solid structure. Hence, they lack the typical features of lipophilicity and lipid solubility. Moreover amorphous silicon dioxide does not have any intrinsic properties, which suggest that it will bioaccumulate in the environment.

In a weight of evidence approach, the overall information indicates a low potential for bioaccumulation.

11.5 Acute aquatic hazard

As the surface modified amorphous silica are hydrophobic, nearly insoluble (<1 µg/L) and complicated to analyse, with a limit of determination in water (1 mg/L) (see Doc IIIA section A4) higher than the solubility limit, these substances are difficult to test according to the standard ecotoxicity guidelines. The studies carried out with higher concentrations than the solubility limit were considered acceptable in the frame of biocide assessment even in absence of analytical measurement, taking into account of the high stability of the molecule. Moreover, the substance tested at high dose rate, up to 10 000 mg/L, showed no toxicity to aquatic organisms as demonstrated hereafter.

These issues were discussed and agreed during Biocide Technical Meeting III10. Indeed, in general cases, the results should be treated as invalid. Nevertheless, the studies can be used in a weight of evidence to show that there are no effect on aquatic organisms. Indeed, due to the large excess of the substance in studies, it was considered that its solubility limit was achieved during the tests. The substance shows no effects on aquatic organisms even at the high concentration tested (1 000 to 10 000 mg/L).

The pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide was tested on environmental organisms under different commercial forms: Aerosil R 974 for acute fish and daphnia, Aerosil R 972 for algae and Aerosil R 812S for microorganisms. The subjects of the Biocidal Product Dossier relevant for the claimed application are reaction products of synthetic amorphous silica after treatment with hexamethylsilazane (CAS 68909-20-6; Aerosil R 812 and Aerosil 812S) or dimethyldichlorosilane (CAS 68611-44-9; Aerosil R 972, Aerosil R 974 and Aerosil R 976). Whatever the reactant used (hexamethylsilazane or dimethyldichlorosilane) the aim of the modification is to block the silanol group of the molecule in order to render the material hydrophobic. The chemical groups added by the reaction have no particular activity by themselves. The main variation between the different types of Aerosil is their surface area conferring to them some different rheological properties necessary for their commercial use. In view of these data, as indicated in the introduction of environmental hazards, France has

considered that results from aquatic studies could be extrapolated from one type of Aerosil to another in the frame of biocide assessment (see also section 1 – Identity of the substance).

Table 11.5.1: Summary of relevant information on acute aquatic toxicity

Method	Species	Exposure	Results[1]			Remarks	Reference
			LC_0	LC_{50}	LC_{100}		
OECD 203 (1984), GLP RI : 2	*Brachydanio rerio*	Static / 96h	>10000 mg/L	>10000 mg/L	>10000 mg/L	Substance tested: Aerosil R 974	Hooftman RN and van Drongelen-Sevenhuijsen D (1992a)
OECD 202 (1984), GLP RI : 2	*Daphnia magna*, immobilisation	Static / 48h	>10000 mg/L	>10000 mg/L	>10000 mg/L	Substance tested: Aerosil R 974	Hooftman RN and van Drongelen-Sevenhuijsen D (1992b)
OECD 201 (1984), GLP RI : 2	*Scenedesmus subspicatus* Biomass and growth	Static / 72h	>10000 mg/L	>10000 mg/L	>10000 mg/L	24-h water extract of Aerosil R 972	Lebertz H (1999)

[1] Concerning the expression of the endpoints, normally the rule is to set the LC_{50} to the solubility limit. Based on the physico-chemical properties of the test substance which is practically insoluble in water, the result obtained for the acute toxicity tests expressed in nominal concentrations was accepted for biocides risk assessment purposes.

11.5.1 Acute (short-term) toxicity to fish

Aerosil R 974 was tested on Zebrafish (*Brachydanio rerio*) in static system during 96 h. The purity of the technical substance was 100%. The nominal test concentrations were a control, 1 000 and 10 000 mg/L.

Some deviations to OECD Guideline 203 have to be reported. Temperature was slightly higher than recommended range for the species used. There was no indication on fish acclimatising before the assay. There was no analytical measurement of the actual test concentrations. Non-dissolved substance was not separated and removed before testing.

Whatever the nominal concentrations tested, no mortality and no sublethal effect occurred. Based on nominal concentrations of test substance, the LC_{50} value was > 10 000 mg/L. However, LC_{50} could not be defined in actual concentration. Thus, it can be concluded that the test substance has a low acute toxicity to the test organism *Brachydanio rerio*.

Please refer to Doc IIIA section 7.4 for further details.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Aerosil R 974 was tested on *Daphnia magna* in static system during 24 h. The purity of the technical substance was 100%. The nominal test concentrations were a control, 1 000 and 10 000 mg/L. As hydrophobic amorphous silicate is nearly insoluble, test suspensions were stirred

in test vessels for about 20 h. All the concentrations were tested non-filtered. The 10 000 mg/L concentration was also tested after a filtration through a wad of perlon wool.

No analytical measurement of test concentrations was performed. The determination of LC_{50} could be made only on the nominal concentrations of test substance.

Whatever the group tested, no immobilisation was observed after 24h, and the EC_{50} was estimated to be > 10 000 mg/L (nominal concentration). It was concluded that the test substance was not acutely toxic to test organisms within its aqueous solubility. Extrapolation to the standard test duration of 48 h appears to be justified as no adverse effect were observed at 24 h with high loading of the test compound taking also into account the insolubility of the substance.

Please refer to Doc IIIA section 7.4 for further details.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

Effects of Aerosil R 972 on algal growth were evaluated with a 72 hour toxicity test in a freshwater algae *Scenedesmus subspicatus*, in static conditions, at the nominal concentrations: 0, 100, 1 000 and 10 000 mg/L. Test suspensions were incubated in a shaking machine for 24 hours and then filtered. Eluates were used for the test. No analytical measurement of test concentrations was performed. The determination of LC_{50} could be made only on the nominal concentrations of test substance.

Cell concentration in control cultures increased at least by a factor 16 within 3 days. No reduction in growth rate was observed in treated group after 72h. A reduction of biomass production of 1.5% was observed only at 100.8 mg/L after 72 h. Therefore, EbC_{50} and ErC_{50} were estimated to be > 10 000 mg/L (nominal concentration). An important pH deviation in the control cultures and test vessels (about 3 units) without explanation is observed but does not discredit the study results.

The test substance does not inhibit the growth of the freshwater algae *Scenedesmus subspicatus* within its aqueous solubility.

Please refer to Doc IIIA section 7.4 for further details.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

No other available data

11.6 Long-term aquatic hazard

No available data

11.6.1 Chronic toxicity to fish

No available data

11.6.2 Chronic toxicity to aquatic invertebrates

No available data

11.6.3 Chronic toxicity to algae or other aquatic plants

No available data

11.6.4 Chronic toxicity to other aquatic organisms

No available data

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

In the frame of Biocide Regulation, only acute toxicity tests for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide were provided and accepted for risk assessment purpose. All available acute L(E)C_{50} values for all three trophic levels are >1 mg/L. Despite the low reliability of these tests, due to the high insolubility of the substance and the lack of measurement concentrations, no effect was observed in the ecotoxitity tests at the hogh loading rate.

Therefore, based on the available information, no classification with Aquatic Acute 1 is necessary.

➔ **No classification**

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

No chronic studies are available for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide for any of the three trophic levels. Therefore acute toxicity tests should be used following the Figure 4.1.1 of the Guidance in the Application of the CLP Criteria – version 5.0 – July 2017. No effect was observed in the acute ecotoxitity tests performed under tested conditions at the nominal concentration of 1000 and 10000mg/L.

Weight of evidence indicating low potential to bioaccumulate.

The conventional biodegradation studies designed to test organic substances are not reasonably applicable for such inorganic substances considering its high stability and inertness. Amorphous silica is considered as no rapidly degradable.

Therefore, based on these consideration, no classification with Aquatic chronic is necessary.

➔ **No classification**

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

No classification for hazards to the aquatic environment is proposed for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Not relevant

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

Not relevant

12.1.2 Comparison with the CLP criteria

Not relevant

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Not relevant

13 ADDITIONAL LABELLING

Although the mechanism of biocidal action of pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide is currently not clear, "*The Manual of Decisions for Implementation of Directive 98/8/EC Concerning the Placing on the Market of Biocidal Products*" updated on 10th July 2008 states in its section 2.3.3 that product containing amorphous silica in a water base *"seems to act through absorption of the lipid layer covering insect's chitin protection, which then leads to desiccation and death of the target organism".* By destroying the natural water barrier, the waxy layer of the cuticle and hence disrupting the functioning of the water preservation mechanism, silica interferes with physiological processes.

Therefore, considering the mode of action of the active substance, a labelling EUH 066: Repeated exposure may cause skin dryness or cracking, is proposed.

14 REFERENCES

References are listed in the Competent Authoritiy report.

15 ANNEXES

Documents IIIA