Synthetic Amorphous Silica (CAS No. 7631-86-9)

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CONTENTS

EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the physico-chemical properties, toxicology, ecotoxicology and environmental fate and impact of (non-crystalline) synthetic amorphous silica (SAS, plural: SASs).

SASs are white, fluffy powders or milky-white dispersions of these powders (usually in water). SASs are hydrophilic, but can be made hydrophobic by surface treatment. SASs are produced by the wet route (precipitated silica, silica gel) or the thermal route (pyrogenic silica). SASs are used in various industrial applications (e.g. thickening of elastomers) and in consumer products (e.g. cosmetics and pharmaceuticals).

Crystalline and/or amorphous silicas are ubiquitous on the earth in soils and sediments, and in living organisms (e.g. diatoms), but only the dissolved form is bioavailable. On a global scale, the level of man-made SAS represents up to 2.4% of the dissolved silica naturally present in the aquatic environment. The rate of SAS released into the environment during the product life cycle is negligible in comparison with the natural flux of silica in the environment. Based on available data, SAS is not toxic to environmental organisms (apart from physical desiccation). In conclusion, SAS presents a low risk for adverse effects to the environment.

When experimental animals inhale SAS dust, it dissolves in the lung fluid and is rapidly eliminated. If swallowed, the vast majority of SAS is excreted in the faeces and there is little accumulation in the body. Following absorption across the gut, SAS is eliminated via urine without modification in animals and humans. SAS is not expected to be broken down (metabolised) in mammals.

Both the mammalian and environmental toxicology of SASs are significantly influenced by the physical and chemical properties, particularly those of solubility and particle size. SAS has no acute intrinsic toxicity by inhalation. Adverse effects, including suffocation, that have been reported were caused by the presence of high numbers of respirable particles generated to meet the required test atmosphere. These results are not representative of exposure to commercial SASs and should not be used for human risk assessment. Though repeated exposure of the skin may cause dryness and cracking, SAS is not a skin or eye irritant, and it is not a sensitiser. Repeated-dose and chronic toxicity studies confirm the absence of toxicity when SAS is swallowed or upon skin contact.

Long-term inhalation of SAS caused some adverse effects in animals (increases in lung inflammation, cell injury and lung collagen content), all of which subsided after exposure. Neither inhalation nor oral administration caused neoplasms (tumours). SAS is not mutagenic in

vitro. No genotoxicity was detected in in vivo assays. SAS does not impair development of the foetus. Fertility was not specifically studied, but the reproductive organs in long-term studies were not affected.

In humans, SAS is essentially non-toxic by mouth, skin or eyes, and by inhalation. Epidemiology studies show little evidence of adverse health effects due to SAS. Repeated exposure (without personal protection) may cause mechanical irritation of the eye and drying/cracking of the skin.

ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemicals. Only the chemical itself is considered in a JACC review; products in which it appears as a component or an impurity are not normally taken into account.

This document presents a critical evaluation of the physico-chemical properties, toxicology and ecotoxicology of synthetic amorphous silica (CAS No. 7631-86-9).

Where relevant, the Task Force has graded the studies by means of a ‘code of reliability’ (CoR) (Appendix A) to reflect the degree of confidence that can be placed on the reported results.

1. SUMMARY AND CONCLUSIONS

Synthetic amorphous (non-crystalline; detection limit 0.01% by weight relative to quartz) silica (SAS, plural: SASs) (CAS No. 7631-86-9) can be divided into two groups according to whether the manufacturing process is by the wet route (precipitated silica, silica gel) or the thermal route (pyrogenic silica). Colloidal silicas (silica sols) are stable dispersions of SASs in a liquid, usually water. Furthermore, SASs, which are generally hydrophilic, may be rendered hydrophobic by surface treatment. SASs exist as highly pure, white, fluffy powders or milky-white dispersions of these powders in fluids (usually water).

SASs were commercialised in the 1950s and current worldwide production exceeds 1 Mt/y. SASs are used in a wide variety of industrial applications, including reinforcement and thickening agents in various systems such as elastomers, resins and inks. SAS is also used as a flow aid for powdery coatings and dry toners. Applications in consumer products include cosmetics, pharmaceuticals and as direct food and feed additives, and in beer and wine clarification.

Silicon ranks next to oxygen in abundance in the earth's crust in the form of silicate minerals. It is also present as the oxide (silica) in soils/sediments, in some organisms such as diatoms and in some plants. Since dissolved silica is the bioavailable form for living organisms, the total flux of dissolved silica into the aquatic environment can be compared with anthropogenic sources. Maximum levels of man-made SAS released per year represent 2.4% of the dissolved silica naturally present in the global aquatic environment. The rate of SAS released into the environment during the product life cycle can be considered negligible in comparison with the natural flux of silica in the environment. Based on available data, there is no evidence of significant toxicity of SAS to environmental organisms. The observed adverse effects of different SASs on insects are related to the physical properties of SAS (desiccation). In conclusion, SAS presents a low risk for adverse effects to the environment.

Analytical data on the kinetics of SAS deposition in the lung of experimental animals during and after prolonged exposure are largely consistent. The initial uptake phase is followed by dissolution in the lung fluid. SASs are rapidly eliminated from the lung tissue, whereas crystalline silicas exhibit a marked tendency to accumulate. Also, after ingestion, there is limited accumulation of SAS in body tissues and rapid elimination occurs. Intestinal absorption has not been calculated, but appears to be insignificant in animals and humans. SASs injected subcutaneously are subjected to rapid dissolution and removal. There is no indication of metabolism of SAS in animals or humans based on chemical structure and available data. In contrast to crystalline silica, SAS is soluble in physiological media and the soluble chemical species that are formed are eliminated via the urinary tract without modification.

Numerous acute inhalation toxicity tests have been performed on both hydrophilic and hydrophobic SAS. Any mortality that was observed was due to suffocation associated with the extremely high particle numbers administered and is not associated with any intrinsic toxicity of the product. In comparison to the particle size used in these short-term inhalation animal tests, only minor amounts (less than 1%) of the commercially available SAS types have been measured as respirable (alveolar fraction < 10 µm mass median aerodynamic diameter). Using the same measurement techniques, > 99% of the particle fraction of the commercial product is in excess of 90 µm in diameter and can only reach the upper airways (nasal passages and throat) or cannot be inhaled at all. The experimental test design for short-term inhalation studies requires the application of high shear stress in order to generate homogeneous particle distribution and exposure to the highest possible fraction of the fine particles able to migrate to the peripheral region of the lung. In contrast, under occupational exposure conditions, such shear forces are not applicable and under such conditions, the commercial product is composed of agglomerates (> 99% > 90 µm) and is therefore not respirable or inhalable. The acute inhalation toxicity tests, therefore, do not represent the toxicological behaviour of the commercial product and should not be considered relevant for hazard definition and risk assessment.

SAS is not a skin or eye irritant, and is not a sensitiser. Repeated exposure of the skin may cause dryness and cracking.

The data available concerning repeated dose toxicity confirm the absence of significant toxicity by oral and dermal routes of exposure.

Numerous repeated-dose, subchronic and chronic inhalation toxicity studies have been conducted with SAS in a number of species, at airborne concentrations ranging from 0.5 mg/m^3 to 150 mg/m^3. Lowest-observed adverse effect levels (LOAELs) were typically in the range of 1 to 50 mg/m^3. When available, the no-observed adverse effect levels (NOAELs) were between 0.5 and 10 mg/m^3. The difference in values may be explained by different particle size, and therefore the number of particles administered per unit dose. In general, as particle size decreases so does the NOAEL/LOAEL. SAS exposure produced transient increases in lung inflammation, markers of cell injury and lung collagen content. There was no evidence of interstitial pulmonary fibrosis. SAS is cleared rapidly from the lungs during the post exposure periods, and most of the increases in markers of lung inflammation or injury decreased, with a majority returning to control levels. Morphology and clearance data indicated that SAS was solubilised and effectively cleared from the lungs. Chronic administration of SAS at a concentration of up to 5.0% in the diet to mice and rats caused no alteration in survival rate, bodyweight, food consumption, behaviour, organ weights or blood chemistry. Neither long-term inhalation nor oral administration caused neoplasms in any examined tissues.

SAS tested in several species did not induce developmental toxicity. No specific study has been carried out on fertility. However, no adverse effects on reproductive organs were found in chronic or carcinogenic studies.

SAS was not mutagenic *in vitro* in bacteria or yeast, or in mammalian cells. No chromosomal aberrations were observed in cultured mammalian cells. *In vivo*, cytogenetics in bone marrow or dominant lethal assays in the rat together with host-mediated assays were clearly negative, indicating that SAS is not genotoxic in *in vivo* assays.

SAS is essentially non-toxic in humans via the oral, dermal/ocular and inhalation routes of exposure and no data exist on systemic effects in humans. The use of untreated SAS as a direct food additive is warranted because no oral toxicity is to be expected. Approximately 50 years of cumulative experience in production plants has not produced a single case of suspected contact allergy. SAS may cause mechanical irritation of the eye and is known to result in drying and possibly cracking of the skin following repeated exposure. Both of these effects are easily avoided using standard personal protective equipment and/or moisturisers.

To date, there is no evidence of cancer or other long-term respiratory health effects (for example, silicosis) in workers employed in the manufacture of SAS. Respiratory symptoms in SAS workers have been shown to correlate with smoking but not with SAS exposure, while serial pulmonary function values and chest radiographs are not adversely affected by long-term exposure to SAS.

The human health effects, including carcinogenicity of SAS have been reviewed by a number of agencies and it has not been listed as carcinogenic or hazardous by the International Agency for Research on Cancer (IARC) or the American Conference for Governmental Industrial Hygienists (ACGIH).

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name: Synthetic amorphous silica (SAS, plural: SASs): pyrogenic (fumed) silica, precipitated silica, silica gel, colloidal silica

IUPAC name: Silicon dioxide, chemically prepared

Synonyms: After-treated synthetic amorphous silica, Amorphous synthetic silica gel, crystalline-free; Colloidal silicon dioxide (European Pharmacopoeia II), Highly dispersed silica, Hochdisperses Silizium Dioxid (Deutsches Artznei Buch), Hydrophobic silica, Light anhydrous silicic acid (Japanese Pharmacopoeia), Precipitated silica (CAS name), Pyrogenic colloidal silica, Pyrogenic (fumed) amorphous silica (CAS name), Silica, amorphous, fumed, crystalline-free; *Silica colloidalis anhydrica*, Silica gel (CAS name), *Silicium dioxydatum dispersum* (Österreichiches Artznei Buch), Silicon dioxide amorphous (WHO, Technical Report Series), Silicon dioxide (US-Food Chemicals Codex), Silicon dioxide, colloidal (fumed); Silicon dioxide (wet process), Synthetic amorphous silica (fumed), Surface-treated silica

Trade names (®): *Pyrogenic silica:* Aerosil, Cab-O-Sil, HDK

Precipitated silica: Acematt, Aerodisp, Agrosil, Baysical, BS, Ciptane, Durosil, Elfadent, Gomasil, Flatting agents OK, HK, TS, TK; Flo-Gard, Hi-Sil, Huberderm, Huberpol, Hubersil, Hubersorb, Lo-Vel, Microsil, Neosyl, Neosil, Oralsil, Perkasil, Rheosil, Rhodoxane, Rhoximat, RxCipients, San-Sil, Sident, Silcasil, Silene, Siloa, Sipernat, Sorbosil, Sylowhite, Tixosil, Ultrasil, VP Disp, Vulkasil, Wessalon, Zeo, Zeocal, Zeocopy, Zeodent, Zeoflo, Zeofoam, Zeofree, Zeolex, Zeopharm, Zeopol, Zeosil, Zeosyl, Zeothix, ZS

Silica gel: Chillgarde, Catalysts EP, ES; Daraclar, Gasil, Lucilite, Sorbsil, Silcron, Silica, Sil-Proof, Syloid, Sylodent, Sylojet, Syloblanc, Trisyl, Quantum

Colloidal silica: A2000, Aerodisp, Cab-O-Sperse, Levasil, Ludox

Danish:	Siliciumdioxid, fremstiller kemiskt
Dutch:	Siliciumdioxide, chemisch bereid
Finnish:	Piidioksidi, kemialliseti valmispettu
French:	Dioxyde de silicium, préparé par voie chimique
German:	Siliciumdioxid, auf chemischen Wege gewonnen
Italian:	Diossido di silicio, preparato chimicamente
Norwegian:	Silisiumdioksid, kiemisk utvunnet
Portuguese:	Dioxido de silicio, preparado quimicamente
Spanish:	Dioxido de silicium, preparado químicamente
Swedish:	Kiseldioxid, kemiskt utvunnet

CAS name: Silica

CAS registry number: 7631-86-9

Silica (including the crystalline polymorph), independent of its form and method of preparation (including by-products), is found under CAS No. 7631-86-9. To differentiate between the silica polymorphs, new polymorph-related CAS registry numbers have been generated (Figure 1). As the polymorphs of silica differ in their hazards to human health, it is essential to distinguish carefully between crystalline silica and non-crystalline or amorphous silica forms. Natural forms of amorphous silica like diatomaceous earth, especially flux-calcined diatomaceous earth, and amorphous silica fume – a by-product of silicon (Si) metal and ferrosilicon alloy manufacturing – may contain impurities, particularly crystalline silica (Rupprecht and Ferch, 1990; Flörke et al, 1993; Ferch and Toussaint, 1996). These polymorphs are beyond the scope of this review and are not considered here (Section 2.1.2).

EC (EINECS) number: 231-545-4

Formula: O_2Si [a]

Molecular mass: 60.08

Structure: SiO_2

2.1.1 Surface-treated SAS

A significant proportion of the global production of SAS is rendered hydrophobic by surface modification mainly with Si-organic compounds. Surface modified (after-treated) SAS can be

[a] In the case of surface treated silicas the chemical modification is not considered in the formula

obtained either by physical or chemical reaction. The most common Si-organic compounds used for the treatment are hexamethyldisilazane (CAS No. 999-97-3), dimethyldichlorsilane (CAS No. 75-78-5) and polydimethylsiloxanes (e.g. CAS No. 9016-00-6). The first compound forms mono-functional moieties upon hydrolysis, whereas the latter two give rise to bi-functional units, as shown below.

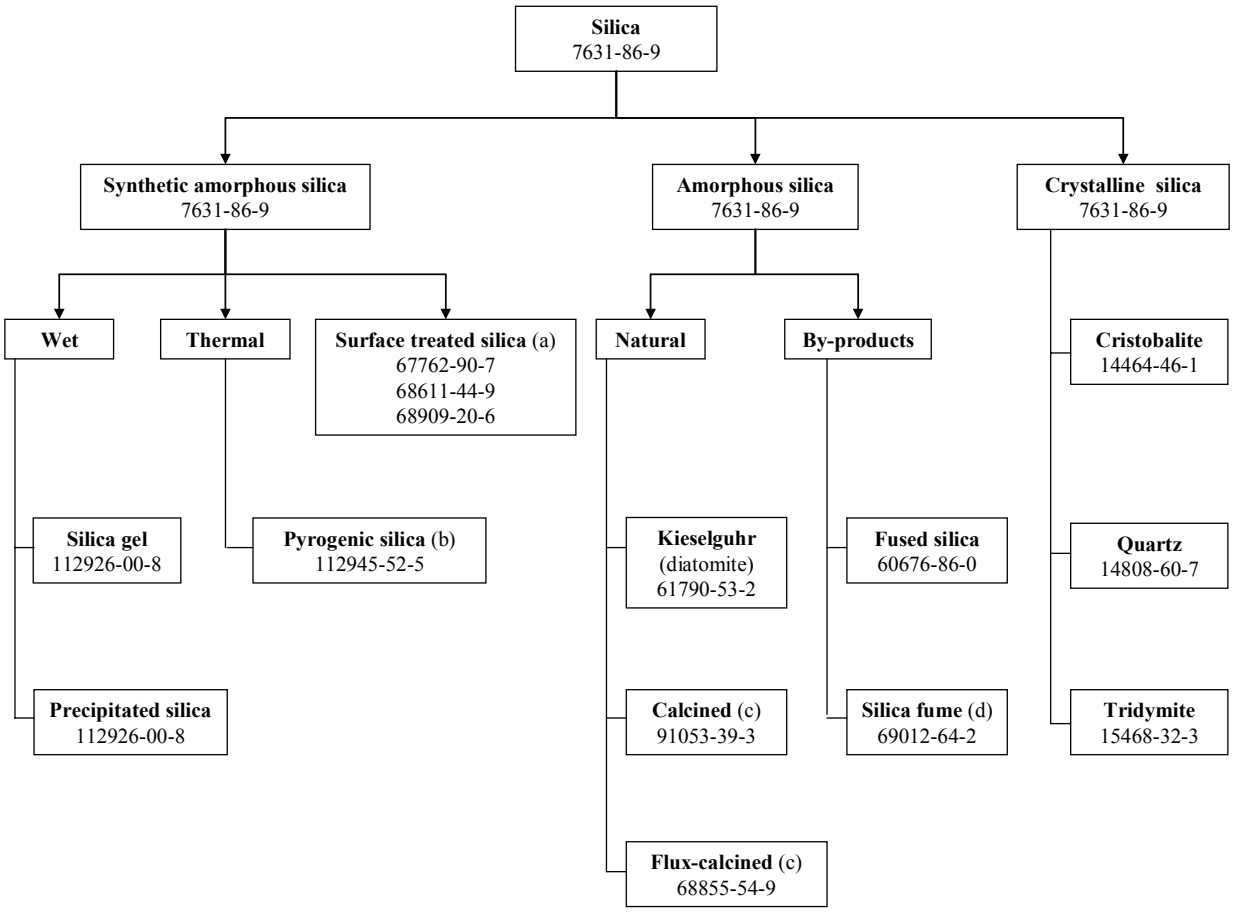
- Hexamethyldisilazane $\rightarrow \equiv Si–O–Si(CH_3)_3$
- Dimethyldichlorosilane $\rightarrow \equiv Si–O–[Si(CH_3)_2–O–]_{x = 1 - 3}$
- Polydimethylsiloxane $\rightarrow \equiv Si–O–[Si(CH_3)_2–O–]_{x = 3 - 6(10)}$

The surface treatment does not change the solid properties e.g. particle size, dissolution kinetics of the inorganic polymer silicon dioxide (silica, SiO_2). However, surface treatment does alter physico-chemical properties, e.g. reduced moisture uptake.

2.1.2 Polymorphs of silica

An overview of the different polymorphs of silica, including synthetic amorphous, amorphous and crystalline silicas, is given in Figure 1.

Figure 1: Different polymorphs of silica with CAS numbers



(a) All forms of SAS can be surface-treated either physically or chemically; most common treating agents are organosilicon compounds (Appendix B: Table B.2)
(b) Pyrogenic silica is also known as fumed silica in the English speaking countries
(c) Partial transformation into cristobalite
(d) By-product from electrical furnace

2.2 EC classification and labelling

SAS is not classifiable according to the Dangerous Substances Directive 67/548/EEC (EC, 1993).

Surface-treated substances are exempt from notification under the EC Directive (EC, 2002), including the three surface-treated SASs listed in the European Inventory of Existing Commercial Chemical Substances (EINECS): silane, dichlorodimethyl-reaction products with silica (271-893-4), silane, hexamethyldisilazane-reaction product with silica (272-697-1), and silane, octyltrimethoxy-reaction product with silica (296-597-2).

Under the US Toxic Substances Control Act (TSCA), surface-treated materials like treated SASs are not generally exempt from notification. Exemption from TSCA pre-manufacture notification requirements and listing in the TSCA Inventory are described under the '(h)(7)-exemption' located at 40 CFR §720.30 (h)(7)ii for inventory purposes. The surface-treated SASs with CAS numbers 67762-90-7, 68611-44-9 and 68909-20-6 are also not required to be on the TSCA inventory.

2.3 Physical and chemical properties

Both the mammalian and environmental toxicology of SASs are significantly influenced by the physical and chemical properties, particularly those of solubility and particle size. This is important when considering the comparative toxicology of SAS and crystalline forms, particularly when assessing the effects of SASs in animal experiments that require significant manipulation of the commercial product (particle size reduction) to meet experimental test guidelines. For these reasons, the physical and chemical properties of SASs are described in considerable detail in this report.

SASs, including pyrogenic silicas, precipitated silicas and silica gels, are white, fluffy and/or powdery amorphous forms of silicon dioxide (silica, SiO_2). SAS sols are milky-white dispersions of discrete SiO_2 particles stabilised in solution (e.g. water, ethanol).

SASs are distinguished by their chemical composition, physical properties, and characteristics of the particles. Characteristic physico-chemical properties of the different types of SAS are listed in Table 1.

Key parameters and the corresponding analytical methods are discussed in Section 2.5.

Table 1: Physical and chemical properties of SAS (Ferch, 1976)

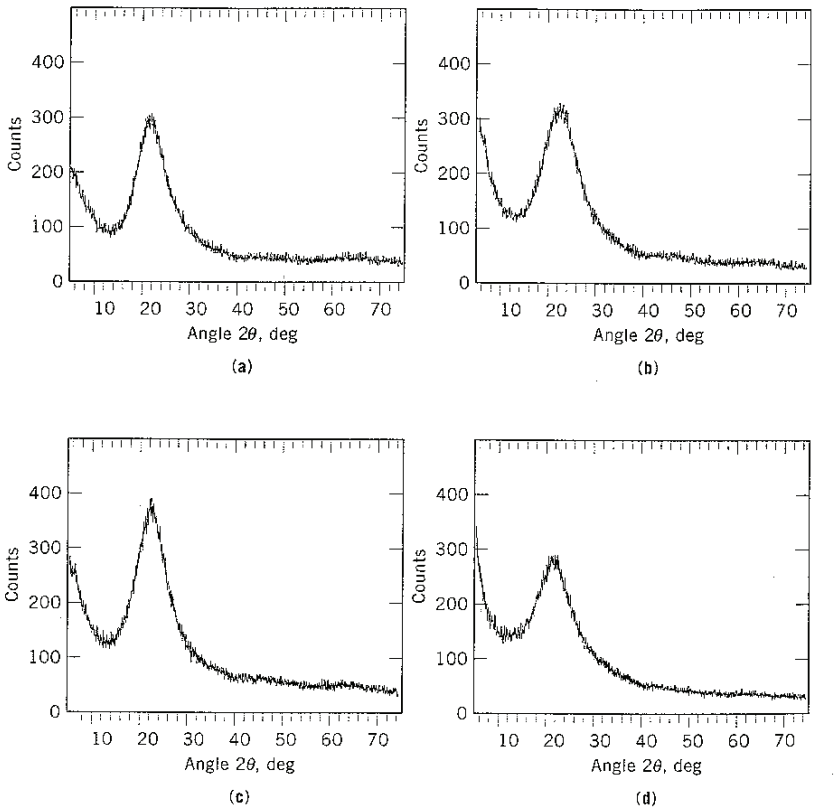
Property [a]	Pyrogenic	Precipitated	Gel	Sol [b]	Unit
Purity, SiO_2	> 99.8	> 95	> 95 [c]	15 - 50	% by weight
Colour	White	White	White	White, milky	
Specific surface area (BET)	50 - 400	30 - 500	250 - 1,000 [d]	50 - 400	m^2/g
Loss on drying	< 2.5	5 - 7	2 - 6	50 - 85	% by weight
pH [e]	3.6 - 4.5	5 - 9	3 - 8	3 - 5 8 - 11	
Tapped (bulk) density	30 - 250	30 - 500	500 - 1,000	NA [f]	g/l
Ignition loss	< 2	3 - 14	2 - 15	50 - 90	% by weight
Particle size					
Primary particle size	0.005 - 0.05 [g]	0.005 - 0.1 [g]	0.001 - 0.01	0.005 - 0.02	µm
Aggregate size	0.1 - 1	0.1 - 1	1 - 20	NA	µm
Agglomerate size	1 - 250	1 - 250	NA	NA	µm
Porosity					
Mean pore size	None	> 0.03	0.0001 - 1	NA	µm
Pore size distribution	None	Very wide	Narrow	Wide	
Specific gravity	2.2	1.9 - 2.2	1.8 - 2.2	1.0 - 1.4	g/cm^3
Structure, DBP [h] absorption	250 - 350	80 - 320	80 - 350	NA	ml/100 g

[a] Section 2.5
[b] After drying according to DIN 66131 or direct by titration with NaOH solution (Sears, 1956)
[c] Dry product, no hydrogel
[d] Porous surface
[e] Hyrophilic grades
[f] Not applicable
[g] Primary particles do not normally exist as individual units (Section 2.5.9)
[h] Dibutyl phthalate

2.3.1 Amorphous structure

X-ray diffraction diagrams of SASs as discussed here, using CuKα radiation with λ = 0.1542 nm, show only a broad halo, revealing an X-ray amorphous structure. The commercial SAS samples analysed are: (a) colloidal (Ludox TM50; DuPont); (b) gel (Sylodent 700; Grace); (c) precipitated (Hi-Sil 190; PPG); and (d) pyrogenic (HDK N20, Wacker) (Appendix B). The detection limit for crystallinity by X-ray is in the order of 0.3% by weight (Figure 2).

Figure 2: X-ray diffraction pattern of different SASs (Kirk-Othmer, 1997)



(a) Colloidal Ludox TM50 (DuPont)
(b) Gel Sylodent 700 (Grace)
(c) Precipitated Hi-Sil 190 (PPG)
(d) Pyrogenic HDK N20 (Wacker)

For pyrogenic SAS the maximum peak is found to be 21.4° at 2 θ; this relates to an average Bragg distance of d = 0.415 nm (ground quartz powder gives 2 θ = 26.5° and d = 0.336 nm). This enlargement of the average atom distance reveals markedly disordered atom arrangements of the SiO_4 tetraeder units in pyrogenic silica (Kirk-Othmer, 1997). X-ray diffraction, in combination with a special sample preparation technique that makes use of phosphoric acid dissolution in order to separate quartz from silicates and amorphous silicas, gives a detection limit of about 0.01% by weight relative to quartz (JM Huber, 1995).

Electron diffraction combined with transmission electron microscopy presents the opportunity to study solid structures of dimensions down to about 10 nm. Diffraction diagrams of pyrogenic SAS with a specific surface area of 200 m²/g show three concentric diffraction patterns that are typical for liquid-like, amorphous structures. Different grades of pyrogenic SASs, with specific surface areas from 125 m²/g up to 400 m²/g, result in similar diagrams, providing the largest average Bragg distance of d = 0.413 nm, and confirm the results of X-ray diffraction. Electron

diffraction on submicron quartz particles achieves well-resolved and sharp diffraction peaks, indicating single crystal behaviour of α-quartz. The detection limit is about 0.01% weight (Wacker, 1987).

A NIOSH standard method for the analysis of amorphous silica in crystalline matrices is given under the number 7501 - Silica, Amorphous (NIOSH, 2003). The method involves sampling on filter (total) or cyclone with filter (respirable) and subsequent measurement by X-ray powder diffraction of the analyte (cristobalite). The limit of detection is 0.005 mg for 0.2 to 2 mg of sample (Degussa, 1991a; Flörke *et al*, 1993).

2.3.2 Chemical reactivity

The reactivity of SAS is strongly dependent on the chemistry of the surface of the solid phase. Two basically different surface groups occur: (i) relatively unreactive hydrophobic siloxane units (-≡Si–O–Si≡-), and (ii) hydrophilic silanol groups (≡Si–OH) with high affinity for polar media. For the latter, different structures have been characterised: isolated, vicinal and geminal silanols (Figure 3).

Figure 3: Surface silanol groups on SAS

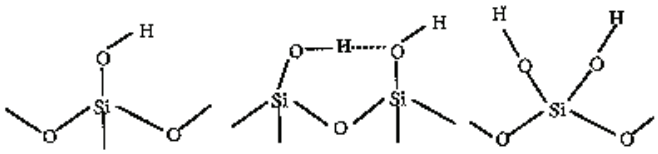


Table 2 shows the infrared absorption peaks of these silanols.

Table 2: Infrared absorption peaks of SAS surface silanols (Iler, 1979; Burneau and Gallas, 1998)

Silanol group	Peak (frequency cm^{-1})
Isolated (free)	3,745 - 3,750
Vicinal	3,650 - 3,660
Geminal	3,540 - 3,550
Water molecule adsorbed on the above	3,400 - 3,500

Silanols are known to be responsible for proton exchange, causing surface ionisation and ion adsorption. The number of silanol groups per unit surface area (nm²) depends on the degree of hydration of the SAS surface.

The reactivity of the silanol groups leads to ready adsorption of water. The silanols may undergo acid-specific reactions, e.g. chlorination (Heston *et al*, 1960; Iler, 1979).

$$\text{Chlorination: } \equiv Si–OH + SOCl_2 \rightarrow \equiv Si–Cl + SO_2 + HCl \quad \text{.....(Eq. 1)}$$

In concentrated sodium chloride (NaCl) solution, the silanols can be neutralised with caustic soda (NaOH), which is completed at a pH of 9 (Sears, 1956; Iler, 1979).

$$\text{Neutralisation: } \equiv Si–OH + NaOH \rightarrow \equiv Si–ONa + H_2O \quad \text{..... (Eq. 2)}$$

Several methods are available which allow quantitative determination of surface silanols, e.g. K. Fischer titration; chlorination with thionylchloride ($SOCl_2$); Zerewitinoff determination with methyl magnesium iodide (CH_3MgI) or methyl lithium (CH_3Li); infrared-spectroscopy; ^{29}Si cross-polarisation magic-angle-spinning (CP-MAS) nuclear magnetic resonance (NMR) spectroscopy; titration with caustic soda (NaOH); and thermo-gravimetric analysis (loss on ignition) (Table 9 in Section 2.5.2).

The silanol numbers vary; typical ranges for different SASs are given in Table 3.

Table 3: Silanol concentration on different SASs

Type of SAS	Concentration (SiOH/nm ²)	Method	Reference
Precipitated	5.0 - 5.7	Thermogravimetry	Kellum and Smith, 1967
Gel	4.6 - 7.9	^{29}Si CP-MAS NMR	Sindorf and Maciel, 1983
Pyrogenic	1. 25 - 2.53	Thionylchlorid	Boehm, 1966
Pyrogenic	1.8 - 2.2	Acid-base titration	Barthel, 1992

The presence of fewer silanol groups on pyrogenic SAS (mean 2 SiOH/nm²) is directly related to the thermal synthesis process, without liquid water.

Iler (1979) estimated the maximum silanol density for a given surface matrix. Assuming a density of 2.2 g/cm³, a mean of 5 SiOH/nm² was calculated for a variety of SASs. This fits well with the experimental findings for precipitated SAS and gel (Table 3).

Surface acidity

The acidity of SAS is related to the number and reactivity of the silanol groups present on the solid SAS surface. Surface silanols are more acidic than monosilicic acid: pKa values are 7.1 and 9.8, respectively. Further, the acidity increases with the degree of polymerisation. Silanol acidity of SAS is lower than that of quartz (Yates and Healy, 1976). A review is given in Burneau and Gallas (1998).

Dissolution kinetics

The overall reaction for dissolution of (solid) silica to monosilicic acid, and reverse precipitation, i.e. polymerisation and de-polymerisation, is given by the following equation.

$$SiO_2\,(s) + 2\,H_2O \underset{k_p}{\overset{k_d}{\rightleftharpoons}} Si(OH)_4 \quad \text{(Eq. 3)}$$

where (s) denotes solid state, and

k_d and k_p are rate constants of dissolution and precipitation

The dissolution rate has been described by the following phenomenological law commonly used in the literature (Löbbus et al, 1998; Vogelsberger et al, 1999).

$$\frac{d[M]_{tot}}{dt} = k_d \times [P_0] \times \left\{1 - \frac{[M]_{tot}}{[M]_{S,tot}}\right\}, \quad [P_0] = \frac{N_S}{N_A} \times \frac{S}{v} \quad \text{(Eq. 4)}$$

where $[M]_{tot}$ and $[M]_{S,tot}$ refer to total concentration and total saturation concentration of dissolved monosilicic acid

t is time

k_d is the rate constant of dissolution

$[P]_0$ is the total concentration of surface sites

N_S is the number of OH groups/unit of surface area

N_A is the Avogadro constant

S is the surface area exposed to dissolution

v is the volume of the solution

The total concentration of surface sites ($[P]_0$) is constant since a sufficiently large amount of solid is used. Therefore, $[P]_0$ can be combined with the rate constant.

The solubility of amorphous and crystalline silica (quartz) has been investigated in the past. The saturation concentration of dissolved silica was 2.0 mmol/l (120 mg SiO2/l) for amorphous silica, whereas quartz exhibited a low solubility of about 5 mg/l (Iler, 1979).

More recently, Vogelsberger *et al* (1996), Vogelsberger (1999, 2003), Roelofs (2002) and Roelofs and Vogelsberger (2004) studied the dissolution kinetics of different industrial SASs, using a sensitive, modified molybdic acid method (Motomizu *et al*, 1989) (Section 2.6.3). The experiments were performed in buffered solution at constant pH of 7.3 to 7.4 and temperature of 37°C (Table 4).

Table 4: Saturation concentration of hydrophilic SASs dissolved in aqueous phase [a]

Type of SAS [b]/ Product name	**$S_{BET\ phil}$ [c] (m^2/g)**	**K [d] (10^{-9}mol/m^2·s)**	**$[M]_{S,tot}$ [e] (mmol/l)**	**Remark**
Pyrogenic				
Cab-O-Sil M5	220.8	1.76 ± 0.18	2.39 ± 0.02	Pore free
HDK T30	305.3 [f]	7.93	2.51 ± 0.03	Pore free
Precipitated				
Zeosil 45	190.1	0.73 ± 0.03	2.34 ± 0.02	Nearly pore free
Gel				
Sylobloc K300	312.6	0.37 ± 0.02	2.345 ± 0.03	Porous, between meso- and macropores
Syloid 74	312.7	0.64 ± 0.04	2.11 ± 0.02	Porous
HDK H15 precursor	150.0 [g]	0.41 ± 0.03	1.91 ± 0.05	Pore free

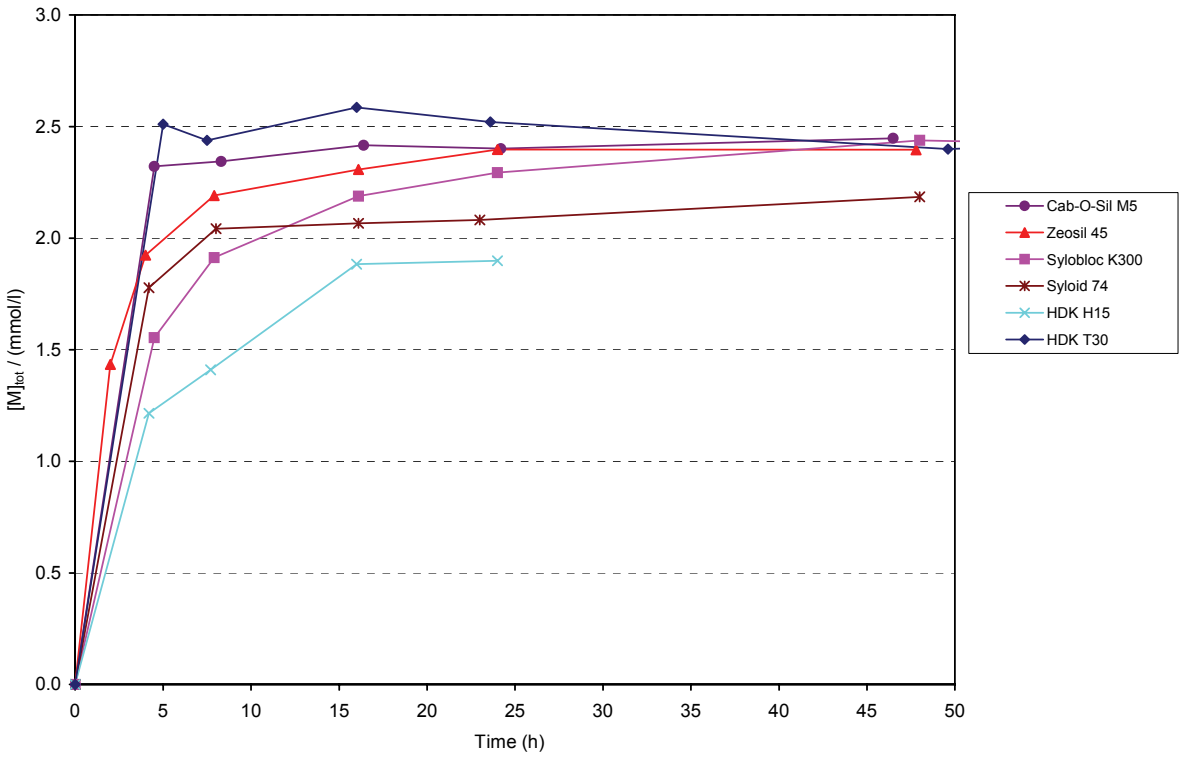
[a] Tris(hydroxymethyl)aminomethane buffer, NaCl concentration 0.112 mol/l; pH 7.3 - 7.4, 37 °C
[b] Appendix B
[c] Specific surface (Section 2.5.2) for hydrophilic SAS
[d] Rate constant
[e] Total mass dissolved at saturation
[f] 40°C
[g] For hydrophilic base SAS (before hydrophobisation)

The saturation concentrations $[M]_{S,tot}$ for all analysed SASs ranged from 1.91 to 2.51 mmol/l. The saturation concentration increased with increasing specific surface area of the corresponding SAS, i.e. higher value with decreasing particle size (Kelvin effect). The surface-treated, hydrophobic silica HDK H15 had a low solubility, compared to the hydrophilic SASs, due to

reduced wetting of its surface in aqueous systems. Wetting was increased by the addition of alcohol, leading to decreasing solubility.

For almost all SASs, the saturation concentration was reached within several hours, except for porous Syloid 74 (312.7 m²/g; see Table 4) where Ostwald ripening lowered the dissolution rate. In Ostwald ripening, small pores are filled up with dissolved material, which re-precipitates (Figure 4).

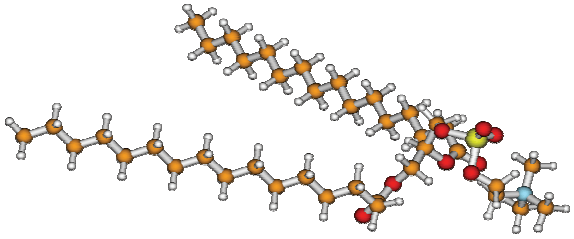
Figure 4: Dissolution of SASs in aqueous systems [a]



[a] Tris(hydroxymethyl)aminomethane buffer, NaCl concentration 0.112 mol/l; pH 7.3 - 7.4 at 37 °C

Roelofs (2002) and Vogelsberger (2003) conducted a further experiment to simulate the dissolution behaviour of SAS in the lung, under physiological conditions and osmotic pressure. A surface-active component was added to the aqueous system to mimic conditions found in cellular lung fluid. The surface-active component was L-α-dipalmitoyl-phosphatidylcholine (DPPC) (Figure 5) in a tris(hydroxymethyl)aminomethane (TRIS) buffered solution (isotonic with mammalian body fluid), the composition of which provided conditions comparable to those found in the lung, in terms of physiological pH, buffer capacity and osmotic pressure (Table 5).

Figure 5: L-α-dipalmitoyl-phosphatidylcholine (DPPC)[a] (Roelofs, 2002)



[a] Chemical formula: $C_{40}H_{80}NO_8P$

Table 5: Experimental conditions used by Roelofs (2002) and Vogelsberger (2003)

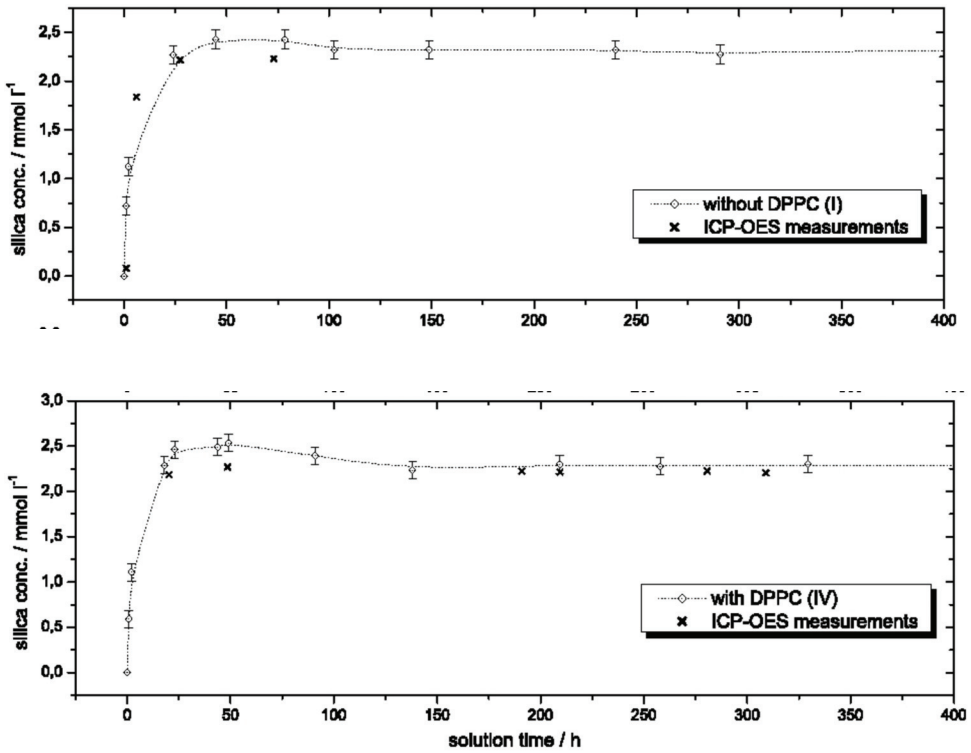
SAS	Cab-O-Sil M5, pore free
SAS specific surface (S_{BET})	220.8 m^2/g
SAS concentration	1 or 10 g/l (0.5 g/500 ml or 0.1 g/100 ml)
SAS dissolution time	Up to 3 months
L-α-dipalmitoyl-phosphatidylcholine (DPPC)	25 g/l
Tris(hydroxymethyl)aminomethane (TRIS)	6.1 g/l (0.05 mol/l)
HCl	35.4 ml/l (0.0354 mol/l)
NaCl	6.54 g/l (0.11 mol/l)
Osmotic concentration	309 mOsm/l
pH	7.4, nearly constant over dissolution time
Temperature	37°C

Possible errors in the determination of the silica concentration were prevented by using polymethylpentene (instead of glass) flasks and doubly de-ionised water; all chemicals were of analytical purity. In addition to the molybdic acid method (Section 2.6.3), inductively coupled plasma atomic emission spectrometry (ICP-AES) was applied to determine the total amount of dissolved silica (as Si) (Section 2.6.4), with a view to possible disturbance of the former by DPCC or remnants thereof. By means of thermodynamic consideration, a model predicting the dissolution behaviour for SAS was established (Roelofs, 2002).

In a first experiment, a 1,000 ml polymethylpentene flask was charged with 0.5 g Cab-O-Sil M5 in 500 ml of TRIS buffer solution. In a second experiment, 0.1 g Cab-O-Sil M5 was dissolved in 100 ml TRIS buffer with 25 mg of added DPPC (homogenised by ultrasound). The flasks were shaken at a constant temperature of 37°C and pH (7.3 - 7.4). The total amount of dissolved silica was determined by the molybdic acid method as modified by Motomizu *et al* (1989) for enhanced sensitivity (Section 2.6.3). Each sample (0.5 - 1 ml) was analysed 4 times after filtration over a

0.2 µm one-way syringe filter. Measurements of dynamic light scattering by the filtrate confirmed nearly complete removal of all particles. Silica concentrations were confirmed by ICP-AES analysis (Section 2.6.4). The results shown here are based on repeated experiments. The time-dependent dissolution curves of Cab-O-Sil M5 without and with DPPC are shown in Figure 6.

Figure 6: Dissolution of SAS (Cab-O-Sil M5) without and with DPPC [a] (Roelofs, 2002)



[a] DCPP, L-α-dipalmitoyl-phosphatidylcholine (Figure 5). (I) and (IV) have no significance here. Graphs were scanned from original thesis (with permission from the author) including decimal comma on Y axis. On X axis, solution time is measured in hours. ICP-OES = ICP-AES, inductively coupled plasma optic/atomic emission spectrometry (Section 2.6.4)

No significant differences between the dissolution of SAS without and with DPPC were noted. Both the maximum silica concentration (2.42 and 2.53 mmol/l without and with DPCC, respectively) and the time to reach saturation (1 day) were practically the same (within the measurement error). ICP-AES confirmed the silica concentrations determined with the molybdic acid method, within the error of estimation. For this reason, a possible influence of phosphate on the results was excluded. Consequently, both methods were equally suitable for the determination of silica concentrations.

For an open system like the lung, where dissolved SAS material is quickly removed, total dissolution can be expected. The impact of confirmed high solubility of SAS in biological media for the clearance mechanism of inhaled SAS will be discussed in Section 7.1.

Surface energy

Hydrophilic SAS has a higher surface energy (solid) than the surface tension of water, which is 72 mN/m [a] for pure water. Therefore, pure water will wet hydrophilic SAS.

The wettability of the SAS can be reduced by deactivation of surface silanols by means of so-called silane coupling-agents such as hexamethyldisilazane (HMDS), which form $(CH_3)_3SiOH$ groups (silylation) that render the SAS surface hydrophobic (Burneau and Gallas, 1998). Various other organosilicones can be used for SAS hydrophobisation by silylation, e.g. dichloro-dimethylsilane and polydimethylsiloxane, to reduce the surface energy of SAS. The resulting hydrophobic SASs are only partially or not wettable by pure water (Flörke *et al*, 1993; Kirk-Othmer, 1997; CEFIC/ASASP, 2004; European IPPC Bureau, 2004).

Surface silylation also decreases the adsorption capacity of the SAS surface (Barthel, 1992), and lowers the BET specific surface area (Section 2.5.2).

Purity and impurities

Silica (SiO_2) is the main component of industrially produced SAS, but traces of other metal oxides, sulphates and/or chlorides are present.

Dried pyrogenic SAS typically contains ≥ 99.8% silica, with alkali and heavy metals in the low ppm range. Suitable cleaning steps in the production process typically reduce the content of hydrochloric acid by-product to less than 100 ppm (by weight) (Table 6).

[a] mN/m (liquid) is of the same dimension as mJ/m² (solid)

Table 6: Composition of pyrogenic SAS (Roempp, 2001)

Parameter	(% by weight)
SiO_2	≥ 99.8
Al_2O_3	< 0.05
Fe_2O_3	< 0.003
TiO_2	< 0.03
Na_2O	< 0.0009
Chlorides as Cl^-	< 0.025

Dried precipitated SASs and SAS gels typically contain ≥ 95% silica (Table 7). These SASs are further distinguished by their microporosity and hydroxylated surfaces.

Table 7: Composition of precipitated SAS and SAS gel (Roempp, 2001)

Parameter	(% by weight)
SiO_2	≥ 95
Na_2O	0.2 - 2.4
Sulphates as SO_3	0.2 - 3.0
Fe_2O_3	< 0.05
Trace oxides	< 0.07

Colloidal SAS (silica sols) are stable dispersions of amorphous silica particles (≥ 30%) in a liquid, most commonly water (Table 8).

Table 8: Composition of colloidal SAS (Grace, 2003)

Parameter [a]	(% by weight)
SiO_2	≥ 30
Na_2O	0.1 - 0.4
Sulphates as $NaSO_4$	0.01 - 0.03
Aluminium oxide (stabiliser)	0.2

[a] Apart from water or solvent

2.3.3 Particle size

With respect to particle size, the German standard DIN 53206 distinguishes between primary particles, aggregates and agglomerates (DIN, 1972).

Primary particles are recognisable by electron (transmission, scanning) microscopy as sub-units of pyrogenic and precipitated SAS or individual particles in SAS sols. For SAS gels, primary particles are not visible: nucleation and condensation give rise to further particle growth. Primary particles in the case of pyrogenic or precipitated SAS do not exist in isolation (Degussa, 1984b).

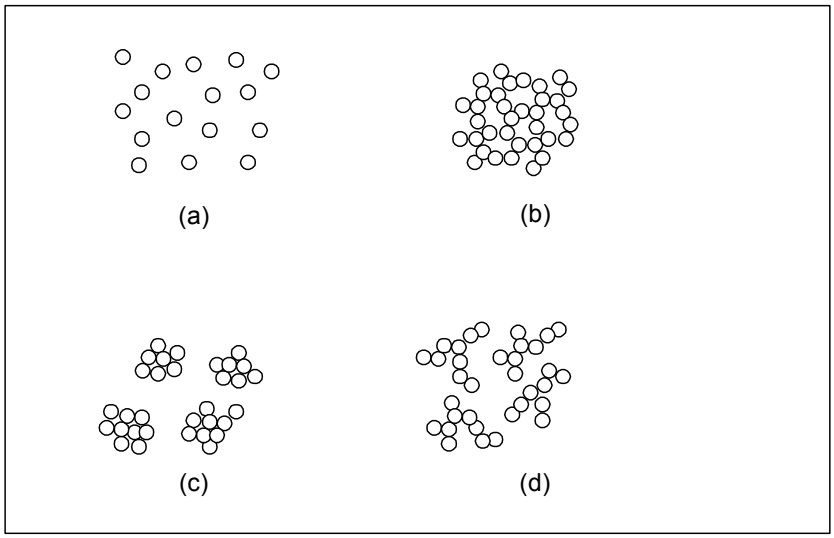
Aggregates are assemblies of primary particles which are grown together face-to-face in the form of chains or clusters. The aggregates are formed by the collision of primary particles during particle growth and/or by the further deposition of silica onto these aggregates. SAS aggregates represent the smallest, stable, non-dispersible particle units of three-dimensional structure, with a size ranging from 100 to 1,000 nm for pyrogenic and precipitated SASs. These aggregates can be found at infinite dilution or after blending in a polymer matrix, e.g. composites. For SAS gels, aggregates form macroscopic structures. SAS sols consist of primary particles and aggregates only in a fluid like water, organic solvent or a polymeric matrix but typically agglomerate irreversibly under drying.

Agglomerates are assemblies of aggregates, held together by strong physical adhesion forces.

The British Standards Institution has defined the term aggregate as used by DIN 53206 as agglomerate, and agglomerate as aggregate (BSI, 2005). In this report, the German definitions are used.

Figure 7 illustrates the different particle structures of SASs manufactured by different routes.

Figure 7: Theoretical SAS particles at infinite dilution



(a) Sol, isolated primary particles
(b) Gel, densified aggregate
(c) Precipitated, compact aggregates
(d) Pyrogenic, open branched-chain aggregates

Redispersed pyrogenic SAS is also considered to be a colloidal SAS (sol), but does not contain isolated primary particles.

By adjusting certain process parameters, the mean particle size, particle size distribution and degree of aggregation and/or agglomeration can be varied over relatively broad ranges. However, the smallest particles in precipitated and pyrogenic SAS remain the corresponding aggregates, not the primary particles (Hurd and Flower, 1988).

Given their size range, commercial SAS do not fall into the class of nanoparticles, which are defined as particles of less than 100 nm in diameter (BSI, 2005).

Microphotographs of actual SAS particles in commercial products are shown in Figures 8, 9 and 10 (courtesy of Stintz M, Technical University of Dresden and Heinemann M, Wacker Chemie, Burghausen, Germany).

Figure 8: Scanning electron microscope image of pyrogenic SAS agglomerate after dispersion

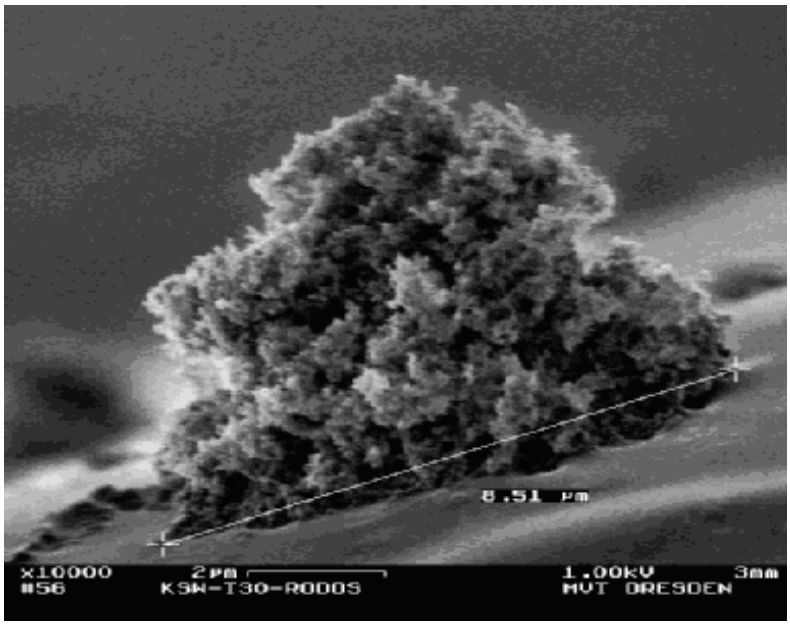


Figure 9: Scanning electron microscope image of precipitated SAS agglomerate

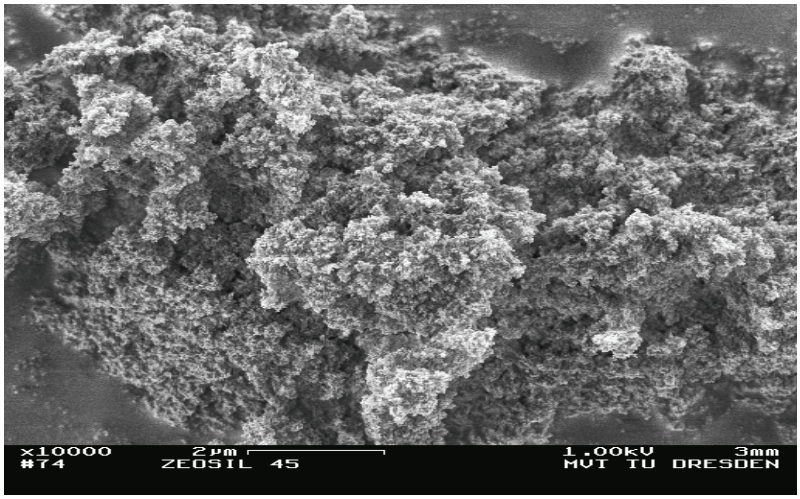
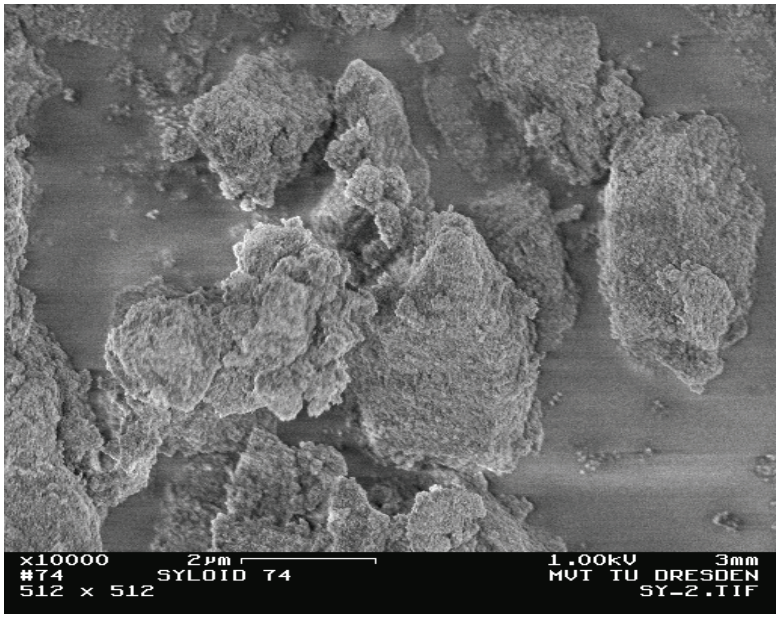


Figure 10: Scanning electron microscope image of gel SAS



2.4 Conversion factors

Conversion factors for vapour concentrations of SAS in air are not applicable.

2.5 Methods for the analysis of SAS

2.5.1 Purity and impurities

Silica (SiO_2) is the main component of industrially produced SAS, but traces of other metal oxides, sulphates and/or chlorides are present. The silica content is determined gravimetrically by fuming off with hydrofluoric acid. The analysis for metal oxides is then normally performed by means of atomic absorption spectroscopy (AAS) using the residue from the fuming off process. Sulphate and chloride content are determined by potentiometric titration.

2.5.2 Specific surface area

The specific surface area of SAS is a key parameter to differentiate between the grades of SAS of a specific type (Table 1). It is usually measured by adsorption of nitrogen at 77.4 K (–196°C), but other gases and vapours are also used. The standard BET (Brunauer, Emmett and Teller) method is used for calculating the specific surface area from an adsorption isotherm (Brunauer *et al*, 1938 cited by Gregg and Sing, 1982), following:

$$p/\upsilon_a \times (p_0 - p) = (1/\upsilon_m \times c) + (c - 1) \times p / (\upsilon_m \times c \times p_0) \quad \text{(Eq. 5)}$$

υ_a is the amount of gas adsorbed (mol/g of adsorbent) when the gas pressure is p

υ_m is the monolayer capacity of the surface (mol/g of adsorbent), i.e. the number of moles required to form a monomolecular layer

p_0 is the saturation gas pressure (Pa) at the temperature used

c is a constant related to the heat of adsorption

With υ_m calculated from the experimental adsorption isotherm data (Figure 11), and using the above equation, the specific surface S_{BET} area is determined by:

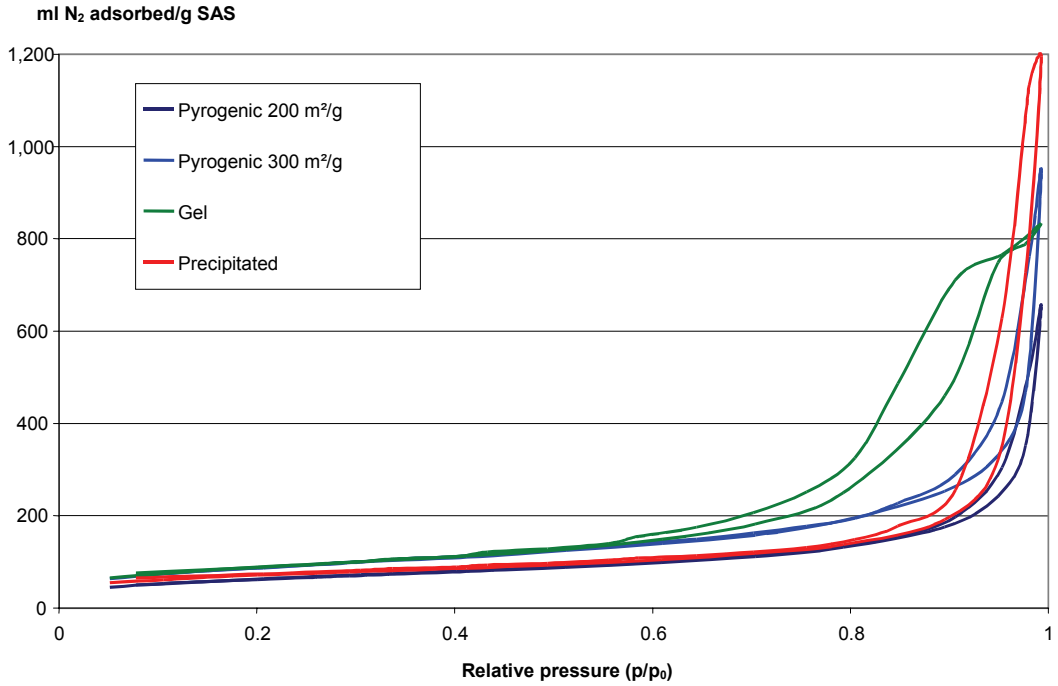
$$S_{BET} = \upsilon_m \times a_m \times N \times 10^{-20} \quad \text{(Eq. 6)}$$

S_{BET} is the specific surface area (m^2/g)

a_m is the molecular cross-sectional area of one gas molecule. The value of a_m for N_2 is 16.2 Å² (Ångstrom) for oxide surfaces

N is Avogadro's number (6×10^{23})

Figure 11: Nitrogen adsorption and desorption isotherms[a] of different SASs



[a] In each case, the lower curve refers to adsorption and the upper curve to desorption, showing hysteresis

The BET algorithm requires a type II adsorption isotherm in the range of $0.05 < p/p_0 < 0.3$ and a large constant ($c \geq 50$). Different shapes of the isotherm refer to typical structural features of the

different SAS types, i.e. gel, precipitated and pyrogenic (Gregg and Sing, 1982). Surface modification (hydrophobisation) of SAS results in a marked decrease of the surface energy and a low BET constant ($c < 50$). Therefore, strictly speaking, the BET method for surface-treated SAS leads to flawed results (Barthel, 1992).

Gas adsorption is a well-established approach to characterise a particular SAS in terms of its surface structure, surface energy and distinct surface groups on highly dispersed solids.

Furthermore, inverse gas chromatography (IGC) is a suitable technique to record adsorption data, particularly for solids and substances of relatively low vapour pressure. The principle of IGC is the reverse of a conventional gas chromatographic (GC) experiment. A cylindrical column is uniformly packed with the solid material of interest, typically a powder, fibre or film. A pulse or constant concentration of gas is then injected down the column at a fixed carrier gas flow rate, and the time taken for the pulse or concentration front to elute down the column is measured by a detector. A series of IGC measurements with different gas phase probe molecules then allows access to a wide range of physico-chemical properties of the solid sample (Jagiello and Papirer, 1991). For SAS surface characterisation, two different methods have been used:

- IGC at infinite dilution, applying the probe at the detection limit of a flame ionisation detector - providing retention volumes and free energies of adsorption. Using linear, cyclic and branched alkanes, IGC enables a description of the surface texture of different polymorphs of pyrogenic SAS. Comparing the adsorption of polar probes to that of alkanes, gives access to specific interactions, and finally acceptor and donor numbers of the SAS surface.
- IGC at finite concentration providing the first derivative of the global adsorption isotherm, which has been shown to be composed of the local adsorption isotherm and the energy distribution function of the adsorption sites on hydrophilic and silylated SASs (Khalfi *et al*, 1996; Papirer and Balard, 1998; Barthel *et al*, 2003)

Infrared (IR) and NMR spectroscopy and other standard analytical methods can be used for SAS surface analysis. These are not specific to SAS and not further discussed here. An overview of all methods is presented in Table 9.

Table 9: Methods for surface analysis

Method/parameter	Technique
Gas adsorption	
Specific surface area (BET)	N_2 adsorption at –196°C
Porosity	N_2 adsorption at –196°C
Porosity	Mercury intrusion
IR spectroscopy	
Silanol groups (qualitative analysis; isolated, bridged)	Fourier transform infrared (FTIR)
Alkyl groups (qualitative analysis)	FTIR
Silanol groups	Diffuse reflectance infrared Fourier transform (DRIFT)
Silanol groups (qualitative analysis)	$LiAlH_4$ titration
NMR spectroscopy	
Determination of the relative amounts of mono-, di- and trialkylsilane groups of surface	^{29}Si-cross polarisation magic-angle-spinning (CP-MAS)
Determination of cross-linking of alkylsilanes	^{29}Si-CP-MAS
Side chains of surface-treated silicas, characterisation of functional groups	^{13}C-MAS or CP-MAS
Remaining ethoxy and methoxy groups	^{13}C-CP-MAS
Extractable organic compounds	^{1}H-NMR
Si-O-Si bond angle distribution	^{29}Si-MAS
Electron spectroscopy	
Composition and chemical state of elements present at the surface	X-ray photoelectron spectroscopy (XPS)
Concentration gradients and diffusion profiles	XPS
Mass spectroscopy	
Trace analysis of the surface	Secondary ion mass spectroscopy (SIMS)
Atomic force microscopy (AFM)	
Morphology	AFM
Porosity	AFM
Gravimetry	
Silanol groups	Thermogravimetry (loss on ignition)
Silanol groups	Thionylchloride ($SOCl_2$) chlorination
Titration	
Silanol groups	K. Fischer
Silanol groups	Acid-base with NaOH
Silanol groups	Zerewitinoff with CH_3MgI or CH_3Li

2.5.3 Drying loss

SASs produced by the wet route contain between 2 to 10% (by weight) of physically bonded water, which can be removed by 2 hours of drying at 105°C. The weight loss, determined by gravimetry, is equivalent to the mass of physically bonded water. Due to the thermal process conditions pyrogenic SASs have a low content of water (< 2.5% by weight) (Table 1).

2.5.4 pH

For the determination of pH, the SAS content is limited to 4%. The pH of surface modified (hydrophobic) SAS is determined in a water-alcohol mixture, to increase wetting.

2.5.5 Tapped density

Tapped density is measured to indicate the weight of the (bulk) product in powder form. Approximately 200 ml of SAS is subject to vibration (tapped 1,250 times) in a graduated cylinder. From the initial weight of the sample and the resulting volume, the tapped density is calculated and indicated in g/l. Common values are in a range of 50 g/l for milled SASs and up to 600 g/l for granulated or very dense SASs.

2.5.6 Ignition loss

To determine the amount of chemically bonded water-interaction of surface silanols with water molecules a sample is heated for 2 hours at a temperature of 1,000°C. The thermo-gravimetric weight difference (loss on ignition) is equivalent to the mass of both physically bonded (drying loss) and chemically bonded water. Common values for the ignition loss are in a range of 2 to 10% by weight.

2.5.7 Particle size

SAS particles may occur as primary particles, aggregates and agglomerates, depending on the type of SAS (Section 2.3.3).

Many different methods can be used to analyse the particle size of SAS. However, each physical measurement principle will generally provide a different distribution curve.

Standard test-methods for the analysis of dry particles in air that have been applied to determine SAS particle size include, primarily, dry-sieving and laser light diffraction, but also particle image velocimetry, time-of-flight, cascade impactor, transmission or scanning electron microscopy and light microscopy (VCI, 1999; Stintz and Heinemann, 2001*)*.

In liquid media, appropriate methods are based on sedimentation, light diffraction (Fraunhofer theory for large particles, see below), light scattering (Mie theory for diffraction by and diffusion of light around small particles), static and dynamic light scattering (photon correlation spectroscopy).

A correlation has been developed between the fractality and structure of pyrogenic metal oxides like pyrogenic SAS and hydrodynamic sizes from photon correlation spectroscopy (Batz-Sohn, 2003).

For highly dispersed metal oxides like SAS, which show fractal and aggregated stable secondary structures (Ehrburger-Dolle, 1998), it has been shown that there is no (simple) relationship between the specific surface area according to BET and the real particle sizes as, for example, recorded by photon correlation spectroscopy or aerodynamic techniques (Batz-Sohn, 2003; Stintz and Heinemann, 2004). For rigid spheres like sols, irregular particles like precipitated and pyrogenic SAS (a, c and d in Figure 7, Section 2.3.3), this can be achieved only by defining an equivalent diameter of spheres with the same measured property, e.g. settling rate similar to the irregular particle. For a gel (b in Figure 7), the size of the particle is equal to the size of the bulk container. To describe irregular particles like precipitated or pyrogenic SAS, form factors have to be used. A form factor is defined as the ratio between equivalent diameters, e.g. settling equivalent diameter to volume equivalent diameter.

Light and electron microscopy may provide additional information on shape and structure of SAS particles. An overview of relevant particle size measurement methods is given in Table 10.

Table 10: Particle size analysis in air and liquids

Method	Principle	Type of particle size	Medium	Size	Remark
Sieving	Mechanical separation according to the mesh size	Mesh size equivalent diameter	Air, liquid	30 - 10,000 µm 5 - 10,000 µm	Adhesive forces of undersize particles must be overcome to move particles through mesh; low shearing
Cascade impactor	Aerodynamic separation, deposition, weighing of deposited material	Aerodynamic equivalent size of spheres with φ=1.0 g/ml	Air, high to medium concentration	0.4 - 17 µm	Low bulk density leads to large deposited volumes and false distribution towards smaller particles; medium shearing
Time-of-flight	Counting of single particles according to their aero-dynamic behaviour in air	Aerodynamic equivalent size of spheres with φ=1.0 g/ml	Air, low concentration	0.2 - 20 (100) µm	Problems occurring with low particle counts in a collective (number of particles), high shearing
Dynamic light scattering	Particle fluctuations recorded as auto-correlation function and fitted to give diffusion coefficient	Hydrodynamic equivalent size of the equivalent spheres	Liquid, e.g. water, alcohol; low concentration	0.01 - 1.0 µm	Reliable and common submicron particle sizing technique; no shearing during measurement
Static light scattering	Scattering related to mass and differential refraction index	Radius of gyration	Liquid, e.g. water, alcohol; low concentration	0.005 - 1.0 µm	Reliable and common technique to provide molecular weights of polymers; no shearing during measurement
Fraunhofer diffraction with air dispersion	Conversion of diffraction pattern into a particle size distribution	Geometrical size of an idealised sphere	Air, high concentration	0.5 - 1,000 µm	Common in technical applications; low to high shearing
Fraunhofer diffraction with liquid dispersion	Conversion of a diffraction pattern into a particle size distribution	Geometrical size of an idealised sphere	Liquid, e.g. water, alcohol; high concentration	20 mm focal length: 0.12 - 20 µm 100 mm focal length: 0.5 - 100 µm	Common in technical applications; low to high shearing

Effective particle density

A conversion factor has been developed to convert geometric particle diameter into aerodynamic diameter. The conversion is based on the known effective density of non-spherical particles. By definition, the aerodynamic diameter (d_{aero}) represents the diameter of a sphere with a density (ρ_{aero}) of 1 g/cm³ which has the same settling velocity in air, according to Stokes Law, as the real particle with geometrical diameter (d_{geo}) and particle density (ρ_{part}). Both equivalent diameters are related by:

$$d_{aero}^2 / d_{geo}^2 = \rho_{part} / \rho_{aero} \quad \text{(Eq. 7)}$$

with $\rho_{aero} = 1$ g/cm³.

Experiments using a direct optical method to measure fractions of aerodynamically classified SAS agglomerates indicated an effective particle density (ρ_{eff}) of a SAS agglomerate of about 0.075 g/cm³. The conversion factor d_{geo} to d_{aero} was estimated to be 3.6 (Stintz *et al*, 1998).

Using the effective density of the agglomerates, the porosity is calculated to be 96.6%, following:

$$\text{Porosity silica agglomerate} = 1 - (\rho_{eff} / \rho_{part}) \quad \text{(Eq. 8)}$$

The effective density of 0.075 g/cm³ (Stintz *et al*, 1998) fits well with the whole particle size range under investigation. Theoretically, this value includes parameters like solid density of the primary particle, and shape and porosity of the SAS agglomerates. This has been demonstrated for low bulk SASs, i.e. those having apparent densities of about 50 g/l.

2.5.8 Particle size under technical handling conditions

To assess the particle size distribution of SAS under technical handling conditions (filling, shipping and storage of product), various methods for non-monodisperse, non-spherical, highly agglomerated particles have been evaluated. Under these conditions, characterised by a dry powder state, high solid concentration and low/no shearing of the product, SAS agglomerates are the relevant particles. Conventional particle size methods often involve high shearing forces which may lead to destruction of the sample, i.e. breakdown of the agglomerates. These methods do not describe the product as it is marketed or used. Appropriate test methods are dry sieving and Fraunhofer laser light diffraction, in which low shearing forces (free settling) are applied. These two methods are non-destructive, i.e. the SAS agglomerates are mostly preserved and the particle aerosol concentration is sufficiently high to reflect real technical handling conditions (Stintz and Heinemann, 2001).

When using dry sieving, the effective bulk density of the product should be determined in advance. This is necessary to avoid overload of the corresponding sieves and allows for the accurate application of the standard method to specific SASs. The effective bulk density measured (by means of a 1 mm mesh size sieve, a powder funnel and a volume-graduated beaker) for three reference SASs, HDK T30, HDK H15 and Cab-O-Sil TS610 (pyrogenic, Appendix B) was 0.035 to 0.040 g/cm³; the total maximum SAS input was 3 g for all sieves. Mesh sizes ranged up to 2 mm, total sieving time was 5 minutes and vibration moderate (amplitude 50% for 9 s, 1 s hold). The SAS fraction remaining on each sieve was weighed in each case. The hydrophilic SAS had to be dried before sieving. Table 11 shows the fractions of SAS mass passing the smaller sieves, based on repeated measurements (Stintz and Heinemann, 2001).

Table 11: Fraction of SASs passing smaller sieves

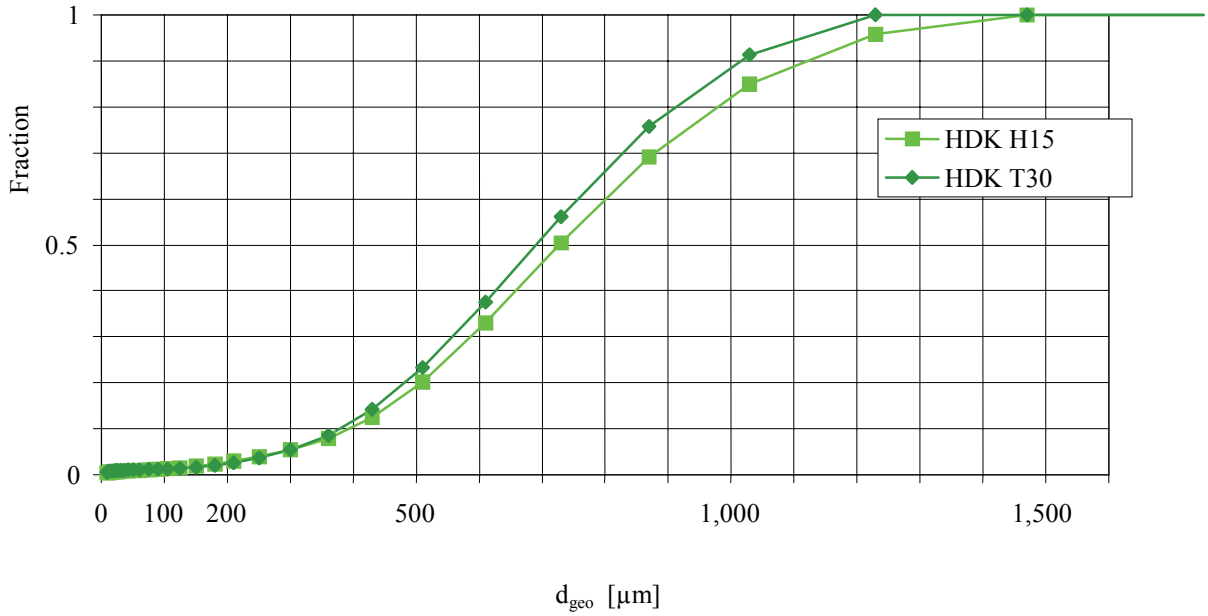
Type/ Product name	**Fraction (% by mass)**		
Mesh size (µm):	**125**	**90**	**63**
Pyrogenic, hydrophilic			
HDK T30 [a]	0.35	0	0
Pyrogenic, treated			
Cab-O-Sil TS610	0.51	0	0
HDK H15	0.83	0	0

[a] Pre-dried

Laser diffraction is based on the Fraunhofer theory that describes the case when spherical particles of equal size are exposed to parallel monochromatic (laser) light; the particles are large compared to the wavelength. The light diffracted by the particles is also parallel and can be focused by a lens, and plotted for individual particles against the measured radius (i.e. d_{geo}) in the plane of observation. Position and motion of the individual particles have no effect. Thus, the measurement can be carried out in free-flowing aerosol or suspension.

The particle size distribution (fraction by volume) of two different pyrogenic SASs, HDK H15 and HDK T30 (Appendix B), were measured using a commercial laser diffraction analyser with an open measuring zone, equipped with a fall-shaft gravity disperser (settling height 51 cm) to ensure a constant mass-flow of the product into the laser measurement zone, while preserving the original particles sizes of the SAS product (unlike common methods, see below). The resulting geometric particle size (d_{geo}) distributions were highly reproducible (Figure 12) (Stintz and Heinemann, 2001).

Figure 12: Geometric particle size distribution



Furthermore, it is possible to convert the measured geometric diameter into aerodynamic diameter by means of the known conversion factor for the reference substance. For HDK H15 and T30 with an effective particle (agglomerate) density of 0.075 g/cm³, the conversion factor is 3.6 (Stintz *et al*, 1998 above). Table 12 provides the aerodynamic diameter calculated for these SASs.

Table 12: Calculated aerodynamic diameter

Type/ Product name	**d_{geo} (µm)**		**d_{aero} (µm)**
	Mean	**Standard deviation**	**Mean**
Pyrogenic, hydrophilic			
HDK T30 [a]	680	12.7	189
Pyrogenic, hydrophobic			
HDK H15 [b]	739	10.6	205

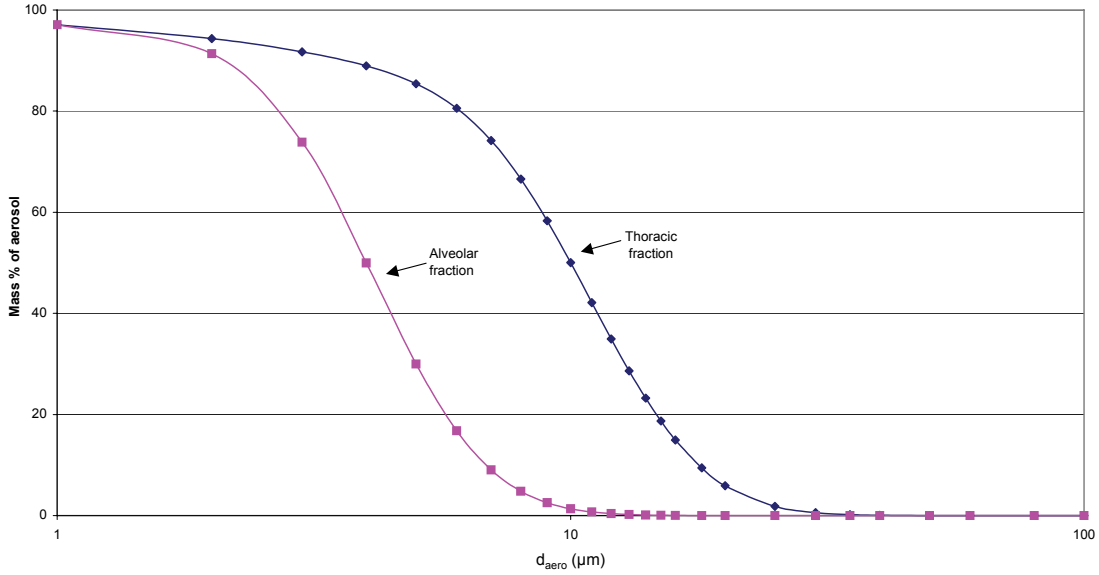
[a] Specific surface area (BET) 300 m²/g, untreated

[b] Specific surface area (BET) 150 m²/g, surface treated with dimethyldichlorosilane

Fraction of respirable particles

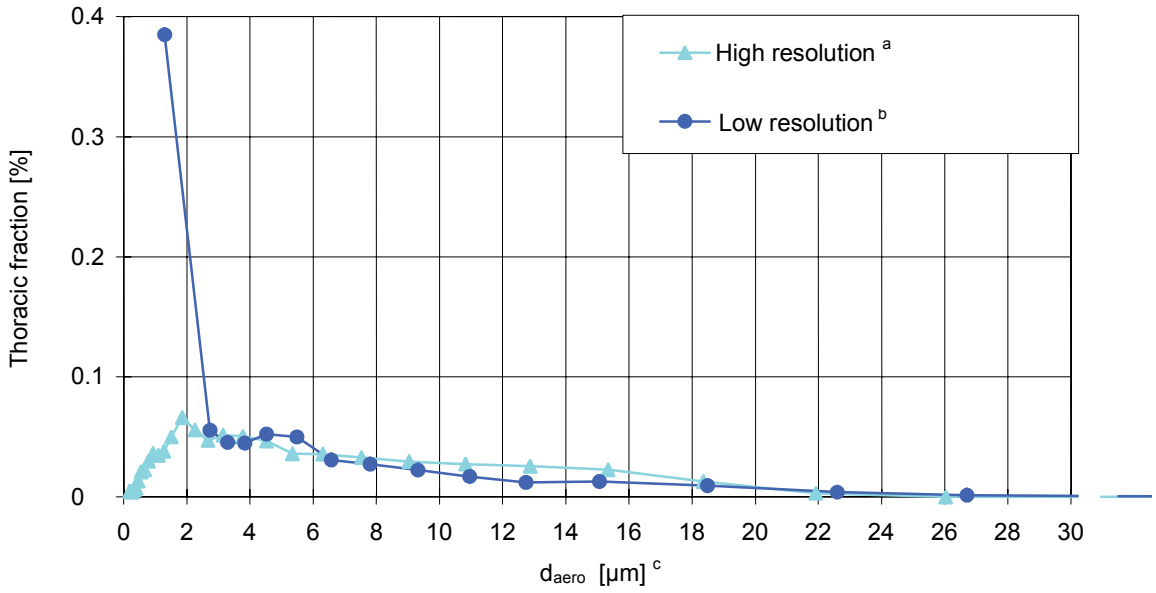
Human health hazard assessment is concerned with the respirable (alveolar) fraction of an airborne aerosol (dust or droplets). For humans, both the thoracic and alveolar mass fractions are respirable as defined by the European standard EN 481 (CEN, 1993), where numerical approximations for derived cumulative log-normal distributions of thoracic and respirable fractions can be found (Appendix B of EN 481) (Figure 13). The graph shows the probability (mass %) that particles of a certain aerodynamic diameter can penetrate the tracheobroncheolar system and alveoli (thoracic fraction, mass median aerodynamic diameter [MMAD] 10 µm) or alveoli only (alveolar fraction, MMAD 4 µm; 99% $d_{aero} < 10$ µm). These definitions are linked to a suitable measurement technique such as laser diffraction (CEN, 1993; DFG, 2004).

Figure 13: Respirable (thoracic and alveolar) fractions according to EN 481



Based on the definitions given in EN 481, the content of the thoracic fraction in a commercial SASs has been measured by laser diffraction using a free fall-shaft gravity dispersion, and the aerodynamic diameter calculated (above). For HDK H15, for example, the thoracic fraction was < 1 % by weight (Figure 14).

Figure 14: Thoracic fraction of HDK H15 measured by laser diffraction



[a] d_{geo} 0.5 - 180 µm at focal length of 100 mm
[b] d_{geo} 0.5 - 1,600 µm at focal length of 1,000 mm
[c] Conversion factor d_{geo}/d_{aero} 3.6

In conclusion, for commercial SAS products, under conditions of technical handling and use, the thoracic fraction is extremely low (Stintz and Heinemann, 2001).

Stability of SAS agglomerates

Under conditions of normal technical handling and use, agglomerates are the relevant particles, both for pyrogenic and precipitated SAS. This stability is due to the large surface area and the chemical interaction of the surface silanol groups (Section 2.3.2 *Surface energy*), rendering the inter-particle network quite stable (Stintz and Heinemann, 2001, 2004; Stintz *et al*, 2002).

2.5.9 Porosity

The adsorption of gases, e.g. nitrogen adsorption-desorption at 77.4 K (–196°C), can be used for simultaneous determination of specific surface area (Section 2.5.2) and porosity, i.e. pore size distribution of SAS. The Union of Pure and Applied Chemistry (IUPAC) distinguishes micropores (diameter d < 2 nm), mesopores (d = 2 - 50 nm) and macropores (d > 50 nm) (Sing *et al*, 1985).

Gas sorption is generally applicable to pore sizes in the mesopore range. However, microporosity can be inferred through mathematical analysis such as time-plots (Storck *et al*, 1998). Gas adsorption starts with the filling of micropores. With increasing pressure mesopores will be filled. Gas sorption is less suitable to determine macropores. For a detailed review, see also IUPAC (Sing *et al,* 1985).

Mercury (liquid) porosimetry can provide information about the distribution of meso- and macro-pores from 3 nm to 400 μm. Mercury porosimetry starts with the filling of macropores; with increasing pressure mercury enters the smaller pores and at high pressure (4,000 bar; 0.4 MPa) pores of 3 nm in size will be filled. For SAS, during the desired pore filling, sample compression may cause the particle structure to collapse, particularly in the case of low-density samples such as pyrogenic SASs (Smith *et al*, 1990).

Furthermore, scattering methods, (X-rays, neutrons and visible light) have been used to characterise porous solids such as SAS. Scattering efficiency is greatest when the wavelength of the radiation used is comparable to the dimension of the (expected) pore size. Other methods like gas/solid NMR, electron microscopy, and atomic force microscopy have been used to characterise the pore network of SAS. Detailed reviews are given by Gregg and Sing (1982) and Legrand (1998).

SAS gels possess pores of all three sizes with the majority of the pores fall into the mesopore range. For precipitated SAS, the majority are meso- to macropores. Standard pyrogenic SAS is non-porous as regards its primary particles, but the interstitial (void) volume between the particles falls into the macropore range.

2.5.10 Structure

Practical applications for SAS as adsorbents, thickening agents, and reinforcing fillers in filled rubbers, are directly related to the free surface of the particle-particle network. Absorptometry with dibutyl phthalate (DBP) is used as indication of the primary structure of SAS. The test measures the quantity of added DBP oil required to change the consistency of the SAS from free-flowing powder to coherent paste. The result is expressed as millilitre of DBP per 100 gram of SAS. Because of health concerns related to DBP (absorption through the skin), dioctyladipate may be used in the future.

SAS gels, which consist of individual spherical particles, have the lowest DBP absorption. Pyrogenic SASs have the largest external surface and exhibit the highest DBP absorption. Common DBP absorption values for SAS are in the range between 50 and 350 ml/100 g.

An earlier, comparable DBP method, ASTM-D2414 (ISO-4656/1DBPA), is used as the primary structure indicator for different carbon black grades (ISO, 1992).

2.5.11 Standard test methods for analysis of SAS

A list of standard test methods used to characterise SAS is shown in Table 13.

Table 13: Standard test methods used to characterise SAS

Property	Test method
Purity, SiO_2 content	DIN [a] 66131, ISO [b] 5794, ASTM [c] C575 and D297
Specific surface area	DIN 66131, ASTM D1993 and D5604, ISO 5794
Colour	ISO 787 Part I and II, ISO 5794 Part I
Drying loss	ISO 787/2, ASTM D 280
pH	ISO 787/9, ASTM D1512
Tapped (bulk) density	ISO 787/10 and 11, ASTM D604
Ignition loss	DIN 55921, ISO 3262/11, ASTM D 1208
Particle size	
Dry sieving	DIN 66165, ISO 3310/18, ASTM C721, D1366
Sieve residue	DIN ISO 787/18, ASTM C117 and D185
Laser diffraction	EN [d] 481, ISO 9276-2
Porosity	
Gas sorption	ASTM D4222 and D4642
Mercury sorption	ASTM D4284, ASTM D4404
Density	DIN ISO 787/10
Absorption of oil	DIN 53601, ISO 4656/1, ASTM D 6854

[a] Deutsches Institut für Normung, Berlin, Germany
[b] International Organization for Standardization, Geneva, Switzerland
[c] American Society for Testing and Materials, West Conshohocken, Pennsylvania, USA
[d] European Committee for Standardization

2.6 Analysis of SAS in products and media

2.6.1 In products

Typical methods for the determination of silica in products are ICP-AES (Si-content), spectrophotometric analysis with ammoniummolybdate and gravimetric determination as silica (Section 2.5.1).

2.6.2 In air and liquids

Table 10 (Section 2.5.7) gives an overview of current methods for the determination of SAS particle sizes in air and liquids. The resulting distribution curves give information about the SAS particle concentration.

In ambient air and at the workplace

The cascade impactor has been often used to measure the particle size distribution of particles, (including SAS) in ambient and workplace air, and in atmospheres generated for animal inhalation testing. Due to the high macroporosity, i.e. high interstitial (void) volume, of especially pyrogenic and precipitated SAS, the deposited mass on the different stages of a cascade impactor is small and weighing of each stage is critical. Furthermore, it has been shown that already deposited particles are re-dispersed and moved to smaller stages because they are destroyed when passing the small orifices above the single deposition stages. Thus, the SAS particle size distribution (and concentration) data may be flawed (Stintz and Heinemann, 2001). In a concentrated aerosol of pyrogenic or precipitated SAS the agglomeration tendency is quite high. To properly link particle size data from the measurement unit to the exposure location, the distance between exposure (exposure chamber for animal inhalation testing) and measurement unit has be taken into account.

Inhalable airborne dust (particulate matter) is commonly classified, according to ISO 7708, into particles with a MMAD of up to 10 µm (PM_{10}) and those with a MMAD of up to 2.5 µm ($PM_{2.5}$), as measured by a cascade impactor. The $PM_{2.5}$ fraction can penetrate the alveoli of the lungs (fine dust). The PM_{10} fraction can be inhaled into the bronchioles while bigger particles will not penetrate beyond the upper respiratory tract. Total dust is determined as the sum of all fractions, respirable, inhalable and non-inhalable fraction (ISO, 1994). Following Section 2.5.8, the thoracic and alveolar fractions as defined by EN 481 would correspond to PM_{10} and $PM_{2.5}$ (DFG, 2004).

Measurement methods to determine worker exposure to airborne amorphous silica (in crystalline matrices) are described by NIOSH (2003). General procedures for the analysis of dust are given by BIA (1989). These methods can also be used for SAS dust measurement.

2.6.3 Analysis of silica in water

The classical analytical method for the determination of silica and silicates in water is the gravimetric determination as silica. The method is suitable for the determination of silica in water with more than 10 mg SiO_2/l (Greenberg *et al*, 1992).

A more common method for the determination of silica or silicates in water is the spectrophotometric analysis with ammoniummolybdate. The water sample is decomposed with hydrofluoric acid/perchloric acid, thereby depolymerising the entire silicic acid and converting it into a form capable of reaction with ammoniummolybdate (Fresenius *et al*, 1988). The extinction absorption of the silicomolybdic acid is measured at 400 nm.

The method does not distinguish between silicic acid (monomers and oligomers) and colloidal silica (polymer). If it is necessary to make this distinction, an effective separation technique is necessary. The ammoniummolybdate method is suitable between 0.5 and 250 mg of SiO_2/l in natural waters.

A modified molybdic acid method has been used to determine the amount of dissolved monosilicic acid under static conditions, i.e. in the presence of undissolved solid. Malachite green has been used to enhance sensitivity. Malachite green reacts with silicomolybdate to form a coloured ion association complex. The dissolved complex can be determined quantitatively by photometry at a wavelength of 595 nm. Thus, H_4SiO_4 concentrations down to $< 10^{-7}$ mol/l (9.6 µg/l) can be determined (Motomizu *et al*, 1989).

Basics could be taken from the handbook of the American Public Health Association (Greenberg *et al*, 1992).

2.6.4 Analysis of silica in biological media

In biological media, the silica content is usually determined as silicon (Si) using ICP-AES. An improved version of ICP-AES in terms of sensitivity was developed to determine the silica concentration in lungs of rats after a subchronic inhalation exposure to pyrogenic SAS. Sample preparation involved digestion of the tissue (e.g. lung) with a mixture of nitric acid (HNO_3, 65% solution) (5 ml), hydrofluoric acid (HF, 30%) (1 ml) and hydrogen peroxide (H_2O_2, 30%) (2 ml), in a polyethylene flask placed in a microwave oven. After decomposition of the sample, the flask was cooled to room temperature, 13 ml of boric acid (H_3BO_3, 4%) was added to neutralise HF and the mixture diluted with milli-Q water to 50 ml. For the determination of Si, 1 ml samples were further diluted (10 ×) with borax (Na_2BO_4) buffer to pH 6 to 8 and nebulised into the ICP-AES. Calibration was carried out with Perkin-Elmer silicon standards with the addition of the corresponding acid mixture and borax. The measurement was carried out with an ICP-AES (ARL 3410 with mini-torch) at 251.611 nm measurement wavelength and 288.159 nm reference wavelength. The mass silicon in the sample was calculated according to the following equation:

$$M_{Si} = C_m \times V_m \times 50 / V_d \quad \text{(Eq. 9)}$$

M_{Si} = mass of silicon in the lung tissue

C_m = measured concentration (µg/g)

V_m = volume of the measured sample (= 10 ml)

50 = weight of the diluted decomposition (g)

V_d = volume of the decomposition taken for the measurement (ml)

The detection limit for silicon was given as 25 µg for a mean lung weight of 1.5 g (Wacker, 1998a).

2.6.5 Summary

A summary of the above and other relevant methods to determine silica in environmental and biological media is given in Table 14. These methods can be applied for SAS as well.

Table 14: Methods for analysis of silica in environmental and biological media

Method	Remark	Reference
Gravimetry		
Gravimetric analysis as silica	Suitable for determination of silica in water with > 10 mg SiO_2/l	Greenberg *et al*, 1992
Spectrometry		
Spectrophotometric analysis with ammoniummolybdate	Does not distinguish between silicic acid (monomers and oligomers) and colloidal silica (polymer). Difficult in aqueous plant or soil extracts due to complex formation and inherent colour of extracts	Fresenius *et al*, 1988
Combination of flow injection analysis and spectrophotometry of silicomolybdic acid in presence of phosphate		Más *et al*, 1991
Silicate determination as blue silicomolybdic complex after reduction with ascorbic acid at 810 nm wavelength	DIN 38 405, part 21. The German standard method for the determination of dissolved silicate	DEV, 1991
Electrochemistry		
Electrochemistry of silicomolybdic acid in aqueous solution		Grasshoff and Hanh, 1959
Extraction in combination with voltametric determination of silicon as silicomolybdic acid	Detection limit (3 s) 4×10^{-8} mol/l (1.12 g Si/l)	Möller *et al*, 1993

Table 14: Methods for analysis of silica in environmental and biological media (cont'd)

Method	Remark	Reference
Polarographic determination of silicon in aqueous media using the catalytic-kinetic reduction of H_2O_2 in presence of Mo(VI) produced by the decomposition of silicomolybdic acid in combination with extraction by a mixture of diethyl-ether/*n*-pentanol.	Detection limit 3.2 µg/l	Barrado *et al,* 1985
Chromatography		
Chromatography in combination with spectrophotometry with sodium molybdate	Provides high selectivity versus phosphates; sulphonated cation exchange stationary phases are used. Detection limit < 20 mg/l silicate standard	Weiß, 1991
ICP-AES		
In lungs and tracheobronchial lymph nodes	Detection limit 25 µg Si/1.5 g lung	Wacker, 1998a
In food and coral soil		Krushevska and Barnes, 1994

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

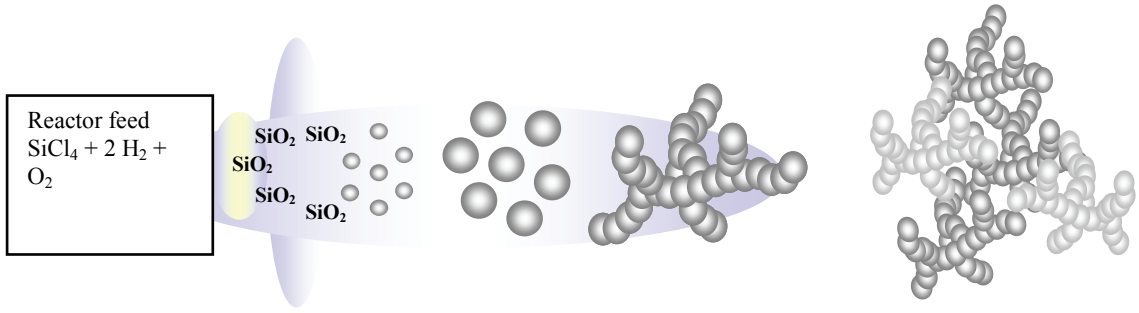
Two principally different process technologies are used for the manufacture of SAS, namely the thermal route which leads to the formation of pyrogenic SAS and the wet route yielding precipitated SAS, SAS gel or sol. The commercial processes are described below (Section 3.1.1 and 3.1.2). Information on production volumes is given in Section 3.1.3.

Furthermore, SASs, which are generally hydrophilic, may be rendered hydrophobic by surface treatment on an industrial scale, either by physical or chemical treatment. Methods for chemical modification of the silica particle surface, i.e. silylation, are many and various. The most common treating agents are organosilicon compounds like dimethyldichlorosilane, hexamethyldisilazane and polydimethylsiloxane fluids (*Surface energy* in Section 2.3.2).

3.1.1 Thermal route

The manufacturing process for pyrogenic SAS is based on the hydrolysis of volatile silanes, especially silicon tetrachloride ($SiCl_4$), in the flame of an oxygen-hydrogen burner. $SiCl_4$ is continuously vaporised, mixed with dry air and then with hydrogen, fed to the reactor and hydrolysed. Hydrolysis is followed by the growth (nucleation, condensation, coagulation) and aggregation of pyrogenic SAS particles (Figure 15).

Figure 15: Pyrogenic SAS particle formation



The basic chemical reactions are:

$$2\ H_2 + O_2 \rightarrow 2\ H_2O \quad \text{(Eq. 10)}$$

$$SiCl_4 + 2\ H_2O \rightarrow SiO_2 + 4\ HCl \quad \text{(Eq. 11)}$$

It is also possible to use methyltrichlorosilane (CH_3SiCl_3) alone or mixed with $SiCl_4$ as raw material. In this case the following overall reaction is:

$$CH_3SiCl_3 + 2\ O_2 \rightarrow SiO_2 + 3\ HCl + CO_2 \quad \text{(Eq. 12)}$$

The equation does not fully describe the complex reaction: first, hydrolysis of Cl via *in situ* water and second, oxidation of the methyl group.

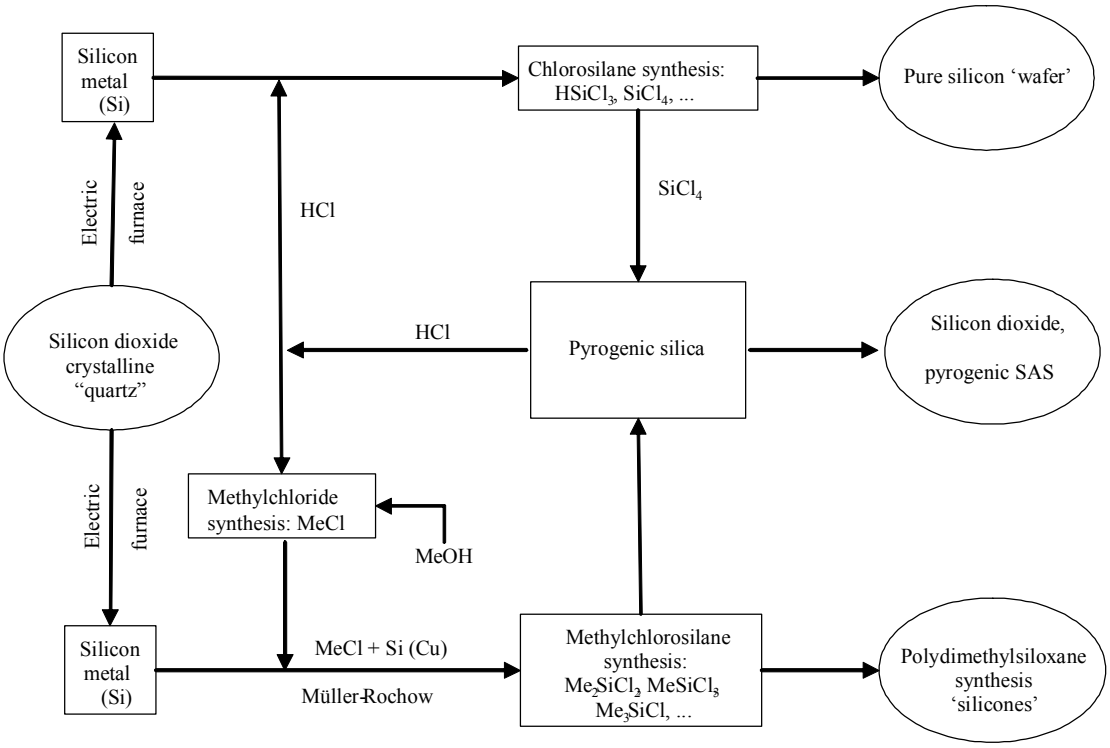
The gases leaving the reactor are cooled down with all of the silica in the form of an aerosol. The silica is separated from the off-gas which contains hydrochloric acid. Any hydrogen chloride (HCl) remaining adsorbed on the surface of the pyrogenic silica is removed in a later step. The finished silica is then transported pneumatically to storage silos and subsequently placed into bags or transported to the consumers by silo cars.

The hydrogen chloride is in the off-gas is washed out by absorption in water to give hydrochloric acid in commercial concentrations, which can be re-utilised, for example, by reacting it with silicon metal to produce $SiCl_4$ and hydrogen. Chlorine is a by-product of the hydrogen chloride. The hydrogen chloride may also be neutralised with caustic soda to form sodium hypochlorite solution, which is converted to sodium chloride solution used in wastewater treatment.

The physico-chemical properties of the pyrogenic silica can be controlled by varying the process parameters such as feedstock, flame composition and flame temperature.

The production of pyrogenic SAS typically forms an integrated part of a factory which also manufactures silicon wafers and silicones. These processes all start using quartz as raw material (Figure 16).

Figure 16: Process flow diagram for the synthesis of pyrogenic SAS



Me, methyl- (CH_3–)

3.1.2 Wet route - Production of precipitated SAS

The production process for precipitated SAS can be divided into the following operations: raw material storage, synthesis, solid-liquid-filtration, drying, packing, storage and shipment. Optionally, after the drying step, the product may be milled or granulated, and its surface treated to promote hydrophobicity. The whole process may be operated in a continuous or batch manner.

Raw materials

Raw materials for the production of precipitated silica and silica gels include an alkali metal silicate dissolved in water (e.g. water glass) and an acid, generally sulphuric acid. Precipitation with hydrochloric acid, organohalosilanes and carbon dioxide, or a combination of the latter with mineral acids, are of minor economic importance.

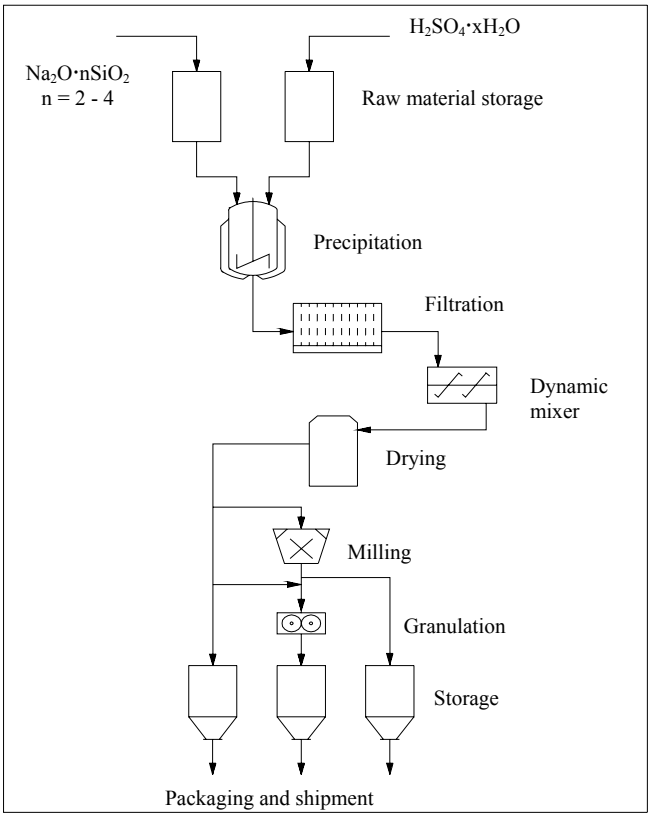
Water glass is an aqueous solution of sodium silicate ($Na_2O{\cdot}nSiO_2$; n = 2 - 4) (CAS No. 1344-9-8) that is produced in two steps. First, water glass cullets are produced by melting

sand and soda ash in a glass furnace at approximately 1,300°C. The cullets are then transferred to an autoclave and dissolved in water, producing water glass.

Water glass is normally stored in closed carbon steel or glass fibre-reinforced plastic tanks of up to 1,000 m³. Aluminium, zinc, zinc-coated steel or glass are not suitable because they are corroded by water glass. To prevent freezing during winter, tanks are preferably installed inside the production units.

A schematic overview of the precipitated production process is shown in Figure 17.

Figure 17: Production of precipitated SAS



Following the reaction of water glass with sulphuric acid in neutral or alkaline conditions, SAS precipitates according to:

$$Na_2O \cdot nSiO_2 + H_2SO_4 \rightarrow n\ SiO_2 + Na_2SO_4 + H_2O \quad (n = 2 - 4) \text{ ..... (Eq. 13)}$$

The properties of the freshly precipitated SAS are influenced by the design of the reactor and the process parameters. Depending on the intended application of the SAS, individual parameters such as temperature (40 - 95°C), pH (4.5 - 12.5), flow, residence time (up to several hours), mixing energy and reactor geometry have to be selected. By regulating these parameters, a wide range of SAS products with different characteristics can be produced. The solids content of this step is typically between 50 and 200 g/l.

Filtration, drying and milling

The SAS suspension received from precipitation is then filtered, usually by means of a (membrane) filter press or belt- and drum-filter. Unlike filter presses which operate in a batch cycle, drum- and belt-filters work in a continuous way. The equipment is selected depending on the properties and structure of the desired SAS product. The solid content of the filter cake typically varies from 15 to 25% by weight.

After filtration, the SAS is washed (normally in the filtration equipment) to remove salts. The level of salt retained in the SAS depends on the intended final application.

Drying is needed since the solid content of the filtered SAS is in the range of only 15 to 25% by weight. Approximately 400 to 600 kg of water has to be evaporated for each 100 kg of final product. Drying represents a considerable fraction of the total production costs. Drying is performed, again depending on the characteristics required for the final SAS product, by means of belt dryers, turbine dryers, recycle dryers, rotary drum dryers and spray dryers. Drying yields a homogenous SAS powder with excellent absorption and free-flow properties.

Finally, after conventional drying the non-regular granulate is milled in jet mills or mechanical mills. This step requires air or steam and is energy intensive. During this process, the particle size distribution and sieve residue characteristics of the product are modified. Furthermore, for certain SAS applications where a dust free product is required, the spray-dried or milled product is granulated, normally in a drum granulator.

3.1.3 Wet route - Production of SAS gel

Like precipitated SASs, SAS gels are produced by neutralisation of an aqueous solution of an alkali metal silicate (e.g. water glass) with (sulphuric) acid. The commercial process comprises raw material dilution (optional), synthesis (sol formation-gelation), washing-ageing and drying, followed by sieving, milling, and possibly surface modification, depending on the final product

specification. Final packaging, storage and shipment are similar to the procedures for precipitated silica.

Hydrosol formation

First, a SAS hydrosol is formed by controlled mixing of water glass and diluted sulphuric acid. The pH and silica content of this hydrosol are determined by the concentration of the raw materials and their mixing ratio. The hydrosol phase extends from the point of mixing the raw materials to the onset of solidification, which is characterised by a sudden increase in viscosity, average molecular weight and modulus of elasticity. Initial sol formation yields an unstable intermediate (monomeric orthosilicic acid) which undergoes rapid, acid-catalysed oligomerisation. In the hydrogel state, larger agglomerates are generated which are cross-linked to form an open, branched-chain structure. The choice of gelation conditions defines the particle size and form of the SAS hydrogel. Normally, in industrial processes, lumps or spherical beads are formed.

Washing-aging

Subsequently, excess salts are washed out to purify the SAS gel. This causes structural changes within the gel's framework. By an appropriate choice of washing conditions such as pH, temperature and time, different specific surface areas are obtained. Washing is performed in a fixed bed or as a slurry, operated continuously or batch-wise. The SAS hydrogel now has a continuous structure, giving it a three-dimensional network of pores filled with water. The total volume of pores per mass-unit (pore volume) is a specific characteristic of the SAS gel type.

Drying and milling

While for few applications SAS hydrogels are used as such, in most instances the gel must be dried. During (slow) drying, as water evaporates from the SAS hydrogel, the structure collapses gradually (and the gel volume diminishes) due to the surface tension of water. Eventually, a point is reached where even though water is still evaporating the gel structure no longer shrinks. At this point the gel is called a xerogel. Fast drying can minimise shrinkage; removal of water by solvent exchange followed by drying has the same effect. SAS gels that are dried with negligible loss of pore volume are known as aerogels.

Commercial SAS hydrogels typically exhibit a water content of between 50 and 70%. As the removal of water from pores will be diffusion controlled (hence requiring longer drying times and/or higher temperatures), there is a need for a highly efficient, but energy consuming, drying

method. The choice of drying equipment will influence the pore volume of the xerogel and, therefore, various drying techniques are applied, e.g. tray dryers, belt dryers, recycle dryers, fixed bed dryers and flash dryers. Following drying, SAS xerogels are sieved (this may be sufficient if coarse material is required, e.g. in adsorption) or further milled for other applications. Depending on the required particle size and particle size distribution, the gels are milled using jet mills or mechanical mills.

3.1.4 Wet route - Production of SAS sol

SAS sols (colloidal SASs) are stable dispersions of SAS particles in a liquid, usually water. Commercial SAS sols contain sub-micron silica particles; the silica content is 15 to 50% by weight. The final products range from faintly opalescent liquids (small particles) to milky white dispersions (larger particles), and flow like water. SAS sols remain stable for many months or even years.

SAS sols are produced directly by hydrolysis of monomeric $SiCl_4$, in aqueous solution followed by condensation of the initial SAS particles into a sol. Hydrolysis of tetraethoxysilane in an alkaline solution of water and alcohol leads to monodisperse SAS sols of exceptionally large particle sizes. Alternatively, a dilute solution of water glass can be passed through a hydrogen exchange resin, where sodium is removed and polymerisation of monomeric SAS takes place. The particle size is controlled by avoiding excessive addition rates of the reactants.

An indirect way of manufacturing SAS sols is by re-dispersion of existing silicas. In this case, SAS gels, precipitated SAS or, less commonly, pyrogenic SAS are re-dispersed by applying large shearing forces to these previously produced SASs.

The most important point in either sol manufacturing process is stabilisation of the dispersed SAS sol particles. This is achieved by the addition of KOH, NaOH, NH_3 or HCl in amounts up to 10% by weight. An alternative method for stabilisation is based on electrostatic repulsion of the particles. By adding small amounts of other metal oxides like aluminium oxide the net charge of the particles in the solution is increased leading to higher repulsive forces between the sol particles.

Finally, the SAS sol is filtered and concentrated to the desired level.

Furthermore, SAS sols can also be spray dried.

3.2 Amount (tonnage)

Published data on the worldwide production of SAS are given in Table 15.

Table 15: Worldwide annual production in 1992
(Kleinschmit and Thompson, 1995; Kirk-Othmer, 1997; Chemical Economics Handbook, 1998)

Type of SAS	Amount (kt)	Remark
Pyrogenic	100	Increasing
Precipitated	800	Constant
Gel	90	Increasing
Sol	24	Increasing

More recent figures have been published for the western European production (Table 16).

Table 16: Western European annual production in 2000 (CEFIC/ASASP, 2000)

Type of SAS	Amount (kt)
Pyrogenic	72
Precipitated	285.5
Gel	34.6

Published data on the quantities of SAS sold in western Europe are given in Table 17.

Table 17: Annual sales[a] in western Europe (CEFIC/ASASP, 2000)

Type of SAS	Amount (kt/y)		
Year:	1997	1998	2000
Pyrogenic	37.806	38.2	50.2
Precipitated	210.9	236.3	286.45
Gel	31.9	30.35	31.3
Total	280.609	304.85	367.95

[a] Including imports

3.3 Storage

SASs are stored under dry conditions in sealed bags or silos, including SAS gels. SAS sols generally undergo precipitation at low temperatures (freezing). Therefore heated tanks or buildings are required for storage.

3.4 Transport

SAS is not a hazardous material for transportation. SASs are commonly transported by road, rail and sea and may be shipped in bags, big bags, bulk containers and silo road tankers. The standard shipping unit is 'bags onto pallets'. To limit water up-take, the pallets are shrink-wrapped in polyethylene foil. Airfreight shipping is also used. For SAS sols, heated silo trucks or rail cars are used.

3.5 Use

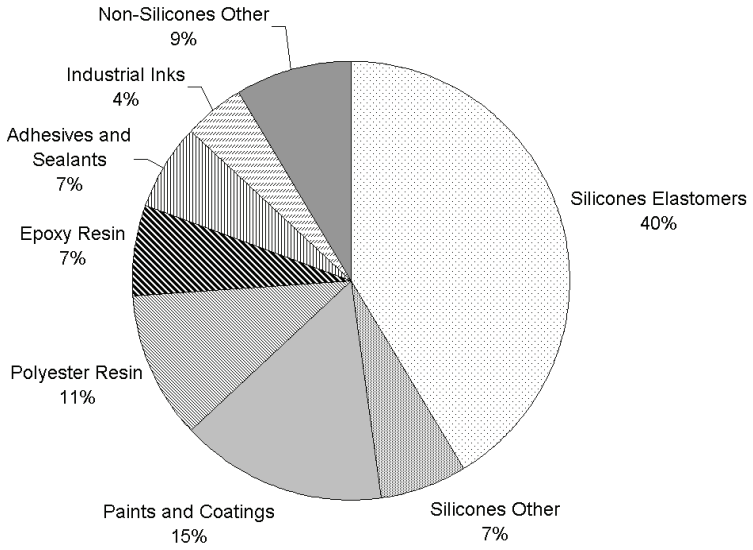
SASs have been commercialised since the 1950s and they are currently used in a wide variety of industrial applications. This summary covers the most important applications. SASs are usually tailor-made to meet the requirements of various users.

The main use of SAS is as reinforcement and thickening agent in various systems. Thus, SASs are incorporated into elastomers, resins, inks and water, for example. SAS exhibits a high absorption capacity due to their high porosity, therefore SASs are used as adsorbing agents. In coating for ink-jet paper, SAS absorbs large volumes of water from ink drops which lead to fast drying times. SASs are also used in dry powder systems to enhance the flow properties, e.g. in powder coating and toner, where they do not occur isolated, but bound to the surface of the corresponding powder particles.

SAS is also used in consumer products including cosmetics, pharmaceuticals and foods. Various SASs meet the requirements of international pharmacopoeias such as Duetsches Artzneibuch (DAB 10), US Pharmacopoeia (USP XXII) and the European Pharmacopoeia. Furthermore, SASs provide pastes and ointments with the desired consistency and inhibit separation of the components. In powdery products like cosmetic powder, salt and food powder, SASs provide the required flow properties as a flow aid. Finally, SAS is also used in beer and wine clarification.

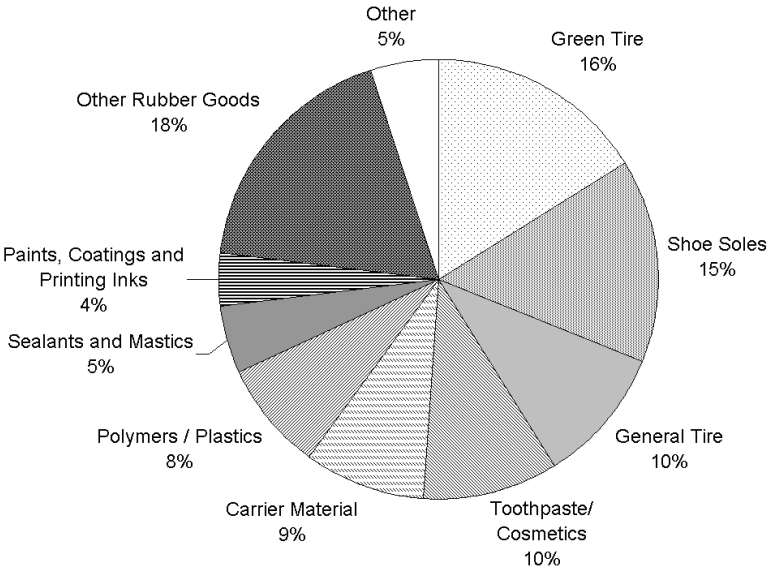
The following figures depict the (western European) use patterns of the most important applications for the various types of SAS: pyrogenic, precipitated, gel and sol in 1996 (Figures 18 to 21). These published figures are somewhat dated and may differ from current consumption, for which only total amounts were available.

Figure 18: Western European consumption of pyrogenic SAS in 1996: 46 kt
(Chemical Economics Handbook, 1998) (SRI Consulting, Zürich, Switzerland)



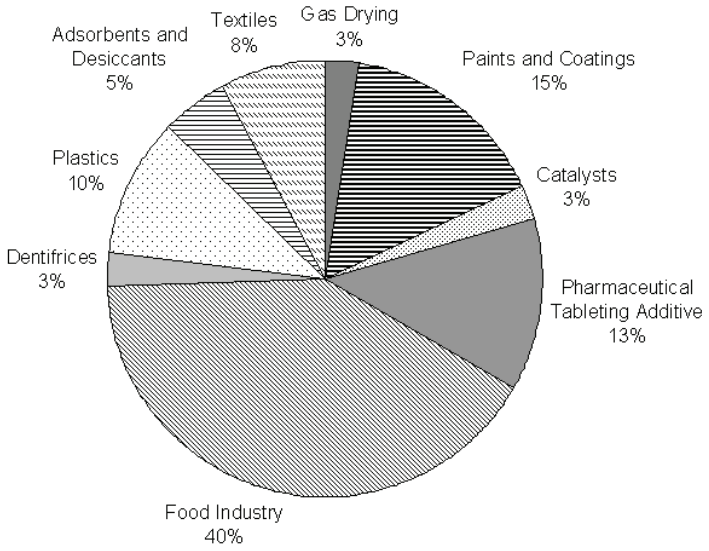
The total pyrogenic SAS consumption in 2000 was 48.5 kt (Chemical Economics Handbook, 2002).

Figure 19: Western European consumption of precipitated SAS in 1996: 231 kt
(Chemical Economics Handbook, 1998) (SRI Consulting, Zürich, Switzerland)



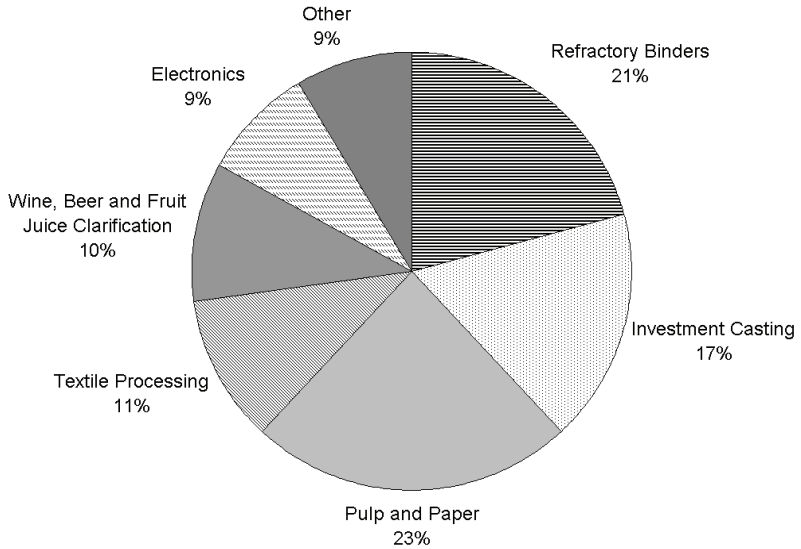
The total precipitated SAS consumption in 2000 was 260 kt (Chemical Economics Handbook, 2002).

Figure 20: Western European consumption of SAS gel in 1996: 20 kt
(Chemical Economics Handbook, 1998) (SRI Consulting, Zürich, Switzerland)



The total SAS gel consumption in 2000 was 20.9 kt (Chemical Economics Handbook, 2002).

Figure 21: Western European consumption of colloidal SAS in 1996: 13 kt
(Chemical Economics Handbook, 1998) (SRI Consulting, Zürich, Switzerland)



The total SAS sol consumption in 2000 was 13.8 kt (Chemical Economics Handbook, 2002).

The typical SAS content of consumer and pharmaceutical products is given in Table 18.

Table 18: SAS in consumer and pharmaceutical products

Product	SAS (% by weight)
Paper	0.1 - 50 [a]
Food	0.1 - 2
Toners	0.2 - 2
Cosmetics	0.2 - 2
Pharmaceuticals	0.2 - 1.5

[a] The higher figure relates to ink jet papers

The typical SAS content of technical products is given in Table 19.

Table 19: SAS in technical products

Product	SAS (% by weight)
Silicon elastomers	5 - 40
Polyurethane elastomers	0.5 - 5
Adhesives	0.5 - 5
Resins	0.5 - 7
Paints	0.5 - 3
Sealants	5 - 10

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Emissions

4.1.1 Natural sources

Silicon (Si) is the second most abundant chemical element after oxygen: it makes up 28.1% of the earth's crust. Silicon is present as metal complex in the form of silicate minerals. It is also found as the oxide (silica, SiO_2) in crystalline silica in rocks, sands and soils, and as biogenic amorphous silica in diatomite and silica fibres or non-biogenic silica in vitreous silica (IARC, 1997).

Kieselguhr (diatomite) (Section 2.1.2, Figure 1) is mined from sedimentary rocks that are mainly composed of skeletons of diatoms, a particular phylum of algae that extract silica dissolved in water to constitute their skeletons. After the death of these organisms, the skeletons will form opaline deposits that characterise the diatomaceous earth. Diatomite contains up to 94% of amorphous silica and, depending on the deposit field, a considerable amount of crystalline silica. Another form of biogenic silica is silica fibre in plants such as rushes, rice and sugar cane (IARC, 1997).

Non-biogenic amorphous silica is vitreous silica such as volcanic glass (obsidian) (IARC, 1997).

4.1.2 Emissions during production and use

Production

The amount of SAS released into the environment during the manufacturing process has been calculated on the basis of western European production (Section 3.1) and the quantity of SAS emitted to the air and water compartments per tonne of SAS produced (CEFIC/ASASP, 2004). The total quantity emitted from direct production of SAS is estimated to be 0.438 kt SiO_2/y to air and 2.1 kt/y to water (Table 20).

Table 20: SAS emitted during production in western Europe in 2000

Product type	Production [a] (kt)	Emission to air		Emission to water	
		Factor [b] (kg/t)	Amount (t)	Factor [b] (kg/t)	Amount (t)
Pyrogenic	72	< 0.3	< 21.6	Negligible	Negligible
Precipitated and gel	320.1	1.3	416.1	6.6	2,113
Total (rounded)			438		2,100

[a] Section 3.1
[b] CEFIC/ASASP, 2004

Use

Emissions of SAS during use were calculated on the basis of western European consumption of each type of SAS, their different uses (Section 3.4) and related percentage of emission deduced from EU technical guidance and risk ranking method (EC, 1996; Hansen *et al*, 1999). This approach is overly conservative because the percentages of emission in the EU method are probably too high. Nevertheless, following this approach, the overall total quantity of SAS released into the aquatic environment is estimated to be approximately 104 kt SiO_2/y (Table 21).

Table 21: SAS emitted to the aquatic compartment during use in western Europe in 1996

Product type/ Use [a]	Use (%) [a]	Main use category [b]	Emission	
			Factor (%) [c]	Total (t/y) [d]
Pyrogenic (46 kt)				
Silicones - elastomers	40	Inclusion into matrix	10	1,840
Polyester resin	11	Inclusion into matrix	10	506
Epoxy resin	7	Inclusion into matrix	10	322
Adhesives and sealants	7	Inclusion into matrix	10	322
Paints and coatings	15	Non dispersive	20	1,380
Industrial inks	4	Non dispersive	20	368
Silicones - other	7	Wide dispersive	100	3,220
Non silicones - other	9	Wide dispersive	100	4,140
Total (rounded)				12,100
Colloidal (13 kt)				
Refractory binders	21	Non dispersive	20	546
Investment casting	17	Non dispersive	20	442
Pulp and paper	23	Non dispersive	20	598

Table 21: SAS emissions to the aquatic compartment during uses (cont'd)

Product type/ Use [a]	Use (%) [a]	Main use category [b]	Emission	
			Factor (%) [c]	Total (t/y) [d]
Electronics	9	Non dispersive	20	234
Wine, beer, fruit juice clarification	10	Wide dispersive	100	1,300
Others	9	Wide dispersive	100	1,170
Total (rounded)				4,600
Gel (20 kt)				
Plastics	10	Inclusion into matrix	10	200
Paints and coatings	15	Non dispersive	20	600
Catalysts	3	Non dispersive	20	120
Textiles	8	Non dispersive	20	320
Gas drying	3	Non dispersive	20	120
Pharmaceutical tableting additive	13	Wide dispersive	100	2,600
Food industry	40	Wide dispersive	100	8,000
Dentifrices	3	Wide dispersive	100	600
Absorbents and desiccants	5	Wide dispersive	100	1,000
Total (rounded)				13,600
Precipitated (231 kt)				
Green tire	16	Inclusion into matrix	10	3,696
Shoe soles	15	Inclusion into matrix	10	3,465
General tire	10	Inclusion into matrix	10	2,310
Polymers/plastics	8	Inclusion into matrix	10	1,848
Sealants and mastics	5	Inclusion into matrix	10	1,155
Other rubber goods	18	Inclusion into matrix	10	4,158
Paints, coatings, printing inks	4	Non dispersive	20	1,848
Toothpaste/cosmetics	10	Wide dispersive	100	23,100
Carrier material	9	Wide dispersive	100	20,790
Other	5	Wide dispersive	100	11,550
Total (rounded)				73,900
Grand total (rounded)				**104,000**

[a] Amount consumed and use pattern from Section 3.4

[b] Following EC, 1996

[c] Hansen *et al*, 1999

[d] Total release (t) = 1,000 × consumption (kt) × use (%) × emission factor (% released)

In conclusion, combining the emission figures for production and use, the total SAS emission is approximately 106 kt/y for the years 1996 to 2000.

4.2 Environmental distribution

Untreated SASs have a relatively low water solubility of 1.91 to 2.51 mmol/l (114 - 151 mg/l) (Section 2.3.2, Table 4) and an extremely low vapour pressure (e.g. < 10^{-3} Pa at 20° C for Aerosil R972). On the basis of these properties it is expected that SAS released into the environment will be distributed mainly into soil/sediment, slightly into water, and probably not at all into air.

With surface-treated SASs, the addition of organosilicon compounds increases the hydrophobicity. Consequently, the water solubility is lower than that of untreated silica. The vapour pressure remains extremely low. Due to the presence of organic substances such as surfactants, salts, acids and alkalis in the environment, it is expected that surface-treated silica will be wetted and then adsorbed onto soils or sediments.

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric, aquatic and terrestrial fate

SAS is regarded as an inert substance and is not expected to undergo any transformation in the atmospheric or terrestrial compartment, apart from dissolution by water.

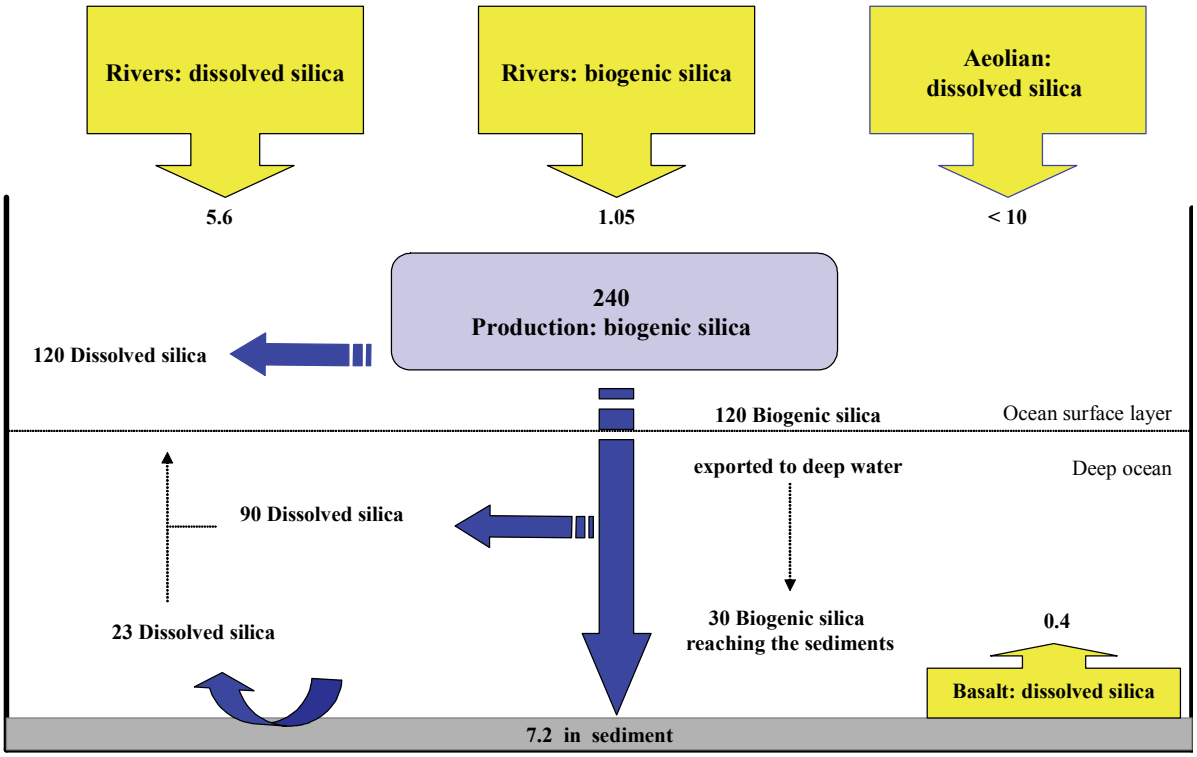
The literature on the fate of silica in the environment concerns dissolved silica in the aquatic environment, irrespective of its origin (man-made or natural), or structure (crystalline or amorphous). Indeed, once released and dissolved into the environment no distinction can be made between the initial forms of silica. At normal environmental pH, dissolved silica exists exclusively as monosilicic acid [$Si(OH)_4$]. At pH 9.4 the solubility of amorphous silica is about 120 mg SiO_2/l (Iler, 1979). Quartz has a solubility of only 6 mg/l, but its rate of dissolution is so slow at ordinary temperature and pressure that the solubility of amorphous silica represents the upper limit of dissolved silica concentration in natural waters (Schleyer and Blumberg, 1982). Moreover, silicic acid is the bioavailable form for aquatic organisms and it plays an important role in the biogeochemical cycle of Si, particularly in the oceans.

In the oceans, the transfer of dissolved silica from the marine hydrosphere to the biosphere initiates the global biological silicon cycle. Marine organisms such as diatoms, silicoflagellates and radiolarians build up their skeletons by taking up silicic acid from seawater. After these organisms die, the biogenic silica accumulated in them partly dissolves. The portion of the biogenic silica that does not dissolve settles and ultimately reaches the sediment. The

transformation of opal (amorphous biogenic silica) deposits in sediments through diagenetic processes allows silica to re-enter the geological cycle. Silica is labile between the water and sediment interface (Tréguer *et al*, 1995).

The oceans receive silicic acid inputs from the lithosphere, via chemical weathering of the continental and oceanic crust, and indirectly through wind transport. Figure 22 summarises the global biogeochemical silicon cycle.

Figure 22: Global biogeochemical silicon cycle [a] (Nelson *et al*, 1995; Tréguer *et al*, 1995)



[a] Amounts in teramoles (Tmol) Si/y

Dissolved silica in rivers results from weathering of sedimentary and crystalline rocks, in particular the weathering of silicate and aluminosilicate minerals by CO_2 charged waters**.** The total flux of dissolved silica, reported in teramoles (Tmol, 1012 mol), through rivers to the oceans is 5.6 ± 0.6 Tmol Si/y (157 Mt Si/y), 74% of the input stems from tropical and 20% from temperate regions. Rivers also transport silica containing suspended matter in much greater quantity than that of dissolved silica. But further dissolution of this particulate material is slow and its contribution to dissolved silica flux from rivers is negligible. In the oceans, the major

geological pathway of transfer of dissolved silica from the lithosphere is weathering of submarine basalt with 0.4 ± 0.3 Tmol Si/y (11 Mt/y) (Tréguer *et al*, 1995).

Aeolian erosion of the land surface, particularly deserts, is the second potentially important pathway for long distance transport of siliceous material to the oceans**.** The flux of particulate lithogenic silica, which reaches the surface layer of the world oceans by wind transport, is in the order of 10 Tmol Si/y. A small fraction, 5 to 10%, is thought to dissolve in seawater. The global input of silicic acid from the atmosphere to the ocean is less than 1 Tmol Si/y (< 28 Mt/y) (Tréguer *et al*, 1995).

The formation of biogenic silica due to diatom growth also occurs in fresh waters. The total flux of biogenic silica carried by rivers has been estimated as 1.05 ± 0.2 Tmol Si/y (29 Mt Si/y). Approximately 16% of the gross riverine load is delivered to the world oceans as biogenic silica. Amorphous silica contained in diatoms dissolves five orders of magnitude faster than silicon contained in mineral silicates and may be considered as bioavailable (Conley, 1997).

The global rate of biogenic silica production in the surface layer of the oceans is estimated to be on average 240 Tmol Si/y (range 200 - 280 Tmol/y) (5,617 - 7,864 Mt/y). Approximately 50% of the biogenic silica produced in the euphotic zone of the oceans dissolves in the upper 100 metres. The fraction of biogenic material that escapes dissolution in the surface layer is exported to the deep ocean; biogenic silica settles down through the water column and reaches the seabed, where dissolution continues. In areas where opal sediments are accumulating, an average of 15 to 25% of the silica produced annually in the surface layer is delivered to the seabed and preserved. In other areas (where 75 to 90% of the global silica biosynthesis occurs) virtually none of the surface produced silica is preserved and all of the biogenic silica is dissolved. The global burial/production ratio of approximately 3%, i.e. 7.2 Tmol Si/y (202 Mt/y), represents the average quantity of silica preserved in sediments, which re-enters in the geological cycle. Regional differences in silica preservation are strongly affected by differences in water depth, surface layer temperature, diatom species composition, frustule morphology, grazer characteristics, aggregate particle formation and perhaps trace element chemistry. These factors interact in a way that apparently favours the preservation of silica produced in diatom blooms over that produced under non-bloom conditions (Nelson *et al*, 1995).

4.3.2 Biodegradation

Biodegradability in sewage treatment plant or in surface water is not applicable to inorganic substances like SAS. Therefore the biodegradation endpoint has limited relevance for SAS.

In surface modified SASs, the most common treating agents are organosilicon compounds and these generally represent less than 5% of the material. Biodegradation in sewage treatment plant or in surface water is not expected. Some biodegradation in soil may occur by analogy with the behaviour of linear polydimethylsiloxane in this compartment (ECETOC, 1994).

4.3.3 Uptake

Silicic acid is the bioavailable form of SAS (and other silicas) that can be absorbed by certain organisms in the environment. Once accumulated into these organisms, silicic acid precipitated as insoluble amorphous silica, plays a structural and defensive role. In animals, silica is a trace nutrient.

In diatoms, dissolved silica is accumulated to constitute their skeletons. The silica levels in diatoms may represent 1% to 50% of the diatom's weight (IARC, 1997).

The Si/C ratio of living diatoms grown in the laboratory in the absence of nutrient limitation has been measured for a wide range of species. The Si/C mole ratio ranged from 0.03 to 0.42, with a mean of 0.13 for temperate and tropical diatom species, and 0.18 for Antarctic diatom species (Nelson, 1995).

Active transport of silicic acid is implicated in the silicification in diatoms, where sodium (Na^+) is probably the coupling ion, at least in marine species. Only 2% of the energy budget of the cell is used in the production of silicified frustules, which comprise some 20% of the cell weight (Raven, 1983).

Active transport followed by precipitation is also suggested for multicellular aquatic plants like phaeophytes, where the measured concentrations ranged between 0.6 and 82 mmol Si/kg fresh weight. Assuming a wet weight to dry weight ratio of 5 to 10, depending on the species, the measured concentrations were in the range of 0.08 to 23 g Si/kg dry weight (Raven, 1983). This is in the same order of magnitude as the values of 3.3 to 21.7 g Si/kg for the aquatic and wetland plants reported by Vymazal (1995 cited by Van Dokkum *et al*, 2001).

Terrestrial plants also accumulate silica. Crop plants can be divided into three major groups with respect to their silica content as a fraction of the dry weight: (i) wetland grasses (e.g. *Oryza sativa*) with high levels of 10% to 15% of the dry weight, (ii) dryland grasses with intermediate levels of 1% to 3% of the dry weight, and (iii) dicotyledons with the lowest level, less than 1% of the dry weight. The silicic acid is precipitated in higher plants in a form close to amorphous silica. Much of this silica is found in the cell wall. Once precipitated, silica in plants seems to be unavailable (Raven, 1983).

The role of (inorganic) silica in the cell wall seems to be as a mechanical, compression-resistant element, analogous to that of (organic) lignin. The inorganic mode is energetically cheaper but metabolically less versatile than the organic mode. The pattern of silica distribution in plants with high silicon levels is mainly peripheral in a position advantageous for mechanical support of the shoot. It is also present in the walls of the conducting elements of the xylem where compression-resistant compounds could help to prevent collapse of the xylem elements due to water loss during transpiration (Raven, 1983).

Silica enhances the fungus resistance of plants that are 'silicon accumulators' like grasses. The induction of insoluble silica in the cell wall of mildew-infected *Leguminosae* has been demonstrated. In the European wine grape (*Vitis vinifera*), powdery mildew resistance in the field has been associated with silicon supply (Blaich and Grundhöfer, 1997).

It has been generally assumed that the presence of silica in animals was attributable to the vast quantities found in the environment. However, a number of experiments have indicated that silicon is a trace element, necessary for normal growth, development and functioning of a large variety of higher animals (Schleyer and Blumberg, 1982).

Finally, silica has been demonstrated to be an essential nutrient in chicken (Carlisle, 1974) and rat (Schwartz, 1974), where it plays a role in the early stages of bone formation. Silica is particularly associated with structural elements of connective tissue, cartilage, skin and bone.

4.3.4 Evaluation

Since the bioavailable form for living organisms of SAS is dissolved silica, the total flux of dissolved silica into rivers can be compared with the man-made input from manufacture and use of SAS.

The global natural flux of dissolved silica into rivers has been estimated to be 5.6 Tmol Si/y, a fraction (20%) originating from temperate regions. Since western Europe represents 6.5% of the temperate regions, the quantity of dissolved silica in European rivers is estimated to be 0.728 Tmol Si/y or 4,374 kt SiO_2/y.

This natural flux of dissolved silica is compared with our estimate of maximal releases of SAS during production and use. Our approach does not take account of any treatment of releases from the different uses of SAS. Possible repartition of silica between dissolved and particulate phases in the aquatic compartment is also not considered. On the basis of this scenario, the estimated maximum of 106 kt of man-made SAS released per year into the aquatic environment represents 2.4% of the dissolved silica naturally present in western European rivers.

Thus, the rate of SAS released into the environment during its life cycle can be considered negligible in comparison with the natural flux of silica in the environment.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 In air

Amorphous silica concentrations of < 0.2 to 135 µg SiO_2/m^3 were reported for the air compartment (Vymazal, 1995 cited by Van Dokkum *et al*, 2001).

On Hawaii, airborne amorphous silica fibres were identified as smoke constituents in ambient air near burning sugar cane fields (Boeniger *et al*, 1991 cited by IARC, 1997). Near rice farming operations in California, a mean level of amorphous silica fibres of 0.004 fibre/ml air was detected; the maximum was 0.02 fibres/ml. In neighbouring towns, on days when there was rice burning, fibres were detected at < 0.004 fibres/ml (Lawson *et al*, 1995 cited by IARC, 1997).

5.1.2 In water

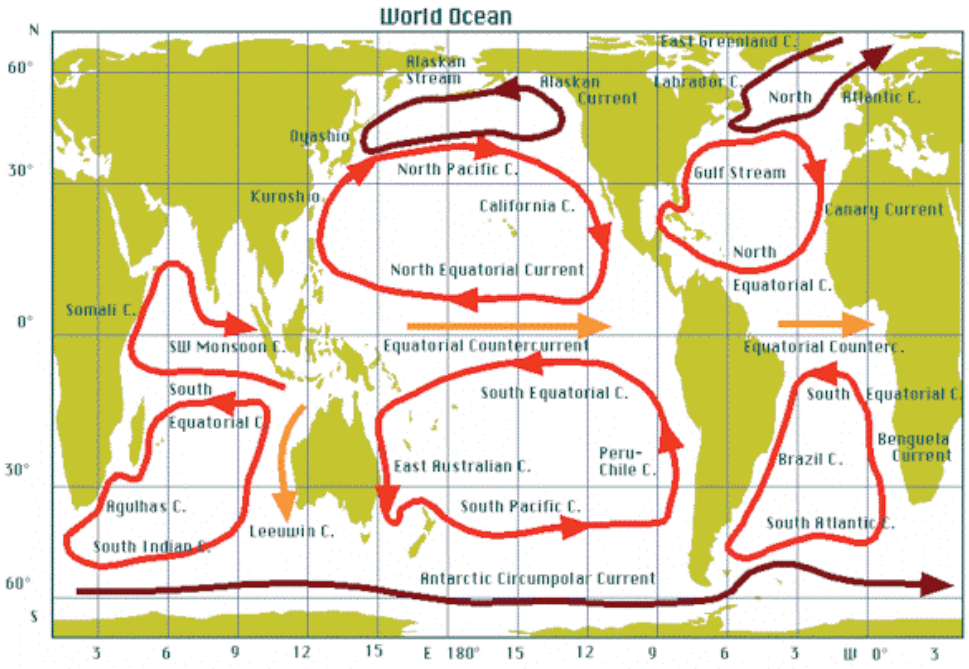
At normal environmental pH values dissolved silica exists exclusively as monosilicic acid (Schleyer and Blumberg, 1982).

The most common concentrations reported for the aquatic compartment are in the range of 0.4 to 26 mg SiO_2/l (Vymazal, 1995 cited by Van Dokkum *et al*, 2001).

The average dissolved silica concentration in rivers worldwide is 9 mg SiO_2/l (Tréguer *et al*, 1995). The median value of silica in US lakes and groundwater is reported to be 4 mg/l and 17 mg/l respectively (Schleyer and Blumberg, 1982).

The concentration of silicic acid in the oceans averages approximately 4.2 mg SiO_2/l. However, there are marked regional differences from less than 0.12 mg SiO_2/l in the surface waters of the central gyres (ocean currents, e.g. Gulf Stream), to 6 mg SiO_2/l in the surface waters of the Antarctic (Figure 23). Deep and bottom waters are usually silicic-acid rich, with concentrations ranging from 0.6 to 2.4 mg SiO_2/l in the north Atlantic, 6 to 9.6 mg SiO_2/l in the Atlantic and 8.4 to 10.8 mg SiO_2/l in the North Pacific (Tréguer *et al*, 1995).

Figure 23: Major ocean surface currents [a] (Tomczak, 1998)



[a] The gyre in the middle of the ocean basin in each hemisphere is known as the central gyre

5.1.3 In soil and sediment

Amorphous silica concentrations of around 706 g SiO_2/kg dry weight were reported for soils (Jorgensen *et al*, 1991 cited by Van Dokkum *et al*, 2001). In sediment, the concentration was 524 g SiO_2/kg, probably expressed as dry weight (Vymazal, 1995 cited by Van Dokkum *et al*, 2001).

Experiments in which soil solution is repeatedly withdrawn from a sample of soil show that a steady silicic acid concentration characteristic of that soil can be maintained. Continuous removal of dissolved silica from the soil solutions by plants and its replenishment by dissolution of soil amorphous silica is envisaged as the major process occurring in soils. Plant biogenic silica is released to soil through burning and normal decay. It may represent less than 1 to 3% in soil (IARC, 1997). The concentration in soil solutions was up to 72 mg SiO_2/l (Raven, 1983).

5.2 Human exposure levels and hygiene standards

5.2.1 Non-occupational exposure

The median concentration of dissolved silica in public water supplies of the 100 largest US cities was 7.1 mg SiO_2/l (Schleyer and Blumberg, 1982).

Silica is also a natural element found in food. Average daily intakes of silica ranged from 43 to 107 mg SiO_2/d, with the lower values for animal based diets and the highest values for plant-based diets. Foods with high silica content include grains, especially oats, barley and some rice fractions (Pennington, 1991).

SAS is incorporated in a variety of food products such as anti-caking agent, thickener and adsorber, at levels typically up to 2% by weight (such food includes beverage mixes, salad dressing, sauces, gravy mixes, seasoning mixes, soups, spices, snack food, sugar substitutes and desserts). SAS is also used as an anti-caking agent and as an excipient in pharmaceuticals for various drug and vitamin preparations (IARC, 1997 and company brochures).

5.2.2 Occupational exposure

Occupational exposure to SAS may occur during production, packaging and shipping of the material and during its use. There are few published quantitative data on industrial exposure to SAS. The available reports were reviewed by IARC (1997). A summary of this information is provided in Table 22.

Since 1996, additional information regarding occupational exposure to SAS during production and packaging of the product has been developed by the industry.

Table 22: Occupational exposure levels of SAS from 1982 to 1996 (IARC, 1997)

Industry, country/region (operation)	**Concentration (mg/m^3)**	**Remark**	**Reference** [a]
Synthesis of amino-acids and vitamins, 1 plant, France (production)	0 - 10.5 total 0 - 3.4 respirable	Precipitated SAS	Choudat *et al,* 1990
Synthesis of amino-acids and vitamins, 1 plant, USA (production)	< 1.0 - 10 total	Precipitated SAS	Wilson *et al,* 1979
Manufacturing of pyrogenic SAS, 9 plants, Europe (filling, packing, bagging and mixing)	0.61 - 6.5 total 0.2 - 2.1 respirable	Thermal process. Range of medians, personal samples (1991 - 1996)	CEFIC, 1996
Manufacturing of precipitated SAS and SAS gel, 9 plants, Europe (filling, packing, cleaning, blending)	1.0 - 8.8 total 0.5 - 2.1 respirable	Wet process. Range of medians, personal samples (1982-1996)	CEFIC, 1996

[a] Cited by IARC, 1997

In a comprehensive monitoring programme and morbidity study on workers in Germany (in progress), more than 1,000 inhalable and respirable dust measurements were performed in SAS-production plants (involved companies: Degussa, Wacker and Cabot). The measurements included total dust and fine dust, determined simultaneously by personal sampler at the breathing zone of the employees, according to BIA (1989). Overall mean dust concentrations were 1.2 mg/m^3 (inhalable) and 0.3 mg/m^3 (respirable). The highest mean values were observed for job categories involved with packaging and loading operations (up to 3 mg/m^3 inhalable and up to 1 mg/m^3 respirable dust). All mean values of all job categories comply with the German MAK workplace threshold limit of 4 mg/m^3 (inhalable dust) (Vormberg, 2004). The results are summarised in Table 23.

Table 23: Occupational exposure to SAS 1996-2003 (Vormberg, 2004)

Plant number	Number of job categories	Number of measurements per job category	Mean total and fine dust concentration (mg/m^3)			
			Inhalable		Respirable	
			Arithmetic	Geometric	Arithmetic	Geometric
1	4	7 - 91	0.17 - 1.14	0.13 - 0.81	0.07 - 0.26	0.05 - 0.19
2	2	3 and 29	0.38 and 0.35	0.03 and 0.35	0.07 and 0.33	0.06 and 0.27
3	5	12 - 27	0.41 - 2.52	0.36 - 2.02	0.19 - 1.08	0.15 - 0.62
4	9	25 - 111	0.42 - 3.15	0.24 - 2.06	0.15 - 0.64	0.10 - 0.49
5	6	22 - 179	0.23 - 1.55	No data	0.10 - 0.34	No data

5.2.3 Occupational hygiene standards

Occupational hygiene standards for SAS are limited. Where a specific occupational exposure limit value is not available, the standard for nuisance dust is often used. These have been adopted by a number of countries (Table 24). Standards for general amorphous silica are shown for comparison. All of these standards are based on irritant properties of the dust.

The US-Occupational Safety and Health Administration (OSHA) permitted exposure level for CAS No. 7631-86-9 includes all types of SAS (OSHA, 2003). It appears that there is an error in the OSHA entry for amorphous silica. A footnote in Table Z-3 is required indicating that the percent silica in the formula (80 mg/m^3 + % SiO_2) refers to crystalline silica content and not to amorphous silica. The current National Institute for Occupational Safety and Health (NIOSH) recommended exposure level is 6 mg/m^3 (respirable) (NIOSH, 2005).

Table 24: Occupational exposure limits for SASs, nuisance dust and amorphous silicas

Type of silica / Country	TWA[a] (mg/m^3)		Reference
	Inhalable fraction	Respirable fraction	
Precipitated SAS, SAS gel			
Belgium	10	-	Moniteur Belge, 2002
Canada, Alberta	10	-	Province of Alberta, 2003
Chile	8	-	Ministerio de Salud, 1999
Spain	10	-	INSHT, 2001
Silica, amorphous			
Canada, Alberta	10	3	Province of Alberta, 2003
Finland	5	-	HTP-arvot, 2005
Germany	4	-	Bundesministerium für Arbeit und Sozialordnung, 2000
Ireland	6	2.4	NAOSH, 2002
Mexico	10	3	Norma Oficial Mexicana, 2000
Norway	-	1.5	Arbeidstyilsynet, 2003
Thailand	0.8 [b]	-	Ministry of Interior, 2001
UK	6	2.4	HSE, 2005
Nuisance dust			
Finland	5	-	HTP-arvot, 2005
France	10	5	INRS, 2005
Germany	4 [e]	1.5 [e]	DFG, 2004
Ireland	10	4	NAOSH, 2002
Mexico	10	3	Norma Oficial Mexicana, 2000
Netherlands	10	5	Lagast, 2005
Norway	10	5	Arbeidstyilsynet, 2003
Spain	10	3	INSHT, 2001
UK	10	4	HSE, 2005
USA	10 [c]	3 [c]	ACGIH, 2005a [d]
USA	15	5	OSHA, 2003

[a] Time weighted average, usually for 8-hour shift

[b] Reported as 20 mppcf (million particles/cubic foot).The 8-hour TWA (in mg/m^3) is calculated from the specified equation for the TWA = 80/(%SiO_2) mg/m^3, using a value of 100% SiO_2. Lower values of % SiO_2 will give higher exposure limits

[c] Automatically applies in other countries like Belgium, Italy and Venezuela

[d] ACGIH (2005b) intends to withdraw the specific values to due to insufficient data

[e] Also applies in Austria

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Micro-organisms

The antibacterial effect of pressed and unpressed high purity SAS (Aerosil, unspecified) (0.2 g silica + 0.15 ml bacteria strain suspension) kept at 22°C has been investigated (SAS is sometimes pressed to remove air before transportation). The following micro-organisms were studied: *Escherichia coli*, *Proteus* sp., *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, *Micrococcus pyrogenes aureus*, *Streptococcus faecalis*, *Streptococcus pyrogenes humanus*, *Corynebacterium diphtheriae*, *Candida albicans* and *Bacillus subtilis*. The SAS was contaminated either by hand contact, by saliva droplets or by contact with the atmosphere. Rod-shaped gram-negative organisms (*Escherichia coli*, *Bacterium proteus*, *Pseudomonas aeruginosa* and *Aerobacter aerogenes*) died between 6 hours and 3 days in contact with unpressed SAS. Gram-positive micro-organisms were somewhat more resistant. In addition, the tests demonstrated that survival of bacteria was shorter in unpressed than in pressed SAS (Kienholz, 1970).

6.2 Aquatic organisms

The available studies are summarised in Table 25. The tests were performed with different types of SAS (Appendix B), in accordance with OECD test guidelines 201, 202 and 203 for algae, crustaceans and fish, respectively, and in compliance with good laboratory practice (OECD, 1982, 1984a,b,c).

Table 25: Toxicity of SAS to fish, crustaceans and algae

Type [a]/ Product name	Organism	Effect/ Parameter [b]	Time (h)	Concentration [c] (mg/l)	Reference	CoR [d]
Hydrophilic	**Fish**	**Lethality**				
Aerosil 200	*Brachydanio rerio*	LC_0	96	≈10,000	Degussa, 1992a	2b
Ultrasil VN3	*Brachydanio rerio*	LC_0	96	≈10,000	Degussa, 1992b	2b
	Crustaceans	**Mobility**				
Aerosil 200	*Daphnia magna*	EC_0	24	≈1,000	Degussa, 1992c	2b
Ultrasil VN3	*Daphnia magna*	EC_0	24	≈10,000	Degussa, 1992d	2b
Hydrophobic	**Fish**	**Lethality**				
Aerosil R974	*Brachydanio rerio*	LC_0	96	≈10,000 [d]	Degussa, 1992e	2b
	Crustaceans	**Mobility**				
Aerosil R974	*Daphnia magna*	EC_0	24	≈1,000 [d]	Degussa, 1992f	2b
	Algae	**Growth**				
Aerosil R972	*Scenedesmus subspicatus*	EC_0 [e]	72	Not stated [f]	Degussa, 1999	2b

[a] Appendix B
[b] LC_0/EC_0, lethal/effect (inhibition) concentration for 0% of species
[c] Nominal, ≈ approximately
[d] Code of reliability (Appendix A)
[e] Test substance was floating on water surface
[f] Biomass and growth rate
[g] Filtrate from 10,000 mg/l suspension

When hydrophilic SASs (Aerosil 200 and Ultrasil VN3; purity 100% and 98%, respectively), were tested for their acute toxicity to fish and crustaceans, the LC_{50} and EC_{50} values were higher than 10,000 mg/l and 1,000 mg/l, respectively (Table 25).

The zebra fish (*Brachydanio rerio)* test was performed with SAS in suspension, due to the insolubility of the SAS. No mortality was observed for the fish after 96 hours of exposure at 1,000 mg/l and 10,000 mg/l. The test media remained turbid throughout the test, indicating that the limit of solubility of the product was exceeded. The actual concentrations were not determined.

With the water flea (*Daphnia magna*), SAS suspensions exceeding the limit of solubility were tested, without analysis during the 24 hours of exposure, and some immobilisation was observed. However, no significant immobilisation was observed when a solution filtered through microfibre glass filter was tested. The observed effects were likely caused by physical hampering of the *Daphnia* due to the presence of undissolved particles. The viscosity has been determined

independently; dispersions of SAS with the concentration given above exhibit low viscosity, close to pure water. In ecotoxicity assays, the tested concentrations should normally not exceed the limit of solubility of the substance and should not affect the test system (Method C2 - Annex V of Directive 67/548/CEE [EC, 1967]). Therefore the immobilisation of *Daphnia*, obtained with turbid suspensions, cannot be considered as a true toxic effect of SAS.

A surface-treated SAS (Aerosil R974; 99.9% pure) was tested on fish and crustaceans. The LC_{50} to fish and EC_{50} to *Daphnia* were found to be higher than 10,000 mg/l and 1,000 mg/l, respectively (Table 25).

In the fish tests, due to the insolubility of the surface-treated SAS, suspensions were tested. No mortality was observed for the fish after 96 hours of exposure, at the concentrations of 1,000 mg/l and 10,000 mg/l. The test media were turbid at the beginning of the test, indicating that the limit of solubility was exceeded. Undissolved substance was present on the surfaces of the test media. The actual concentrations were not determined.

The *Daphnia* tests were performed with a suspension of 1,000 mg/l. It was not possible to test a suspension of 10,000 mg/l because the *Daphnia* were not visible due to undissolved material. This suspension of 10,000 mg/l was then filtered using a wad of perlon wool, before being tested. Both suspensions were turbid, and undissolved substance was observed on the surface of the test media. No analysis of the substance was performed during the 24 hours of exposure. No immobilisation was observed in the 1,000 mg/l suspension and in the 10,000 mg/l filtered suspension.

Another surface-treated SAS (Aerosil R972; purity 99.9%) was tested for possible effects on algae. The EC_{50} to algae was found to be higher than 10,000 mg/l filtered suspension (Table 25). The surface-treated silica suspensions were filtered after 24 hours through filter paper before being tested. The actual dissolved concentrations were not determined. There was no inhibition of the biomass or of the growth rate with the 10,000 mg/l filtered suspension.

No toxic effect on the growth of green algae SA-3 strain (exsymbiotic from *Paramecium bursaria*) and *Chlorella vulgaris* c-27 was reported after exposure to 0.01% SAS Aerosil A300 (100 mg/l) for 9 to 12 days. The conditions of this study were different from a standardised OECD test since the green algae were incubated in a poorly nutritious medium and the pre-cultures were not growing exponentially. Nevertheless, under the conditions of this study, Aerosil A300 appeared to stimulate the algal growth via an acceleration of their life cycle (Gerashchenko *et al*, 2002).

6.3 Terrestrial organisms

The specific toxicity of SAS to insects was studied in relation to the use of silica as a biocide carrier in some insecticide formulations.

Samples of pyrogenic (HDK H20, HDK N20, Cab-O-Sil series), precipitated (Sipernat 22), and gel (Gasil series) SAS were tested for their toxicity by contact to the cockroach *Blatella germanica* (Table 26). The mortality was measured after 24 hours of exposure, at 30°C and 75% relative humidity. There was no control group during this test. The LD_{50} values ranged from 23 to > 786 µg SAS/cm^2, depending on the silica samples. SAS was not toxic when the relative humidity reached 95% or when water was provided. Moreover it was demonstrated that SAS has no toxicity to *B. germanica* by ingestion. It is suggested that SAS may act by sorption of the cuticular lipid, inducing the death of the cockroaches by water loss (Le Patourel and Zhou, 1990).

This hypothesis of dehydration of the insects was also developed in another study, where the authors studied the accumulation of SAS (Sipernat 22S) on the body of the rice weevil *Sitophilus oryzae* moving through treated wheat grains. The weight of silica carried by beetles after 48 hours of exposure in wheat treated with silica at 150 mg/kgbw was 3.83 µg/insect, and no mortality was observed among the insects, due to the high wheat moisture content. Some silica accumulated on the insects appeared translucent rather than opaque, and the authors interpreted that characteristic as being due to the saturation of silica with lipids from the cuticle. Based on this observation they hypothesised that SAS acts by adsorbing cuticular wax from the insect cuticle, leaving the insect vulnerable to desiccation (Le Patourel *et al*, 1989).

The toxicity of the precipitated SAS (Wessalon S) was also studied on the grain weevil *Sitophilus granarius* (Table 26). The silica was deposited as a dry powder or as aqueous suspension on different surfaces (glass, tile, concrete, sacking and wheat grain). Mortality of the organisms was measured after 96 hours of exposure except in the case of grains (7 days of exposure) at 25 to 27°C and under a relative humidity of 55 to 60%. The LD_{50} values ranged from 21 to 362 µg/cm^2 and 451 to 1,137 µg/g, indicating some toxicity of the silica to insects in relation to the type of surfaces and to a lesser extent to the form of silica deposits (dry powder or aqueous solution). The observed toxicity depended on the intensity of contact between the insects and silica (Gowers and Le Patourel, 1984).

Due to deficient methodologies and/or documentation these studies are assigned CoR 3a or 3b.

Table 26: Acute toxicity of SAS to insects

Type/ Product name	Organism	Time	LD_{50} [a]	Reference	CoR [b]
Hydrophilic					
Cab-O-Sil EH5, H5, M-7D	*Blatella germanica*	24 h	53 - 241µg/cm^2	Le Patourel and Zhou, 1990	3b
Gasil, Sipernat 22	*Blatella germanica*	24 h	23 - > 786 µg/cm^2	Le Patourel and Zhou, 1990	3b
HDK N20	*Blatella germanica*	24 h	53 - 241 µg/cm^2	Le Patourel and Zhou, 1990	3b
Wessalon S (dry powder)	*Sitophilus granarius*	96 h 7 d	21 - 149 µg/cm^2 451 µg/g wheat	Gowers and Le Patourel, 1984	3a
Wessalon S (aqueous suspension)	*Sitophilus granarius*	96 h 7 d	33 - 362 µg/cm^2 > 1,137 µg/g wheat	Gowers and Le Patourel, 1984	3a
Hydrophobic					
HDK H20	*Blatella germanica*	24 h	53 - 241 µg/cm^2	Le Patourel and Zhou, 1990	3b

[a] Expressed as µg/cm^2 for surfaces treated with silica and as µg/g for grains treated with silica
[b] Code of reliability (Appendix A)

6.4 Effects on ecosystems

Silicon is an essential element for diatoms; silica is necessary for their growth and development.

At concentrations of less than 0.1 mg SiO_2/l, dissolved silica is a limiting factor for diatom development in fresh waters. Under normal environmental conditions, silica concentrations are sufficient to maintain diatom populations (Schleyer and Blumberg, 1982).

Marine mesocosm experiments indicate that diatoms dominate as long as the silica concentration is above 0.1 mg SiO_2/l (Egge and Aksnes, 1992). Other experimental studies showed minimum silica concentrations required for growth of several species of diatoms that ranged from about 0.5 to as much as 5 µg Si/l (0.03 - 0.3 mg SiO_2/l), well within the range of both coastal and offshore surface concentrations (Officer and Ryther, 1980).

Diatom growth is conditional upon a minimum level of silica in the aquatic medium and the addition of excess soluble silica above the limiting value will not stimulate the development of diatom populations (Schleyer and Blumberg, 1982).

Phosphate enrichment increased diatom growth, which was followed by sedimentation, causing silica depletion in water and limitation of diatom production in freshwater (Schelske *et al*, 1986). Silica is not used by zooplankton. It is excreted as particulate siliceous detritus, which rapidly sinks (and slowly dissolves) through the water column into the sediment, thus inducing silica

depletion of the surface water (Figure 22). In contrast, organic phosphorus and nitrogen are recycled quickly to inorganic forms through zooplankton grazing and through respiration and decay (Officer and Ryther, 1980). In eutrophic freshwaters, when silicon is depleted, diatoms can then be replaced by green and blue-green algae species, which have much lower requirements for silicon (Schleyer and Blumberg, 1982).

Nutrient enrichment and a subsequent decrease of silica concentration in the river Mississippi since 1950 have been described. This decrease has resulted in a reduction of the annual supply of riverine silicate to the coastal waters of the southern United States (Rabalais *et al*, 1996).

Depletion of silica in the surface layers of Lake Michigan has been explained as a seasonal phenomenon with much of the loss of the silica from the water column each spring and early summer being associated with the sinking of diatom tests and copepod faecal pellets containing silica. These materials are recycled the following winter and then support an annual spring diatom bloom (Conway *et al*, 1977 cited by Officer and Ryther, 1980).

In the marine environment, a common event is the diatom bloom during late spring when solar conditions are appropriate. Since silicon is recycled more slowly than nitrogen and phosphorus, this diatom bloom may be followed by a flagellate bloom depending on the nutrient levels. Unlike diatoms, flagellates are frequently poor food for most grazers; this results in a dramatic increase of flagellate populations and subsequent anoxic conditions associated with their decomposition when they die. The sequence of events has been observed, for example, in some of the most biologically productive oceans in the world (e.g. west coast of Africa, South America and Antarctica) where, under normal conditions, surface waters are replaced by nutrient rich sub-surface waters due to winds and currents which leads to a plankton dominated by diatoms supporting some of the most important fisheries. When these up-welling systems fail, the diatoms are replaced by dinoflagellates. Thus, the hypothesis is made that silicon depletion allows the succession from the diatom population to the flagellate population (Officer and Ryther, 1980).

The above studies explain the planktonic community shifts associated with changes in nutrient concentrations and particularly silicon in relation to phosphorus and nitrogen. There are several other factors that may explain the succession of the planktonic populations, including physical parameters as light and temperature, sinking and turbulence resuspension, growth rate, differential susceptibility to grazing, and even parasitism.

The relative importance of the different factors controlling phytoplankton successions have been analysed in Lake Constance which is a deep, nutrient rich lake. This study demonstrates that the interaction between the organisms and their physical and chemical environment, and the interaction between the organisms themselves generates a new set of environmental conditions

under which the members of the community of tomorrow are selected. Nutrient concentration is one of these controlling factors (Sommer, 1987).

6.5 Summary and evaluation

Dissolved silica to some extent influences the succession of phytoplankton communities in fresh and marine waters. However, this is only one of a number of controlling factors, which include light, temperature, nutrients, and others.

There is no evidence of significant acute toxicity of SAS to organisms in the environment. The observed effects on insects are most probably related to physical properties of SAS (desiccation). SAS did not exhibit toxicity when tested on aquatic organisms under laboratory conditions. The quantities released into the aquatic environment are negligible compared to the natural flux of dissolved silica.

In conclusion, SAS presents a low risk of adverse effects in the environment.

7. KINETICS AND METABOLISM

7.1 Absorption, distribution and elimination

7.1.1 Physiology-orientated-multicompartmental kinetics model

For practically insoluble particles, the creation of a pulmonary retention model is relatively simple. These models describe the distribution, elimination and retention of inhaled and deposited respirable particles. Linear and non-linear system models designed in the past have given reasonable simulations of experimental data. For example, a physiology-orientated-multicompartmental kinetic (POCK) model was able to successfully predict pulmonary retention data of biopersistent, non-cytotoxic aerosols in long-term inhalation exposures of rats.

The existing POCK model has been adapted for moderately soluble particles, in particular SAS, in a theoretical investigation, accounting for dissolution rate coefficients that exceed the classical clearance rate coefficients for highly soluble macrophaged particles deposited in the lung. The simulation for SAS was compatible with the observed dissolution pattern (Section 2.3.2), which shows a relatively fast dissolution of various SASs in equilibrium with water (closed system). In an open system, the dissolved silicic acid is quickly removed from the solvent, as is expected to occur in living organisms. Provided that the solubility in the biological system is similar to that *in vitro*, the dissolved silicic acid is relatively quickly removed from the animal body. In conjunction with a low standard deviation of particle size distribution (practical monodispersity) of the product, the POCK model predicts that clearance of SAS by dissolution is at least 20 times faster than particulate clearance by macrophages (Stöber *et al*, 2000; Koch and Stöber, 2001). Therefore, with respect to SAS, a relatively fast elimination and limited biopersistence in the lungs is expected, compared to insoluble 'inert' particles like quartz.

In this report, the behaviour of different types of SAS in the animal lung is discussed based on solubility and surface area data (Section 8.1.3 and 8.3.3).

7.1.2 Human

Silica levels in blood were determined in 264 subjects. The mean value was 8.3 ± 24 ng SiO_2/ml total blood. There was no significant influence of sex, age, employment, lung disease (dust lung) or other disease (Worth and Campen, 1951).

Renal silica-secretion after oral administration of two SASs, Aerosil (pyrogenic silica, not further specified) and FK700 (precipitated silica), in 2 portions of 1.25 g (suspended in apple juice) was determined in humans (two groups of 5 men and 1 woman; aged 22 - 28 y). The total urine was

collected and analysed for the monomer silica content. During the following three days no significant changes of the renal silica secretion were seen after administration of Aerosil. With precipitated silica in 5/6 persons the renal SiO_2 secretion was increased by 7 to 23 mg. In 1/6 persons it was decreased by 26 mg. In 5/6 persons the average daily precipitated silica secretion of the following 3 days was increased by 4 to 20 mg and slightly decreased in 1/6 persons. The changes in silica excretions were considered by the authors to be within the range of normal physiological variation, and there was little indication of absorption across the gut wall (Degussa, 1966a; Langendorf and Lang, 1967).

The short-term safety and efficacy of Syloid HC gel was studied in 6 human adults (3 men, 3 women; aged 20 - 51 y) with primary type II hyper-lipoproteinaemia. For 3 weeks, Syloid HC was administered with the morning and evening meal, starting with an oral dose of 1 g/d that was increased by 1 g/d daily, up to a final dose of 16 g/d. Syloid HC was not absorbed significantly from the intestine. No marked adverse side effects were observed. The substance did not markedly enhance bile acid excretion (Grace, 1982).

7.1.3 Studies in animals

Inhalation

An inhalation study was conducted in rats, including two pyrogenic SASs [a] (hydrophilic Aerosil 200 and hydrophobic Aerosil R974) and precipitated, hydrophilic Sipernat 22S. Rats were exposed (6 h/d, 5 d/wk) to SAS for 13 weeks to concentrations of 1.3, 5.9 or 31 (Aerosil 200) or 35 (Aerosil R974 and Sipernat 22S) mg SiO_2/m^3 with recovery up to 52 weeks. Small amounts of SAS, compared to the administered dose, could be detected in lungs at the end of the exposure period (average 0.2 mg) in all animals of the high dose group. One male exposed to 31 mg/m^3 showed a small amount of silica in the regional lymph nodes. During the recovery period no SAS could be detected in the lungs or nodes of any animal (Degussa, 1987; Reuzel *et al,* 1991).

Rats were exposed by inhalation for 5 hours to 55 mg/m^3 precipitated SAS (FK700). The mean retention value (20 h later) was 0.138 mg SiO_2/lung. The average silica content of the lungs was 1.022 mg after 4 months of exposure, and 3.443 mg after 12 months. The corresponding values for the mediastinal lymph nodes were 0.033 mg after 4 months, 0.052 mg after 5 months and 0.069 mg after 12 months. The average silica content of the lungs was 0.457 mg (elimination 87%) 5 months after exposure (Degussa, 1968b). This indicates that there was no significant elimination of SAS via the mediastinal lymph nodes, such as that observed with quartz.

[a] The various SASs studied are listed in Appendix B. The physical and chemical properties are discussed in Section 2.3.

During exposure (5h/d, 5d/wk) of rats to 50 to 55 mg SiO_2/m^3 (total dust; ≈ 30 mg/m^3 respirable) of hydrophilic SAS (Wacker HDK V15) for 12 months, about 0.25 mg was found in the lungs after 3 days and 0.5 mg after 6 weeks. After 12 months, about 1% of administered total respirable dust was estimated to be still retained in the lungs. Lung deposition increased rapidly upon initial exposure, then slowed down from 18 weeks to 12 months (6 wk: 0.5 mg SiO_2; 18 wk: 1.2 mg; 12 months: 1.37 mg). The mediastinal lymph nodes contained about 0.02 mg silica after 6 weeks and 0.13 mg after 12 months. After 5 months of recovery, the mean silica levels were 0.16 mg/lung and 0.047 mg/lymph node, i.e. a reduction of 88% in lungs and more than 50% in lymph nodes (Klosterkötter, 1969).

Rats were briefly exposed (5 h/d) to 50 mg/m^3 of hydrophobic SAS (Wacker HDK H20) for 1 or 3 days and killed at 20 hours, 1 month or 3 months after exposure. Elimination was 78% (1 d exposure) or 75% (3 d) after 1 month recovery, and 87% (1 d) or 92% (3 d) after 3 months recovery. The silica concentration in the mediastinal lymph nodes was very low. Following prolonged exposure (5 h/d, 2 d/wk) of rats to 50 mg/m^3 for 8 or 12 months, the lungs had retained 1.448 mg SiO_2 (1.3% of total exposure) and 1.759 mg (1.1% of total exposure), respectively, and the lymph nodes 0.051 mg and 0.113 mg. After 12 months exposure and 1 month recovery, the lungs contained 1.1 mg SiO_2 (elimination 37.5%) and the lymph nodes 0.16 mg. After 3 months of recovery, the silica content of the lungs was 0.43 mg (lymph nodes 0.12 mg) and after 5 months it was 0.41 mg (elimination 76.7%). By this time the silica content of the lymph nodes was 0.13 mg (Klosterkötter, 1971).

After exposure (4 h/d, 5 d/wk) of rats to hydrophilic SAS (Aerosil 150) at 40 to 50 mg/m^3 for 2 to 12 weeks, the overall elimination was high without accumulation in the lungs. Equilibrium between retention and elimination was reached shortly after the onset of exposure. Only 5 to 6% of theoretically deposited silica was found after 120 days exposure. On the other hand, there was substantial transfer of silica to the mediastinal lymph nodes under these conditions: about 31% of total deposited (1.5 - 2% of theoretically deposited) silica. The involvement of lymphatic elimination appeared not to be relevant up to 8 weeks of exposure. There was an indication that SAS particles were able to pass the lymph nodes and were removed from the lymph nodes in a short period of time (Klosterkötter, 1963).

Rats inhaled (5 h/d; 5 d/wk) 100 mg/m^3 of hydrophobic SAS (D500) for up to 1 year. The silica content of lungs and mediastinal lymph nodes was determined during and after exposure. The following mean values were reported: at 3 months 4.33 and 0.132 mg in lungs and lymph nodes, respectively, at 5 months 6.71 and 0.214 mg, and at 12 months 11.46 and 0.378 mg. Six months after cessation of exposure, 55.5% of the silica was eliminated. Relevant elimination via the lymph nodes could not be observed. After short exposure (5 h/d) of rats to a high D500 concentration (200 mg/m^3) for 3 days, 0.91 mg silica was found in the lungs. Three months after

exposure 81% of the silica was eliminated. Elimination via the lymph nodes was marginal (Degussa, 1966b).

Rats inhaled (5 h/d; 5 d/wk) 112 mg/m^3 of hydrophilic SAS (OX50) for up to 1 year. The silica content (median values) of the lungs and mediastinal lymph nodes was 1.578 and 0.151 mg, respectively, after 4 months, and 1.82 mg and 0.43 mg after 12 months. Approximately 50% of the silica was eliminated 4 months after exposure. Relevant elimination via the lymph nodes was observed. Similar results were reported following short exposure of rats to a higher OX50 concentration (130 mg/m^3) for 3 days (Degussa, 1968a).

In contrast to these results, higher retentions after 3 months were seen in other studies.

During inhalation exposure of rats to 53 mg/m^3 of a pyrogenic SAS (Aerosil, not further specified) for up to 12 months, a rapid increase of silica in the lungs was observed. This effect was not seen in studies at lower exposure concentrations. The average lung content was 1.5 mg SiO_2 after 3 months of exposure (6% of lung-ash weight), thereafter remaining at a steady state level. After 2 months of recovery, the average lung level decreased to about 0.3 mg SiO_2 per lung (Schepers *et al*, 1957a).

In guinea pigs exposed to the same SAS under identical conditions as mentioned above, the average lung content reached 2.5 mg SiO_2 per lung (4% of lung-ash weight) after 12 months, lower than in the rat (6%) (Schepers *et al*, 1957b).

Female rats were exposed (4 h/d) by inhalation for up to 6 days to various pyrogenic and precipitated SASs (concentration not measured). Within 3 months of SAS exposure, on average 73.8% silica had been eliminated from the lungs. In the mediastinal lymph nodes small amounts of silica were present (0.6 - 3.5% of silica eliminated from lungs and 0.2 - 2.8% of total retained). In another study, female rats were exposed to pyrogenic and precipitated SAS, and quartz for comparison. The elimination of silica from the lungs was examined. There was little influence of particle size. The lymphatic glands were moderately enlarged and the silica content was less than 2% of the amount eliminated. These results differed considerably from those obtained with quartz (or other insoluble dusts). Most of the SASs were eliminated within 1 to 2 months and relatively small amounts were detected in the lymph nodes. The less soluble (precipitated) SASs were eliminated more slowly than the more soluble (pyrogenic) types (Klosterkötter and Bünemann, 1961, 1962).

Rats (10/group) were exposed (5 h/d) by inhalation to 30 mg/m^3 of precipitated SAS (TK 800 and Ultrasil VN3) for 3 days. The amount of silica recovered per lung after TK 800 exposure was 0.31 mg at 20 hours post exposure, 0.11 mg after 1 month and 0.06 mg after 3 months. The amount of TK800 recovered in the mediastinal lymph nodes 3 months post exposure was 0.009 to

0.012 mg SiO_2. Recovery of VN3 after the last exposure was 0.21 mg SiO_2/lung at 20 hours, 0.07 mg at 1 month and 0.06 mg at 3 months post exposure. The amount of VN3 retained by the mediastinal lymph nodes was 0.005 mg SiO_2 at 1 month and 0.013 mg at 3 months post exposure. Elimination of either SAS had a biological half-life of less than 30 days (Degussa, 1970).

In a comparative study including 3 hydrophilic SASs (precipitated Zeosil 45, gel Syloid 74 and pyrogenic Cab-O-Sil M5), Wistar rats (10/sex/group) were exposed (6 h/d) for five days to 1, 5 and 25 mg SAS/m^3, respectively. Satellite groups were exposed similarly and kept for a recovery period of 1 or 3 months. Additional animals were exposed to 25 mg/m^3 crystalline silica (quartz) as positive controls. The silica content of the organs was measured by analysis of silicon [a] in an inductively coupled plasma-atomic emission spectrometer. One day after exposure, 30 to 40 µg Si (64 - 86 µg SiO2) was detected in lungs of high dose animals after Zeosil 45 exposure, 76 µg Si (163 µg SiO2) (average) after Syloid 74 exposure and 43 µg Si (92 µg SiO2) (average) after Cab-O-Sil M5 exposure. In all cases, the silicon content of the lungs after 1 and 3 months of recovery was below the detection limit, except for one unexplained observation of the presence of Zeosil 45 at 3 months. On the contrary, in crystalline silica exposed animals, silicon accumulation was 4 to 5 times higher (150 - 160 µg; 320 - 340 µg SiO2) and still persisted on a high level after recovery for 1 month (80 µg in females, 140 µg in males; 171, 300 µg SiO2) and 3 months (110 µg in females, 130 µg in males; 240, 280 µg SiO2). No increased silicon levels were observed in the lymph nodes at any concentration tested (Arts and Kuper, 2003a,b; Arts *et al*, 2003).

Wistar rats (10/sex/group) were exposed (6 h/d, 5 d/wk) by inhalation to hydrophobic pyrogenic SAS (HDK SKS300). Male rats were exposed to target concentrations of 0, 0.51, 2.05 and 10.01 mg/m^3 for 13 weeks. Additional rats were similarly exposed and kept for recovery (13 weeks). At the end of the exposure period, silica was found in the lungs of all exposed animals in a concentration-related way. In tracheobronchial lymph nodes, silica was detected in 3 out of 5 animals of the high concentration group. After 13 weeks of recovery, silica was still present in the lungs and tracheobronchial lymph nodes of animals that had been exposed to 10 mg/m^3; mean lung silica levels appeared to be lower and mean lymph node levels slightly higher than shortly after the end of exposure. After recovery, lung silica levels were below the detection limit in animals exposed to 0.51 mg/m^3, while some silica was still detected in lungs of animals exposed to 10.01 mg/m^3 (Wacker, 1998a,b).

In a subchronic inhalation study (Section 8.3.3), Fischer 344 rats were exposed (6h/d, 5 d/wk) to 50 mg SiO_2/m^3 of hydrophilic pyrogenic SAS (Aerosil 200) for up to 13 weeks. Additional rats were exposed to crystalline silica (cristobalite) at 3 mg/m^3. The lung burden was

[a] Atomic mass 28.086

883 µg SiO_2/lung for SAS and 819 µg SiO_2/lung for crystalline silica. Three months after exposure, the SAS burden was significantly (81%) reduced to 165 µg SiO_2/lung and by 8 months it had decreased further to 93 µg SiO_2/lung, which represents a 90% reduction. The crystalline silica burden post exposure remained relatively unchanged at 658 and 743 µg SiO_2/lung after 12 and 32 weeks, respectively. The authors explained the rapid clearance of SAS from rat lung by its solubility in the lung (Johnston *et al*, 2000).

Oral

After daily oral administration of an aqueous suspension of precipitated silica (FK700) to rats at a dose of 1,500 mg SiO_2/kgbw for 1 month, there was no accumulation of silica in the animals. The average silica content of the liver was 1.5 µg, kidney 6.4 µg and spleen 5.3 µg. The corresponding control values were not significantly different (1.8, 7.2 and 7.8 µg SiO_2, respectively) (Degussa, 1968b).

In rats receiving 20 daily oral doses of 100 mg (≈ 500 mg/kgbw/d) of hydrophilic, pyrogenic silica (HDK V15) silica levels in liver and kidney were slightly increased compared to controls. The values were in liver 4.2 µg (control 1.8 µg), spleen 5.5 µg (7.2 µg) and kidney 14.2 µg (7.8 µg), respectively (Klosterkötter, 1969).

Guinea pigs were fed with SAS (precipitated, sol) mixed in the diet, or administered diluted SAS directly, or by intraperitoneal (*i.p.*) injection. There was no significant difference in total and dissolved silica levels excreted in urine (analysed colorimetrically). The concentration of silica in tissues (liver, kidney, lung, heart, muscle) was determined by the silicomolybdic acid reaction. The absolute level was low in all tissues (maximum 12.63 mg/100 g dry matter in lungs). The silica concentration of tissues was apparently not influenced by the silica concentration in the diet. Experiments with radio-labelled 31SiO2 indicated that orally administered silica sol was rapidly absorbed and excreted. The prolonged ingestion of a SAS-containing diet did not result in any appreciable storage of silica in tissue (Sauer *et al*, 1959a,b).

The natural silicate content of rabbit tissues has been measured and was reported as 18.3, 23.9 and 128 µg SiO_2/g wet tissue in liver, kidney and lung, respectively. SiO_2 levels in serum, plasma and whole blood were lower at 4.8, 5.3 and 4.3 µg/l. The silica level of urine was 92 µg/l. The elimination rate was in the range of 9.6 mg/d. A correlation between blood and urine levels was noted. These values were comparable to those reported in the literature on humans and other mammalian species such as guinea pig, cattle, cat, sheep, goat, pig and dog (Ammon and Mohn, 1959).

An oral dose of 8,000 mg/kg/d of silica (not further specified) was applied in the diet of beagle dogs and CD rats for 4 weeks. At the end of exposure period all animals were killed and evaluated histopathologically. There was no indication of any treatment-related effect in either species (Newberne and Wilson, 1970).

Other routes

SAS (precipitated, sol) was also injected *i.p.* in the study of Sauer *et al* (1959a,b), with similar results (see above).

Following intratracheal instillation in rats of a particle suspension containing 2 mg pyrogenic SAS (Aerosil 150), 82% was retained in the lungs after 6 hours and 18% after 2 days. Elimination of this 18% was slower with a half-life of approximately 11 days (Ernst *et al*, 2002).

Pyrogenic SAS (HDK V15) (10 mg) injected subcutaneously in 0.3 ml water in rats, was rapidly removed from the site of injection. The mean recovery was 6.90 mg at 24 hours post exposure, 0.65 mg (≈ 10% left) after 1 month and 0.30 mg (< 5% left) after 2 months (Klosterkötter, 1969).

Similar results were obtained in rats after subcutaneous application of 30, 40 or 50 mg pyrogenic SAS (Aerosil 150) as suspension in water or in 0.5% Tween, or as dry powder. After 6 weeks, 95 to 97% of the silica was eliminated (Degussa, 1964a).

7.2 Metabolism

No data are available. It seems that SAS is generally considered to undergo no metabolism except perhaps some conjugation.

7.3 Evaluation

Analytical data on the kinetics of SAS deposition in the lung of experimental animals during and after prolonged exposure are largely consistent. In comparison to crystalline silica, which exhibits a marked tendency to accumulate, SASs accumulate to a plateau level at which elimination equates with deposition. After cessation of exposure SASs are rapidly eliminated from the lung tissue. These data are in accordance with the results predicted by the POCK model that was developed for SASs (Stöber *et al*, 2000; Koch and Stöber, 2001). Also after ingestion, there is limited accumulation of SASs in body tissues and rapid elimination occurs. Intestinal absorption has not been calculated, but appears to be insignificant in animals and humans. SASs injected subcutaneously are subjected to rapid dissolution and removal.

There is no indication of metabolism of SAS in the organism based on chemical structure and available data.

In contrast to crystalline silica, SAS is soluble in physiological media and soluble chemical species are formed which are eliminated via the urine without modification after intestinal resorption.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

In retrospect, the amount of toxicological testing on SASs may appear excessive. It should be borne in mind that earlier studies done to primitive protocols had to be repeated. Also, because of concerns associated with the toxicology of crystalline silica, manufacturers were obliged to test all of the various SAS polymorphs to demonstrate the difference in toxicological profiles between SAS and crystalline silica.

8.1 Acute toxicity

8.1.1 Oral

The available studies and resulting median lethal dose (LD_{50}) values following oral administration of hydrophilic and hydrophobic SASs [a] to rats are summarised in Table 27.

[a] The various SASs studied are listed in Appendix B. The physical and chemical properties are discussed in Section 2.3.

Table 27: Acute oral toxicity of SAS to rats

Type/ Product name	Strain, number, sex	Vehicle	Dose (mg/kgbw)	LD_{50} (mg/kgbw)	Reference	CoR [a]
Hydrophilic						
Pyrogenic						
Aerosil 200	Sprague-Dawley, 10 M, 10 F	Aqueous methylhydroxyethylcellulose	2,000, 3,300	> 3,300	Degussa, 1977a	1b
Cab-O-Sil fluffy [b]	Boltzman, 5 M	0.5% aqueous methylcellulose	1,000, 2,750, 3,160	> 3,160	Cabot, 1958a	2b
Cab-O-Sil EH-5	Sprague-Dawley, 5 M, 5 F	Water for injection (US Pharmacopoeia)	5,000	> 5,000	Cabot, 1990a	2b
Cab-O-Sil M5	Sprague-Dawley, 5 M, 5 F	Deionised water	5,000	> 5,000	Cabot, 1981a	2b
Cab-O-Sil M5 and F2	Mice, Swiss, 10 M	Corn oil	178, 316, 562, 1,000, 1,780, 3,160	> 3,160	Cabot, 1964	2b
Cab-O-Sil F2	Mice, Swiss, 10 M	Corn oil	178, 316, 562, 1,000, 1,780, 3,160	> 3,160	Cabot, 1964	2b
Precipitated						
Sident 9	Wistar, 5 M, 5 F	Aqueous carboxymethylcellulose	5,110	> 5,110	Degussa, 1990	1a
Sident 20	Sprague-Dawley, 5 M, 5 F	1% aqueous gum arabic solution	20,000, 25,200, 31,800	> 31,800	Degussa, 1977b	2b
Sipernat 22	Sprague-Dawley, 10 M, 10 F	Aqueous carboxymethylcellulose	2,000, 5,000	> 5,000	Degussa, 1977c	2b
Sipernat D10	Sprague-Dawley, 5 M, 5 F	Olive oil	4,000, 5,040, 6,350	> 6,350	Degussa, 1977d	2b
Tixosil 53	Sprague-Dawley, 5 M, 5 F	Aqueous arabic gum 10%	0, 5,000	> 5,000	Rhône-Poulenc, 1986	1a
Zeo 49	Sprague-Dawley, 5 M, 5 F	Water	10,000, 12,600, 15,800, 20,000	> 20,000	JM Huber, 1978a	2b
Zeofree 153	Sprague-Dawley, 5 M, 5 F	Water	10,000, 12,600, 15,800, 20,000	> 20,000	JM Huber, 1978b	2b
Zeofree 80	Sprague-Dawley, 5 M, 5 F	Water	10,000	> 10,000	JM Huber, 1973	2b
Zeosyl 113	Sprague-Dawley, 5 M, 5 F	Water	10,000, 12,600, 15,800, 20,000	> 20,000	JM Huber, 1978c	2b
Zeosyl 200	Sprague-Dawley, 5 M, 5 F	Water	10,000, 12,600, 15,800, 20,000	> 20,000	JM Huber, 1978d	2b

Table 27: Acute oral toxicity of SAS to rats (cont'd)

Type/ Product name	Strain, number, sex	Vehicle	Dose (mg/kgbw)	LD_{50} (mg/kgbw)	Reference	CoR
Hydrophilic (cont'd)						
Gel						
Syloid 244 [c]	Sprague-Dawley, M	Saline	5,000	> 5,000	US-FDA, 1974	2b
Syloid 244	Sprague-Dawley, 30 M	Distilled water	5,620	> 5,620	Grace, 1974a	2b
Syloid 244	Sprague-Dawley, 5 M, 5 F	Water	31,600	> 31,600 24-h observation	Grace, 1976	2c
Sol						
Ludox (30% SiO_2)	Strain not specified, M	Aqueous colloidal	10,000	> 10,000	DuPont, 1955	2d
Positive Sol 130M (26% SiO_2)	Sprague-Dawley, 10 M	Aqueous colloidal	40,000	> 40,000	DuPont, 1968	2g
Hydrophobic						
Pyrogenic						
Aerosil R972	Sprague-Dawley, 10 M, 10 F	Peanut oil	2,500, 5,000	> 5,000	Degussa, 1977e	2b
Cab-O-Sil N70TS [d]	Sprague-Dawley, 5 M, 5 F	Corn oil	5,000	> 5,000	Cabot, 1981b	2b
Cab-O-Sil silane-treated [e]	Sprague-Dawley, 10 M	Corn oil	178, 316, 562, 1,000, 1,780, 3,160	> 3,160	Cabot, 1963a	2b
Cab-O-Sil ST22 [f]	Sprague-Dawley, 5 M, 5 F	Distilled water	1,000, 1,590, 2,510, 3,980, 6,310, 10,000	9,200 M > 10,000 F	Cabot, 1970a	2b

Table 27: Acute oral toxicity of SAS to rats (cont'd)

Type/ Product name	Strain, number, sex	Vehicle	Dose (mg/kgbw)	LD_{50} (mg/kgbw)	Reference	CoR
Pyrogenic (cont'd)						
Cab-O-Sil TS500	Sprague-Dawley, 5 M, 5 F	Corn oil	5,000	> 5,000	Cabot, 1995a	1b
Cab-O-Sil TS530	Sprague-Dawley, 5 M, 5 F	Corn oil	5,000	> 5,000	Cabot, 1995b	1b
Cab-O-Sil TS610	Sprague-Dawley, 5 M, 5 F	Corn oil	5,000	> 5,000	Cabot, 1995c	1b
HDK SKS300	Wistar, 5 M, 5 F	Polyethylene glycol 400	2,000	> 2,000	Wacker, 1996a	1a
Precipitated						
Sipernat D17	Sprague-Dawley, 5 M, 5 F	Olive oil	5,040, 6,350, 7,900	> 7,900	Degussa, 1977f	2b

[a] Code of reliability (Appendix A)
[b] Same as or very similar to Cab-O-Sil M5
[c] Also known as FDA 71-48
[d] Current name TS720
[e] Treating agent not stated; actual identity of this product remains unclear
[f] Aminopropylsilane-treated pyrogenic SAS

Many studies examining the effects of oral administration of SAS to rats have been conducted.

In general, no deaths occurred and no signs of toxicity were seen during the observation periods after single oral administration of different types of SAS. No macroscopical findings were observed at necropsy. Animals died at high doses of 10,000 and 20,000 mg SiO_2/kgbw. At doses of 5,620 mg/kgbw and higher the faeces were white coloured in some animals (US-FDA, 1974; Grace, 1976; JM Huber, 1978a). After 3 days the faeces had normal appearance.

Evaluation

The results of the acute oral toxicity studies indicate a very low order of toxicity of SAS: no signs of toxicity were observed at doses of up to 5,000 mg SiO_2/kgbw. No difference was found between LD_{50} values for the various types of SAS studied.

8.1.2 Dermal

Studies and LD_{50} values following dermal application of (hydrophilic) SAS to rabbits are detailed in Table 28.

Table 28: Acute dermal toxicity of hydrophilic SAS to rabbits [a,b,c]

Type/ Product name	Number/group	Dose (mg/kgbw)	LD_{50} (mg/kgbw)	Reference	CoR [d]
Precipitated					
Zeo 49	4	2,000, 3,000, 4,000, 5,000	> 5,000	JM Huber, 1978e	2c
Zeosyl 113	4	2,000, 3,000, 4,000, 5,000	> 5,000	JM Huber, 1978f	2c
Zeofree 153	4	2,000, 3,000, 4,000, 5,000	> 5,000	JM Huber, 1978g	2c
Zeosyl 200	4	2,000, 3,000, 4,000, 5,000	> 5,000	JM Huber, 1978h	2c
Gel					
Syloid 244 [e]	10	2,000	> 2,000	Grace, 1976	2c

[a] New Zealand strain
[b] Following application to intact and abraded skin for 24 h
[c] Sex not specified
[d] Code of reliability (Appendix A)
[e] Also known as FDA 71-48

Evaluation

After application of different SAS types to intact and abraded skin for 24 hours only slight erythema with intact skin and slight erythema and oedema with abraded skin were observed. These effects were reversible within 5 days. There was no indication of systemic adverse effects related to SAS in any test.

It is concluded that SAS is not toxic by the dermal route.

8.1.3 Inhalation

Several tests were conducted with hydrophilic and hydrophobic SASs. These are summarised in Tables 29 and 30, respectively.

Due to the strong binding forces between the aggregates and the tendency to form agglomerates (Section 2.5.7 and 2.5.8), the respective maximum attainable concentrations used in these tests for pyrogenic, precipitated and gel SAS were lower than the highest test concentration of 5 mg/l recommended for acute dust inhalation testing according to OECD and EC guidelines.

Hydrophilic

The data on hydrophilic SASs are discussed first (Table 29).

Table 29: Acute inhalation toxicity of hydrophilic SAS to rats

Type/ Product name	Strain, number, sex	Surface area [a] (m^2/g)	Particle size MMAD [b] (µm)	Exposure duration (h), regime	Concentration (mg/m^3)	LC_{50} (mg/m^3), remark	Reference	CoR [c]
Pyrogenic								
Aerosil 200	Wistar, 5 M, 5 F	200 [d]	Not stated, 56% of particles < 5	4, nose-only	139 [e]	> 139	Degussa, 1983a	2c
Cab-O-Sil EH5	Albino, strain not stated (10 M)	380 [d]	No data	1, nose-only	0 or 207,000 (nominal)	> 207,000	Cabot, 1972a	3a
Cab-O-Sil M5	Albino, strain and sex not stated	200 [d]	No data	1, nose-only	0 or 191,300 (nominal)	> 191,300	Cabot, 1972b	3a
Cab-O-Sil M5	Sprague-Dawley, 5 M, 5 F	200 [d]	0.76	4, nose-only	2,080	> 2,080	Cabot, 1981c	1c
Precipitated								
Sipernat 22S	Wistar, 5 M, 5 F	190 [d]	Not stated, 45% of particles < 5	4, whole-body	691 [e]	> 691	Degussa, 1983b	1b
Gel								
Syloid 244 [f]	Sprague-Dawley, 10 M	Not specified	Not specified	1, nose-only	2,200 [e]	> 2,200 1/10 animals died	Grace, 1977	2c

Table 29: Acute inhalation toxicity of hydrophilic SAS to rats (cont'd)

Type/ Product name	Strain, number, sex	Surface area (m^2/g)	Particle size MMAD (µm)	Exposure duration (h), regime	Concentration (mg/m^3)	LC_{50} (mg/m^3), remark	Reference	CoR
Sol								
Hydrophilic silica 'solid' [g]	Not specified, 2 M	Not specified	Not specified	4, nose-only	3,100 (nominal)	> 3,100	DuPont, 1952	3b
Ludox 30% SiO_2	Not specified, 2 M	Not specified	Not specified	2.5, 6 Mist, nose-only	560, 520	No deaths; preliminary test	DuPont, 1955	3b
Ludox 5% SiO_2	Albino, M	Not applicable	Not specified	3.25	760	No deaths	DuPont, 1952	3a
Ludox 20% SiO_2	Albino, M			4, 2	2,240, 2,500	No deaths		
Ludox 30% SiO_2	Albino, M Number not stated			1.5 Mist, whole-body	3,300	No deaths		

[a] Referring to the surface of the hydrophilic base silica (BET)
[b] Mass median aerodynamic diameter (method: cascade impactor)
[c] Code of reliability (Appendix A)
[d] From material data sheets
[e] Maximal attainable concentration
[f] Also known as FDA 71-48
[g] Type not specified

Wistar rats were exposed to Aerosil 200 by inhalation of the maximal attainable concentration (respirable dust) of 139 mg SiO_2/m^3 for 4 hours and subsequently kept for 2 weeks observation. No clinical signs or other findings were observed. No macroscopic organ abnormalities were found at necropsy (Degussa, 1983a). In a similar test with Sipernat 22S at the maximum attainable concentration of 691 mg/m^3, no mortality after 4-hour exposure or during the observation period occurred. No clinical signs, except decreased body weight gain in females during 2 days after exposure, were noted. The body weight increased in a normal way thereafter (Degussa, 1983b). In another study, Sprague-Dawley rats were exposed to 2,200 mg/m^3 Syloid 244 for 1 hour. One out of the 10 exposed animals died 2 hours later. During exposure, signs of respiratory irritation and dyspnoea were apparent in most animals (Grace, 1977).

In all these tests the maximum attainable concentration (respirable dust) was below the recommended highest test concentration of 5 mg/l (5,000 mg/m^3) in acute dust inhalation testing according to OECD and EC guidelines because of the strong binding forces between the aggregates to form agglomerates.

In the two tests with Cab-O-Sil EH-5 and M-5 only nominal concentrations (193,300 and 207,000 mg SiO_2/m^3) were used, without distinction between respirable and non-respirable dust. During the 1-hour exposure, initial vigorous cleansing activity and subsequent hypoactivity, abdominal respiration, gasping nasal exudation and closed eyes were observed. During the first 2 days after exposure all rats had dried crust-like material around the nose and mouth, and the fur appeared chalky to the touch. These conditions subsequently disappeared and all rats appeared normal throughout the remainder of the 14-day observation period (Cabot, 1972a,b).

Hydrophobic

The acute inhalation data on hydrophobic SAS are presented in Table 30.

Table 30: Acute inhalation toxicity of hydrophobic SAS to rats

Type/ Product name	Strain, number and sex	Surface area [a] (m^2/g)	Particle size MMAD [b] (µm)	Exposure duration (h), regime [c]	Concentration (mg/m^3)	LC_{50} (mg/m^3), remark	Reference	CoR [d]
Pyrogenic								
Aerosil R809	Wistar, 5 M, 5 F	80	1.4 - 1.8	4	1,094, 2,863, 3,730, 5,382	2,863 - 3,730	Degussa, 1984a	2b
Aerosil R972	Strain not specified, 5 M, 5 F	130	0.15	1	2,280	> 2,280	Cabot, 1982a	2b
Aerosil R974	Wistar, 5 M, 5 F	200	< 5 (56%) ≥ 7.7 (44%)	4	477	> 477	Degussa, 1983c	2b
Cab-O-Sil N70TS	SD, 5 M, 5 F	200	0.36	4	0 (control), 4,900	< 4,900 All died at 4,900	Cabot, 1981d	2b
Cab-O-Sil N70TS	SD, 5 M, 5 F	200	0.54	4	0 (control), 2,190	< 2,190 All died at 2,190	Cabot, 1981e	2b
Cab-O-Sil N70TS	SD, 5 M, 5 F	200	0.48	1	0 (control), 1,260, 2,830, 6,280	1,260 - 2,830	Cabot, 1982b,c	2b
Cab-O-Sil silane-treated [e]	Wistar, 10 M [f]	Not specified	Not specified	6	250 (nominal)	> 250	Cabot, 1963b	2c
Cab-O-Sil ST22 [g]	Albino rat, strain not specified, 10 M	Not specified	Not specified	1, not stated	670, 690, 710, 1,540, 3,150	> 3,150	Cabot, 1970b	3a

Table 30: Acute inhalation toxicity of hydrophobic SAS to rats (cont'd)

Type/ Product name	Strain, number and sex	Surface area (m^2/g)	Particle size MMAD (µm)	Exposure duration (h), regime	Concentration (mg/m^3)	LC_{50} (mg/m^3), remark	Reference	CoR
Pyrogenic (cont'd)								
Cab-O-Sil TS610	Wistar, 5 M, 5 F	130	1.175 -1.275	4	210, 540, 2,100	450	Cabot, 1994a	1b
Cab-O-Sil TS530	Wistar, 5 M, 5 F	300	0.95 - 2.15	4	90, 840	90 - 0.840	Cabot, 1994b	1b
HDK SKS130	SD, 5 M, 5 F	130	< 0.2	4	350, 770, 2,530, 5,300	1,650	Wacker, 1996b	1a
HDK SKS130	SD, 5 M, 5 F	130	7.2 - 7.7	4, nose-only	900, 2,200 [h]	> 2,200 [h]	Wacker, 1996c	1a
HDK SKS300	SD, 5 M, 5 F	300	< 0.1	4	90, 350, 5,000	90	Wacker, 1996d	1a
HDK SKS300	SD, 5 M, 5 F	300	7 - 7.1	4, nose-only	400, 600	500	Wacker, 1996e	1a
HDK SKS300 VI	SD, 5 M, 5 F	300	< 0.4	4	80, 340, 1,200, 5,000	800	Wacker, 1996f	1a
HDK SKS300 VI	SD, 5 M, 5 F	300	6.3 - 7.7	4, nose-only	400, 700, 2,000	600	Wacker, 1996g	1a
J-DCA TX104	SD, 3 M, 3 F	300	1 - 5 (83%) 5 - 100 (17%)	4	120, 400, 1,370, 3,360	660	Dow Corning, 1972	2b

[a] Referring to the surface of the hydrophilic base silica (BET)
[b] Mass median aerodynamic diameter (method: cascade impactor)
[c] Whole-body, unless stated otherwise
[d] Code of reliability (Appendix A)
[e] Treating agent not stated; actual identity of this product remains unclear
[f] Same test and results in mice (Swiss, 10 M) and guinea pigs (English short hair, 10 M)
[g] Aminopropylsilane-treated pyrogenic SAS
[h] 4/10 died at this (maximal attainable) concentration

With hydrophobic SAS types, higher respirable dust concentrations with lower MMADs can be achieved, mainly due to the lower binding forces between the particles (Section 2.5.8). This may explain the mortality observed in some of the studies (Table 30).

Sprague-Dawley rats were exposed to HDK SKS130 by inhalation of concentrations of 350, 770, 2,530 or 5,300 mg $SiO2/m^3$ for 4 hours. Combined sex mortality was 0, 0, 100 and 100%, respectively. At necropsy, severe red discoloration of the lungs was observed in all animals that had died during exposure (Wacker, 1996b). An additional test with the same SAS with higher MMAD was carried out. Two groups of rats were exposed for 4 hours to concentrations of 900 and 2,200 mg/m^3. No mortality was observed at 900 mg/m^3; at 2,200 mg/m^3 combined sex mortality was 40%. At necropsy, the animals that had died at 2,200 mg/m^3 exhibited severe discoloration of the lungs; all other animals were within normal limits. Of the animals exposed to 900 mg/m^3, 1 male and 2 females showed trace red discoloration of the lungs (Wacker, 1996c). Similar results were observed with HDK SKS300 and SKS300 VI (Wacker, 1996 d-g). These results are an indication that only the number of particles (surface area) is responsible for the observed effects.

Wistar rats were exposed to Cab-O-Sil TS610 concentrations of 210, 540 and 2,100 mg/m^3 for 4 hours, followed by 14 days of observation (Cabot, 1994a). At the highest concentration, all animals died within 2.5 hours of exposure with pre-death signs of few faeces, closed eyes, wetness and red staining of the nose/mouth area, laboured breathing, respiratory distress and hunched position. Necropsy findings included eye opacity, lungs larger than normal with red areas, and white material in the nasal turbinates. At the middle concentration (540 mg/m^3), 7 out of 10 animals died during exposure. During exposure, closed eyes, red staining of the nose/mouth area, fur coated with test substance, laboured breathing, respiratory distress and hunched position were noted. After exposure, the rats showed signs of lethargy, piloerection, dyspnoea, ptosis, few faeces, eyes crusting/lachrymation, unkempt appearance, wetness of the anogenital area and opaque. From days 4 to 14, all surviving rats appeared normal. Body weights in the surviving females decreased on day 7 but had recovered by day 14. Necropsy findings in the animals that had died included wetness of the anogenital area, opaque eyes, lungs larger and darker than normal with red areas, white material in the nasal turbinates and red areas in the intestines. Necropsy findings in the survivors included lungs darker than normal with red and white areas. At the lowest concentration (210 mg/m^3), all animals survived. During exposure, closed eyes, laboured breathing, licking inside of mouth and laying on back were noted in one or more animals. During the post exposure period, sporadic instances of few faeces, anorexia, chromodacryorrhoea, laboured breathing, wetness of the nose/mouth area and diarrhoea were observed. Transient decreases in body weight gain were noted. At necropsy, the lungs of all animals were darker than normal and had white and red areas (Cabot, 1994a). Similar results were observed with Cab-O-Sil TS530 (Cabot, 1994b).

The inhalation toxicity of Aerosil R974 was studied in Wistar rats by exposing them to the maximum attainable concentration of 477 mg/m^3 for 4 hours, followed by 14 days observation. Exposure resulted in a transient loss of body weight during the first 2 days of the observation period. Thereafter the animals gained weight in a normal way. No mortality occurred during the test. No abnormalities were found during gross pathological examination (Degussa, 1983c).

Degussa (1964a) and Cabot (1982d) reported that the SASs tested had completely occluded some of the smaller bronchioles at 40 to 80 (Aerosil R972) and 2,190 mg/m^3 (N70TS). Additionally, extravasation of blood was observed. These effects were seen as an indication of suffocation (Degussa, 1964a). The adverse effects in these studies appear to be primarily due to the physical presence of the test material rather than to a direct toxic effect of the substance.

Rats, mice and guinea pigs exposed to SAS (silane-treated Cab-O-Sil) at a concentration of 250 mg/m^3 for 6 hours showed preening in all species, hunching in rats, and occasional prostration among mice and rats; the response of the guinea pigs was not remarkable. No deaths were observed among mice. One guinea pig died after 250 minutes of exposure and one rat died 1 day after exposure. These deaths were considered coincidental to the inhalation of SAS. Only the occurrence of consolidation, seen in the lungs of 2 of 9 guinea pigs, was considered to be associated with an effect of the compound. No significant gross pathological changes were noted in surviving animals that could be attributed to inhalation of SAS (Cabot, 1963b).

8.1.4 Summary and evaluation

Numerous acute inhalation toxicity studies have been conducted on both hydrophilic and hydrophobic SAS. For hydrophilic SASs, LC_{50} values are higher than the highest technically achievable concentrations. The mortality observed with hydrophobic SAS is due to suffocation associated with the extremely high particle numbers administered and not with any intrinsic toxicity of the SAS tested.

In all of the acute inhalation tests where particle size data are available, the silica tested differs significantly from the commercial SAS product, based on particle size distribution. This is due to the experimental design that causes a significant reduction of the particle size, so that nearly 100% of the particle fraction has a MMAD below 10 µm (respirable, alveolar particle fraction). It is the alveolar fraction that is responsible for the observed adverse effects, including suffocation and lung overload due to poor dust clearance mechanisms.

In contrast to the particle size distribution of SASs used in acute inhalation animal tests, only a minor fraction (less than 1%) of commercially available SAS types has been measured to be respirable (alveolar fraction < 10 µm MMAD), using test method EN/DIN 481 (Stintz and

Heinemann, 2001) (Section 2.5.7). Using the same method, more than 99% of the particle fraction of the commercial SASs has an MMAD in excess of 90 µm, which will only reach the upper airways (nasal passages and throat) or not be inhaled at all. Thus, the available tests do not represent the toxicological behaviour of the commercial SAS product and are, therefore, not relevant for hazard assessment.

One of the tests described above was a limit test for acute inhalation toxicity. The substance was administered at the technically maximum attainable concentration of 477 mg/m^3 for 4 hours. The MMAD was 2.9 µm, which, although significantly smaller, was the most similar to the commercial product of all SASs tested. No mortality was observed and the LC_{50} value was higher than 477 mg/m^3.

In conclusion, the experimental design for acute inhalation studies with SAS requires the application of high shear stress in order to warrant a homogeneous particle distribution and generation of the highest possible fraction of fine particles that are capable of migrating to the peripheral region of the lung. In such studies, nearly 100% of the particle size distribution is below 10 µm in diameter and therefore able to migrate to the peripheral region of the lung.

In contrast, under occupational exposure conditions, shear forces are not or are no longer operative. Under such conditions, commercial SASs are composed of agglomerates (> 99% of particles > 90µm in diameter) and therefore not respirable or inhalable.

8.2 Skin, respiratory tract and eye irritation, sensitisation

8.2.1 Skin irritation

SAS skin irritation data are detailed in Table 31.

Table 31: Skin irritation studies on SAS in rabbits

Type/ Product name	Number of animals	Exposure conditions	Result	Reference	CoR [a]
Hydrophilic					
Pyrogenic					
Aerosil 200	12	Occlusive application of 500 mg as a 12% solution in MEC [b] to intact/abraded skin for 24 h	No signs of irritation	Degussa, 1978a	1b
Cab-O-Sil M5	6	Occlusive application of 500 mg in 3 ml saline to intact/abraded skin for 24 h	No signs of irritation on intact sites; at 24 h, very slight erythema (score 1) on abraded sites in 3 animals	Cabot, 1978	1b
Cab-O-Sil M5	6	Occlusive application of 500 mg moistened with saline to intact/abraded skin for 24 h	Very slight erythema (score 1) at 1 intact site in 1 animal at 24 h; very slight to well-defined erythema on abraded sites. No signs of irritation at 72 h at all sites	Cabot, 1981f	1b
Precipitated					
Sident 9	3	Occlusive application of 500 mg to intact skin for 4 h	No signs of irritation	Degussa, 1991b	1a
Sipernat 22	12	Occlusive application of 500 mg as a 23% solution in MEC to intact/abraded skin for 24 h	No signs of irritation	Degussa, 1978b	1b
Tixosil 375	6	Occlusive application of 33 mg to intact/abraded skin for 24 h	Very slight erythema (score 1) on 4 abraded sites and 5 intact sites at 24 h	Rhône-Poulenc, 1992a	1c
Tixosil 63	6	Occlusive application of 190 mg to intact/abraded skin for 24 h	Very slight erythema (score 1) on 3 abraded sites and 4 intact sites at 24 h	Rhône-Poulenc, 1992b	1c

Table 31: Skin irritation studies on SAS in rabbits (cont'd)

Type/ Product name	Number of animals	Exposure conditions	Result	Ref	CoR [a]
Precipitated (cont'd)					
TS100	12	Occlusive application of 500 mg as a 50% solution in olive oil to intact/abraded skin for 24 h	No signs of irritation	Degussa, 1978c	1b
Ultrasil VN3	12	Occlusive application of 500 mg to abraded/intact skin for 24 h	No signs of irritation	Degussa, 1973	1b
Zeofree 80	6	Occlusive application of 500 mg to intact skin for 24 h	No signs of irritation	JM Huber, 1973	1b
Gel					
Syloid 244 [c]	8	Occlusive application of 20 mg to 2 intact/abraded skin for 24h	No signs of irritation	Grace, 1974b	1b
Hydrophobic					
Pyrogenic					
Aerosil R972	12	Occlusive application of 500 mg as a 6% solution in MEC to intact/abraded skin for 24 h	No signs of irritation	Degussa, 1978d	1b
Cab-O-Sil N70TS [d]	6	Occlusive application of 500 mg moistened with PEG [e] to intact/abraded skin for 24 h	No signs of irritation	Cabot, 1981g	1b
Cab-O-Sil silane treated	6	Occlusive application of 500 mg moistened with corn oil to intact/abraded skin for 24 h	No signs of irritation	Cabot, 1963a	1b

Table 31: Skin irritation studies on SAS in rabbits (cont'd)

Type/ Product name	Number of animals	Exposure conditions	Result	Ref	CoR
Pyrogenic (cont'd)					
Cab-O-Sil ST22 [f]	6	Occlusive application of 500 mg in 2 ml water to intact/abraded skin for 24 hours	No signs of irritation	Cabot, 1970c	1b
Cab-O-Sil TS500	6	Semi-occlusive application of 500 mg to intact skin for 4 h	No signs of irritation	Cabot, 1995d	1a
Cab-O-Sil TS530	6	Semi-occlusive application of 500 mg to intact skin for 4 h	No signs of irritation	Cabot, 1995e	1a
Cab-O-Sil TS610	6	Semi-occlusive application of 500 mg to intact skin for 4 h	No signs of irritation	Cabot, 1995f	1a
HDK SKS300	6	Semi-occlusive application of 500 mg to intact skin for 4 h	No signs of irritation	Wacker, 1996h	1a
Precipitated					
Sipernat D17	12	Occlusive application of 500 mg as a 50% solution in olive oil to intact/abraded skin for 24 h	No signs of irritation	Degussa, 1978e	1b

[a] Code of reliability (Appendix A)
[b] Methyl ethyl cellulose
[c] Also known as FDA 71-48
[d] Current name Cab-O-Sil TS720
[e] Polyethylene glycol
[f] Aminopropylsilane-treated pyrogenic SAS

Application of various SASs to the skin of rabbits for up to 24 hours generally produced no signs of irritation. Occasionally, very slight erythema (primary irritation index 0.25 - 0.44 out of 8 maximum) has been reported; such effects were rapidly reversible.

In all, SAS is not considered a skin irritant.

8.2.2 Respiratory tract irritation

No data are available.

8.2.3 Eye irritation

The available eye irritation studies on SAS are summarised in Table 32.

Table 32: Eye irritation studies on SAS in rabbits

Type/ Product name	Number of animals	Exposure conditions	Result	Reference	CoR [a]
Hydrophilic					
Pyrogenic					
Aerosil 200	8	Instillation of 100 mg; eyes rinsed after 5 min (3) or not rinsed (5)	No signs of irritation	Degussa, 1978f	1b
Cab-O-Sil fluffy [b]	3	Instillation of 3 mg	Slight to mild erythema, disappeared at 48 h	Cabot, 1958a	3a
Cab-O-Sil M5	6	Instillation of 3.5 mg	Slight conjunctival erythema or chemosis in some animals at 24, 48 and 72 h: mean score 0.6 and 0.1, respectively; transient corneal opacity observed in 2 animals at 4 h	Cabot, 1978	1b
Cab-O-Sil M5	9	Instillation of 100 mg; eyes rinsed at 30 s (3) not rinsed (6)	No signs of irritation in washed eyes at 24, 48 and 72 h: mean score 0.15; very slight conjunctival erythema up to 48 h	Cabot, 1981h	1b
Precipitated					
Sident 9	3 3	Instillation of 40 mg Instillation of 100 mg	No signs of irritation at 40 mg. At 100 mg: slight redness at 24, 48 and 72 h: mean score 0.7; reversed by day 4	Degussa, 1991c	1a
Sipernat 22	8	Instillation of 100 mg; eyes rinsed after 5 min (3) or not rinsed (5)	No signs of irritation	Degussa, 1978g	1b

Table 32: Eye irritation studies on SAS in rabbits (cont'd)

Type/ Product name	Number of animals	Exposure conditions	Result	Reference	CoR
Precipitated (cont'd)					
TS100	8	Instillation of 0.1 ml of 50% dilution in olive oil; eyes rinsed within 5 min (3) or not rinsed (5)	No signs of irritation in washed eyes; very slight erythema (score 1) observed up to 24 h after application	Degussa, 1978h	1b
Zeo 49	9	Instillation of 100 mg; eyes rinsed at 4 s (3) or not rinsed (6)	No signs of irritation	JM Huber, 1978i	1b
Zeofree 80	6	Instillation of 100 mg, 0.2 ml of 50% slurry	No signs of irritation	JM Huber, 1973	1b
Zeosyl 113	9	Instillation of 100 mg; eyes rinsed at 4 s (3) or not rinsed (6)	No signs of irritation	JM Huber, 1978j,k	1b
Zeofree 153	9	Instillation of 100 mg; eyes rinsed at 4 s (3) or not rinsed (6)	No signs of irritation	JM Huber, 1978l,m	1b
Zeosyl 200	9	Instillation of 100 mg; eyes rinsed at 4 s (3) or not rinsed (6)	No signs of irritation	JM Huber, 1978n,o	1b
Gel					
Syloid 244 [c]	9	Instillation of 9 mg; eyes rinsed at 2 s (3), 4 s (3) or not rinsed (3)	No signs of irritation	Grace, 1975a	1b

Table 32: Eye irritation studies on SAS in rabbits (cont'd)

Type/ Product name	Number of animals	Exposure conditions	Result	Reference	CoR [a]
Hydrophobic					
Pyrogenic					
Aerosil R972	8	Instillation of 100 mg; eyes rinsed after 5 min (3) or not rinsed (5)	No signs of irritation	Degussa, 1978i	1b
Cab-O-Sil N70TS [d]	9	Instillation of 25 mg; eyes rinsed (3) 30 s or not rinsed (6)	No signs of irritation in washed eyes; 2 unwashed eyes showed slight erythema for 24 h after application (mean score 0.1 at 24, 48 and 72 h)	Cabot, 1981i	1b
Cab-O-Sil silane treated [e]	9	Instillation of 3 mg; eyes rinsed at 2 s (3), 4 s (3) or not rinsed (3)	Transient slight to moderate conjunctival erythema observed at 1 and 4 h after application; disappeared within 24 h	Cabot, 1963a	1b
Cab-O-Sil TS500	9	Instillation of 10 mg; eyes rinsed 30 s (3) or not rinsed (6)	No signs of irritation	Cabot, 1995g	1a
Cab-O-Sil TS530	9	Instillation of 10 mg; eyes rinsed 30 s (3) or not rinsed (6)	No signs of irritation	Cabot, 1995h	1a
Cab-O-Sil TS610	9	Instillation of ≈ 10 - 20 mg; eyes rinsed 30 s (3) or not rinsed (6)	No signs of irritation in washed eyes; 2 unwashed eyes showed slight erythema for 24 h after application (mean score 0.1 at 24, 48 and 72 h)	Cabot, 1995i	1a
Cab-O-Sil TS720	9	Instillation of 6 mg; eyes rinsed at 2 s (3), 4 s (3) or not rinsed (3)	No signs of irritation	Cabot, 1970c	1b
HDK SKS300	3	Instillation of 100 mg; eyes rinsed at 4 s (3) or not rinsed (6)	No signs of irritation	Wacker, 1996g,h	1a

Table 32: Eye irritation studies on SAS in rabbits (cont'd)

Type/ Product name	Number of animals	Exposure conditions	Result	Reference	CoR [a]
Precipitated					
Sipernat D17	8	Instillation of 0.1 ml of 50% dilution in olive oil; eyes rinsed within 5 min (3) or not rinsed (5)	No signs of irritation in washed eyes; very slight erythema (score 1) observed up to 48 hours after application	Degussa, 1978j	1b

[a] Code of reliability (Appendix A)
[b] Same as or very similar to Cab-O-Sil M5
[c] Also known as FDA 71-48
[d] Current name Cab-O-Sil TS720
[e] The actual identity of this product remains unclear

Instillation of SAS into the rabbit eye resulted in no or slight irritation; the effect was completely and rapidly reversible. After washing the eyes, no irritation was observed.

In all, SAS is not considered an eye irritant.

8.2.4 Sensitisation

No data are available.

Based on its structure and physico-chemical properties, SAS is not expected to cause skin sensitisation.

8.2.5 Summary and evaluation

SAS is not a skin irritant. The very slight erythema seen in some studies was rapidly reversible.

The inflammation observed with SAS in repeated inhalation studies (Section 8.3.3) could be related to respiratory irritation. However, no specific data have been reported for this endpoint.

The slight eye irritation seen with SAS in some tests was completely and rapidly reversible. After washing the eyes, there was no irritation. In all, SAS is not an eye irritant.

There are no data for skin sensitisation of SAS, but no such effect is expected.

8.3 Repeated dose toxicity

8.3.1 Oral

An overview of oral toxicity studies following repeated dosage of hydrophilic and hydrophobic SASs is presented in Table 33.

Table 33: Repeated oral toxicity of SAS to rats

Type/ Product name	Strain, number and sex/group	Exposure route and duration	Dose		Results/remarks	Reference	CoR [a]
			(% of diet)	(mg/kgbw/d) [b]			
Hydrophilic							
Pyrogenic							
Cab-O-Sil fluffy [c]	Charles River, 15 M, 15 F	Diet, 13 wk	0, 1, 3, 5 3 cosmetic talc: +ve control	(0, 1,000, 3,000, 5,000) (3,000 talc)	No gross signs of systemic toxicity; no effect on growth rate, food consumption or survival; no gross or microscopic pathological changes	Cabot, 1958b	3a
Precipitated							
FK700	Strain and number not specified, F	Gavage, 4 wk	–	0, 1,500	Body weight gain, food consumption and behaviour not influenced	Degussa, 1968b	3a
Sipernat 22	Wistar, 10 M, 10 F	Diet, 13 wk	0, 0.5, 2, 8	(0, 250, 1,000, 4,000)	Increased food intake associated with a decreased food efficiency in the top dose, mean absolute and relative weight of the caecum was increased in the top dose, gross and microscopic pathological examination did not reveal any treatment related abnormality; NOEL [d] = 4,000 mg/kgbw/d	Degussa, 1981	2c
Gel							
Syloid 244 [e]	SD, 5 M, 5 F	Diet, 2 wk	0, 10 5, d 1-10 20, d 11 - 14	(0, 16,500) (5,800) (24,200)	No clinical symptoms or other findings (food or water consumption, body weight gain, behaviour)	Grace, 1974c	2c

Table 33: Repeated oral toxicity of SAS to rats (cont'd)

Type/ Product name	Strain, number and sex/group	Exposure route and duration	Dose		Results/remarks	Reference	CoR [a]
			(% of diet)	(mg/kgbw/d)			
Gel (cont'd)							
Syloid 244	CD, 5 M, 5 F	Diet, 6 months	0, 3.2, 10	(M 2,170, 7,950) (F 2,420, 8,980)	No effects on physical appearance, food consumption, growth, survival, haematology, clinical-chemistry; no gross pathological or microscopic findings	Grace, 1975b	2c
Sol							
Ludox 30% SiO_2	Strain not specified, 6 M	Diet (5 ×/wk), 2 wk	–	7,500	All animals lost weight during treatment, but gained over the weekend and during post observation period; no significant effects on organs	DuPont, 1955	3a
Silicone dioxide (not specified)	CD, number not specified, M, F	Diet, 4 wk	–	0, 800 [f]	No treatment related changes (clinical symptoms, urine and blood parameters, necropsy or histopathology)	Newberne and Wilson, 1970	3a
Hydrophobic							
Pyrogenic							
Aerosil R972	Wistar, 5 M, 5 F	Diet, 5 wk; 8 wk high dose	–	0, 500, 1,000, 2,000 (d 14: stepwise increase to 16,000 [g])	At 2,000 mg/kgbw, pronounced reduction of bw associated with decreased food intake. No significant modification of biological parameters or macroscopic findings. Microscopic examination of the liver revealed severe atrophy in the liver epithelium. NOAEL assumed to be 1,000 mg/kgbw/d	Degussa, 1964b,c	2e
Aerosil R972	Wistar, 20 M, 20 F	Gavage (5 ×/wk), 6 months	–	500	No clinical symptoms, no macroscopic findings	Degussa, 1963, 1965a,b	2e

Table 33: Repeated oral toxicity of SAS to rats (cont'd)

Type/ Product name	Strain, number and sex/group	Exposure route and duration	Dose		Results/remarks	Reference	CoR [a]
			(% of diet)	(mg/kgbw/d)			
Pyrogenic (cont'd)							
Cab-O-Sil silane-treated [h]	Charles River, 10 M, 10 F	Diet, 13 wk	0, 1, 2, 4	(0, 1,000, 2,000, 4,000)	No effect on physical appearance, behaviour, growth, survival, clinical studies or gross pathology; no cytopathological changes; minimal change in the thyroid gland morphology in M at 2,000 and 4,000 mg/kgbw	Cabot, 1970d	2e

[a] Code of reliability (Appendix A)
[b] Converted values in parenthesis, calculated with default factor of 10
[c] The same as or very similar to Cab-O-Sil M5
[d] Reported as NTEL, no toxic effect level
[e] Also known as FDA 71-48
[f] Same result in dogs (beagle, 9 M, 8 F) following same protocol
[g] 25% of daily food intake
[h] Treating agent not stated; actual identity of this product remains unclear

Hydrophilic

Charles River rats were fed with hydrophilic SAS (Cab-O-Sil fluffy) at levels of 1, 3 or 5% in the diet (equivalent to daily doses of ≈ 0, 1,000, 3,000 or 5,000 mg/kgbw) for 90 days. Rats received the diet alone or with a dietary level of 3% cosmetic talc (3,000 mg/kgbw/d) served as negative and positive controls, respectively. There were no gross signs of systemic toxicity that could be associated with the dietary ingestion of SAS. Growth rates, food consumption, and survival for the dose groups were comparable to control groups. There was no treatment related increase in silica content of liver, kidney, spleen, blood, and urine after 45 and 90 days of dietary feeding. No gross pathological changes could be associated with SAS ingestion. Microscopic pathological evaluation after 90 days revealed no significant findings (Cabot, 1958b).

The toxicity of Sipernat 22 was evaluated in a 13-week feeding study in Wistar rats, which received SAS in the daily diet at 0 (control), 0.5, 2 and 8% (≈ 0, 250, 1,000, 4,000 mg/kgbw/d). General condition, behaviour, survival, body weights, water intake and haematological and urinary parameters were not adversely affected at any dose. Increased food intake associated with decreased food efficiency occurred in the top-dose group. These changes were attributed to the high amount of (inert) SAS in the diet. Other slight changes were not of toxicological significance. Gross and microscopic pathological examination did not reveal any abnormality that could be ascribed to the ingestion of SAS. The highest dose (8% in the diet or 4,000 mg/kgbw/d) was considered to be a no-observed effect level (NOEL) (Degussa, 1981).

Hydrophobic

Hydrophobic SAS (Aerosil R972) was administered in the diet of Wistar rats for 5 weeks at dose levels of 0 (control), 500, or 1,000 mg/kgbw/d, and for 8 weeks at 2,000 mg/kgbw/d. Because the animals tolerated 2,000 mg/kgbw, the high dose was elevated to 4,000 mg/kgbw after 2 weeks, 8,000 mg/kgbw/d after another 2 weeks, and finally 16,000 mg/kgbw/d. Only after this stepwise increase to 16,000 mg/kgbw/d (≤ 5% of food) were treatment-related effects observed. Clinical signs of toxicity included shyness, dirty fur, reduced activity, cachexia, and haemorrhages in the mucous membranes of the eyes and nose. Two males and 2 females died with severe cachexia in week 8. The dose of 16,000 mg/kgbw/d caused a pronounced reduction to the body weight, concomitant with decreased food intake. (It should be noted that the acceptance of the treated diet was markedly reduced and that the fraction of the test substance in the diet amounted to approximately 25% by weight. Malnutrition can cause changes similar to those found, such as weight loss, cachexia, and decrease of the glycogen content in the liver cells.) No significant changes were observed in the examined haematological parameters or after macroscopic evaluation of the treated animals. Microscopic examination of the livers from rats consuming the highest doses revealed severe atrophy in the liver epithelium. (It is not clear, therefore, whether

the test substance in a very high dose, the reduced food intake, or the two combined caused the described effects.) To a lesser degree these changes (atrophy of the liver epithelium, decrease of the basophilic nuclei and of the glycogen content) were sporadically seen (two females) in the mid dose group (1,000 mg/kgbw/d). The authors suggested that the findings in the mid dose group in the liver could be the result of infection, observed frequently in rats which were used in this laboratory (Degussa, 1964b,c). The no-observed adverse effect level (NOAEL) is assumed to be 1,000 mg/kgbw/d.

When hydrophobic SAS (Aerosil R972) was administered by gavage to Wistar rats at doses of 500 mg/kgbw/d for 6 months, there were no clinical symptoms or macroscopic findings (Degussa, 1963, 1965a,b). After 4.5 months, 5 animals/sex were used for a fertility test (Section 8.6.1).

Administration of silane-treated Cab-O-Sil to rats in the diet for 90 days did not cause compound-related, cytopathological changes. Morphologically, the thyroid glands revealed minimal smaller follicles lined by slightly taller epithelial cells in male rats that received 2 and 4% (2,000 and 4,000 mg/kgbw/d). Although this difference in the male thyroids might reflect a compound-related change, the magnitude and statistical significance were minimal. The female thyroids were comparable to controls (Cabot, 1970d).

Summary

The data which are available concerning repeated dose toxicity confirm the absence of significant toxicity by oral routes of exposure.

8.3.2 Dermal

Only one report concerning toxicity following repeated dermal application of SAS was available (Table 34).

Table 34: Repeated dermal toxicity of hydrophilic SAS in the rabbit

Type/ Product name	Strain, number and sex	Exposure regime	Dose (mg/kgbw/d)	Results/remarks	Reference	CoR
Pyrogenic						
Cab-O-Sil fluffy [a]	Albino, strain not specified, 2 M, 2 F	18 h/d, 5d/wk, 3 wk, intact or abraded skin	0, 5,000, 10,000 10,000 +ve control: cosmetic talc	No evidence of systemic toxicity or of gross or microscopic pathology; no significant difference in dermal irritation between control and dose groups	Cabot, 1958c	3a

[a] Same as or very similar to Cab-O-Sil M5

The dermal toxicity and irritative potential of hydrophilic SAS (Cab-O-Sil fluffy) was evaluated in the rabbit following a series of 15 applications to the intact and abraded skin. An aqueous solution of methylcellulose and cosmetic talc were tested as negative and positive controls, respectively. There was no evidence of systemic toxicity or of gross or microscopic pathological changes that could be associated with the application of methylcellulose, cosmetic talc or SAS. The silica content of blood, urine, spleen, liver and kidney of treated animals was comparable to that of controls. Application of SAS and either control material produced mild dermal irritation consisting of erythema, stonia and desquamation. There appeared to be no significant difference between the positive and negative controls and animals treated with SAS (Cabot, 1958c).

In summary, the limited data that are available show no toxicity of SAS by the dermal route of exposure.

8.3.3 Inhalation

The available data on toxicity studies with hydrophilic and hydrophobic SAS following repeated inhalation, for up to 1 year or more, are summarised in Tables 35 and 36, respectively.

Hydrophilic

The data on repeated inhalation toxicity of hydrophilic SAS are discussed first (Table 35).

Table 35: Toxicity of hydrophilic SAS following repeated inhalation

Type/ Product name	Species, strain	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Pyrogenic							
Cab-O-Sil M5	Rat, Wistar	10 M, 6 M control 10 M, 6 M control, 1 or 3 months recovery	6 h/d, 5 d	0, 1.39, 5.41, 25.3	1.39 mg/m^3 had no significant effect. Incidence of pulmonary inflammation increased after exposure at the mid and high doses. Observed changes disappeared or tended to disappear during recovery	Arts and Kuper, 2003a	1a
Aerosil 200	Rat, Wistar	10 M, 10 F	6 h/d, 5 d/wk, 2 wk	0, 17, 44, 164	Signs of respiratory distress in all test groups. Body weight gain and food consumption reduced in M at 44 and 164 mg/m^3. Haematological parameters unremarkable. Concentration-related increase in absolute/relative lung weight. Lungs of several animals in all test groups discoloured, spotted, spongy or irregular surface. Mediastinal lymph nodes of several animals/groups enlarged. In lungs increased septal cellularity, alveolar interstitial pneumonia and early granulomata. Early granulomata also in mediastinal lymph nodes at 44 and 164 mg/m^3. NOAEL < 17 mg/m^3	Degussa, 1986a	1d

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species, strain	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Pyrogenic (cont'd)							
Aerosil 200	Rat, Wistar	70 M, 70 F	6 h/d, 5 d/wk, 13 wk	0, 1.3, 5.9, 31.0	At 31.0 mg/m^3, lung collagen content increased immediately after exposure, but did not return to control levels during 52 wk recovery. At 31.0 mg/m^3, alveolar macrophage accumulation, cellular debris, intra-alveolar polymorpho-nuclear neutrophils (PMNs) infiltration, alveolar bronchiolisation, increased septal cellularity, focal interstitial fibrosis, and cholesterol clefts occurred at varying times post exposure. At 1.3 mg/m^3, lung collagen content increased, alveolar macrophage accumulation, intra-alveolar PMN infiltration, and increased septal cellularity occurred, which returned to normal during recovery	Degussa, 1987; Reuzel *et al,* 1991	1b

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Pyrogenic (cont'd)							
Aerosil 200	Rat, Fischer 344	Not specified, M	6 h/d, 5 d/wk, 13 wk	50	Lung burden of silica significantly increased during exposure and declined rapidly during recovery to non-significant level at 32 wk. Changes in bronchio-alveolar lavage (BAL) fluid content compared to controls included increases in total cells, neutrophils, protein, lactate dehydrogenase (LDH) and β-glucuronidase. The percentage of alveolar macrophages decreased while the percentage of lymphocytes and viable cells remained unchanged compared to controls. Significant increase in terminal transferase dUTP nick-end-labelling (TUNEL)-staining was detected in macrophages and terminal bronchiolar epithelial cells indicating cytotoxicity. All parameters returned to control level after 8 months recovery period	Johnston *et al,* 2000	1b
Cab-O-Sil	Rat, Sprague-Dawley	80 M	6 h/d, 5 d/wk, 12 months	0, 6.9 respirable	Small numbers of macrophage cell aggregates present. Interstitial fibrosis observed, but was also seen in control animals	Groth *et al,* 1981	2
Cab-O-Sil	Guinea pig, Hartley	20 M	6 h/d, 5 d/wk, 12 months	0, 6.9 respirable	Small numbers of macrophage cell aggregates present	Groth *et al*, 1981	2

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Pyrogenic (cont'd)							
Cab-O-Sil	Monkey, Cynomolgus	10 M	5.5 h/d, 5 d/wk, 13 months	0, 6.9 respirable	Large numbers of macrophage cell aggregates present. Significant collagen and early nodular fibrosis evident. FVC, IC, TLC, CL, FEF_{75}, FEF_{90} decreased and RL and CV increased (abbreviations explained in text)	Groth *et al,* 1981	2
Pyrogenic (Dow Corning Silica)	Rat, Wistar	35 M + F (25 M + F recovery) 42 M + F control	6 h/d, 5 d/wk, 12 months (6 months)	53	High spontaneous death rate. Material cleared to the lymphatics, with associated formation of parenchyma nodules. Nodules consisted of chromophobic macrophages, plasma cells, reticulum, and collagen. Foamy macrophages accumulated in alveoli and alveolar ducts, with apparent fusion to form giant cells. Over time, giant cells degenerated, and emphysematous lesions became apparent. During recovery, pulmonary lesions steadily diminished, including emphysema	Schepers *et al,* 1957a	3

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Pyrogenic (cont'd)							
Pyrogenic (Dow Corning Silica)	Guinea pig, Saranac	45 M + F (37 M + F recovery) 80 M + F control	6 h/d, 5 d/wk, 12 or 24 months	53	Vacuolated cell aggregates at alveolar ducts/terminal bronchioles junction, infiltrating alveolar walls. With time, cellular masses atrophied and adjacent alveoli expanded, creating emphysematous lesions. Alveolar walls replaced by reticulum and collagen. During recovery, cellular aggregation and infiltration subsided, but focal fibrosis of alveolar walls and stenosis of alveolar ducts and bronchioles persisted. Emphysematous lesions decreased in upper lobes, but progressed in lower lobes	Schepers *et al,* 1957b	3
Pyrogenic (Dow Corning Silica)	Rabbit, New Zealand White	6 M + 4 F 50 M + F control	6 h/d, 5 d/wk, 12 months	53	Cellular masses filled alveolar spaces and infiltrated alveolar walls. Cellular nodules, consisting primarily of macrophages, evident in perivascular tissues. Abundant reticulum observed in association with nodules, along blood vessels, and in alveolar walls. Collagen deposition also evident. Emphysema and dilatation of alveolar ducts apparent. During recovery, cellular reactions and emphysema regressed, but some alveolar-wall collagen still evident	Schepers *et al,* 1957c	3

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Pyrogenic (cont'd)							
Non-crystalline, prepared from sodium silicate using alcohol; surface area 145 m^2/g	Rabbit, New Zealand White	Not stated	8 h/d, 5 d/wk, up to 27 months	0, 28.2, 134, 360	High spontaneous death rate. Dose-related elevated right and left ventricular pressure, partly reversible during recovery. Various radiographic/electrocardiographic changes, modified lung functions, haemolytic and electrolytic disturbances. Autopsy: congestive cardiac failure, emphysema and chemical pneumonitis prevalent in high dose group. Lesions disappeared after exposure ceased	Schepers, 1959	3
Precipitated							
Zeofree 80	Rat, CD	24 M	6 h/d, 3 d	0, 10, 100	Indices of pulmonary inflammation increased, and returned to normal by 8 d recovery	Warheit *et al,* 1995	1b
Zeosil 45	Rat, Wistar	10 M, 10 F 10/sex, 1 month recovery 10/sex, 3 months recovery	6 h/d, 5 d	0, 1.16, 5.39, 25.2	1.16 mg/m^3 had no effect. Incidence of pulmonary inflammation increased after exposure at the mid and high doses. Observed changes disappeared or tended to disappear during recovery.	Arts *et al*, 2003	1a
Not stated	Rat, Fischer 344	Not stated	6 h/d, 8 d	30	Inflammatory cells increased, which resolved by 5 or 12 d recovery. Lavagable protein and several lipids increased, but levels were normal by 5 d recovery	Low *et al,* 1985; Hemenway *et al*, 1986	4b

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Precipitated (cont'd)							
Sipernat 22S	Rat, Wistar	10 M, 10 F	6 h/d, 5 d/wk, 2 wk	0, 46, 180, 668	Signs of respiratory distress in all test groups. Body weight gain and food consumption reduced in M at 180 and 668 mg/m^3. Changes in haematological parameters not concentration-related. Concentration-related increase in absolute/relative lung weight. Lungs of several animals at 668 mg/m^3 spotted and swollen, irregular surface. In lungs of most M at 180 and 668 mg/m^3 and in all F/groups increased septal cellularity, alveolar interstitial pneumonia and accumulation of alveolar macrophages and particulates. Some of these changes also in mediastinal lymph nodes (same animals). Early granulomata in lungs at 668 mg/m^3 and in mediastinal lymph nodes at 180 and 668 mg/m^3, and in one M at 46 mg/m^3. NOAEL < 46 mg/m^3	Degussa, 1986b	1d
Sipernat 22S	Rat, Wistar	70 M, 70 F	6 h/d, 5 d/wk, 13 wk	0, 34.9	Lung collagen content increased immediately after exposure, and returned to control levels by 52 wk recovery. Alveolar macrophage accumulation occurred at varying times post exposure	Degussa, 1987; Reuzel *et al,* 1991	1b
Not stated	Mice, not stated	74 M + F, 75 control	10 min/h, 1 y	0, not stated	Incidence of primary lung tumours increased. Hyperplastic lymph node tissues were present, but lung fibrosis was absent. Apparent increase of pneumonia in exposed mice	Campbell, 1940	3a

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Precipitated (cont'd)							
Hi-Sil	Rat, Sprague-Dawley	80 M	6 h/d, 5 d/wk, 12 months	0, 6.9 respirable	Small numbers of macrophage cell aggregates present. Interstitial fibrosis observed, but was also seen in control animals.	Groth *et al,* 1981	2e
Hi-Sil	Guinea pig, Hartley	20 M	6 h/d, 5 d/wk, 12 months	0, 6.9 respirable	Small numbers of macrophage cell aggregates present.	Groth *et al,* 1981	2e
Hi-Sil	Monkey, Cynomolgus	10 M	5.5 h/d, 5 d/wk, 18 months	0, 6.9 respirable	Large numbers of macrophage cell aggregates present. Reticulin fibres and small amounts of collagen present. FVC and TLC decreased.	Groth *et al,* 1981	2e
Hi-Sil 233	Rat, Wistar	57 sex not stated (27 clearance), 50 control	8 h/d, 7 d/wk, 15 months (6 months)	126	25 to 37% died from viral pneumonia. Particle-filled macrophages accumulated in alveoli, bronchioles and lymphoid tissue	Schepers, 1981	3b
Hi-Sil 233	Rabbit, not stated	10 sex not stated (9 clearance), 50 control	8 h/d, 7 d/wk, 12 months (12 months)	126	Mild deposition of reticulin fibres occurred in alveolar walls, but there was no evidence of collagen formation	Schepers, 1981	3b
Hi-Sil 233	Guinea pig, not stated	82 sex not stated (34 clearance), 100 control	8 h/d, 7 d/wk, 24 months (12, 15, 21 months)	126	Histological changes were reversible and paralleled lung clearance of particles	Schepers, 1981	3b

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Precipitated (cont'd)							
Not stated	Monkey, Rhesus (*Macaca mulatta*)	5 F, 15 control	8 h/d, 7 d/wk, 12 months	15	Alveolar septa degenerated, and alveolar wall sclerosis led to emphysema, followed by *cor pulmonale*. Tracheobronchial lymph nodes became enlarged, but were not fibrotic. No evidence of pulmonary fibrosis	Schepers, 1962	3b
Gel							
Syloid 74	Rat, Wistar	10 M, 6 M control 10 M 1 month recovery 10 M 3 months recovery	6 h/d, 5 d	0, 0.94, 5.13, 25.1	At 0.94 mg/m^3 no significant effect. Incidence of pulmonary inflammation increased after exposure at the mid and high doses. Observed changes disappeared or tended to disappear during recovery	Arts and Kuper, 2003b	1a
Silica G	Rat, Sprague-Dawley	80 M	6 h/d, 5 d/wk, 12 months	0, 9.4 respirable	Small numbers of macrophage cell aggregates present. Interstitial fibrosis observed, but was also seen in control animals	Groth *et al,* 1981	2e
Silica G	Guinea pig, Hartley	20 M	6 h/d, 5 d/wk, 12 months	0, 9.4 respirable	Small numbers of macrophage cell aggregates present	Groth *et al*, 1981	2e
Silica G	Monkey, Cynomolgus	10 M	5.5 h/d, 5 d/wk, 13 months	0, 9.4 respirable	Large numbers of macrophage cell aggregates present. Reticulin fibres and small amounts of collagen present. CL, FEF_{75}, FEF_{90}, N_2 washout decreased and RL increased (abbreviations explained in text)	Groth *et al*, 1981	2e

Table 35: Toxicity of hydrophilic SAS following repeated inhalation (cont'd)

Type/ Product name	Species (strain/sex)	Number of animals/group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Sol							
Ludox	Rat, CD	18 M	6 h/d, 5 d/wk, 2 or 4 wk	0, 10, 50, 150	10 mg/m^3 had no effect. 50 and 150 mg/m^3 increased markers of lung injury and inflammation, caused minimal defects in alveolar macrophage function, and increased cell turnover. Most biochemical parameters and cell proliferation returned to control values by 3 months recovery	Warheit *et al,* 1991, 1995	1d
Ludox	Rat, CD	25 M	6 h/d, 5 d/wk, 28 d	0, 10, 50, 150	10 mg/m^3 had no effect. 50 and 150 mg/m^3 caused PMN infiltration, Type II cell hyperplasia, and tracheal and mediastinal lymph nodes enlargement. Pulmonary effects decreased, and particles translocated to lymph node tissues by 3 months post exposure. 150 mg/m^3 caused nodule formation, but collagen fibre deposition was minimal. Nodules consisted of intra-alveolar epithelioid cell granulomas into the interstitium and were not due to interstitial fibroblast proliferation.	Lee and Kelly, 1992, 1993	1d

Pyrogenic

In a short-term inhalation study, male Wistar rats were exposed to hydrophilic, pyrogenic SAS (Cab-O-Sil M5) at concentrations of 0 (control), 1.39, 5.41 or 25.3 mg SiO_2/m^3 for 5 days. Additional control and treated rats were allowed to recover for 1 or 3 months. (Crystalline silica, cristobalite, was included as positive reference as reported by Arts *et al*, 2003 below.) The MMAD of 1.2 to 1.3 µm on day 1 to 3 apparently increased to 2.2 to 3.5 µm on day 4 and 5, due to a shortened tube connecting exposure chamber and measurement apparatus (Note: i.e. the aerosol was potentially 100% respirable). There were no deaths or exposure-related abnormalities. Besides standard clinical observation and histopathological inspection, the most sensitive cell and biochemical parameters for the elucidation of an inflammatory tissue reaction were applied including white blood cell count, viability and cell differentiation as well as determination of biochemical parameters in the bronchio-alveolar lavage (BAL) fluid. The incidence of pulmonary inflammation increased after exposure to SAS at 5.41 and 25.3 mg/m^3. The effects disappeared almost completely during recovery, with some macrophage aggregates left in the tracheobronchial lymph nodes. The presence of macrophages in the lungs at 25.3 mg/m^3 was considered a normal response to particulate exposure. Clear signs of reversibility were noted. No effects were seen at 1.39 mg/m^3. The nominal concentration of 1 mg/m^3 was the NOAEL (Arts and Kuper, 2003a). The authors reported similar studies with precipitated SAS and gel (below).

Wistar rats were exposed to Aerosil 200 at concentrations of 0 (control), 1.3, 5.9 or 31.0 mg SiO_2/m^3 for 13 weeks. Additional animals were exposed to crystalline silica (quartz) at 58.5 mg/m^3. The MMAD was not determined, but there was a wide range for the geometric agglomerate/aggregate size distribution (1 - 120 µm). Animals were killed immediately after the exposure and at 13, 26, 39 and 52 weeks post exposure. In males exposed to 31.0 mg/m^3, the total silicon content of lungs and tracheobronchial lymph nodes was approximately 0.2 mg (0.43 mg SiO_2) immediately after exposure, declined at 13 weeks, increased again (no explanation given by authors) at 26 weeks, and became undetectable by 39 weeks of recovery. In females, the silicon content of lungs and lymph nodes was also approximately 0.2 mg immediately after exposure, then declined steadily to below detection by 39 weeks (silicon content data read from Figure 3 of publication). In both males and females at 31.0 mg/m^3, lung collagen content increased immediately after exposure. In animals exposed to 5.9 and 31.0 mg/m^3, lung collagen content decreased following exposure but was still 20% above control at 52 weeks of recovery. Rats exposed to 1.3 mg/m^3 revealed lung collagen levels similar to controls by 52 weeks, indicating reversibility. Microscopic assessment of lung lesions indicated dose-related changes in rats exposed to 1.3, 5.9 and 31.0 mg/m^3. Exposure to 1.3 mg/m^3 produced few histological lesions (alveolar macrophages, intra-alveolar polymorphonuclear leukocyte (PML) infiltration, and increased septal cellularity) immediately after exposure, which resolved rapidly. In males, 31.0 mg/m^3 caused alveolar macrophage accumulation, increased septal cellularity and focal

interstitial fibrosis cellular without complete recovery at 52 weeks post exposure. Other effects included increased cellular debris, intra-alveolar PML, alveolar bronchiolisation, and cholesterol clefts with recovery at 13, 13, 39, and 39 weeks post exposure respectively. In females, 31.0 mg/m^3 caused alveolar macrophage accumulation, increased septal cellularity, and focal interstitial fibrosis without complete recovery up to 52 weeks post exposure. Other effects included increased cellular debris and intra-alveolar PML infiltration with recovery at 13 and 26 weeks respectively (Reuzel *et al,* 1991). The authors reported similar studies with precipitated and hydrophobic SAS (below).

Fischer 344 rats were exposed to Aerosil 200 at a concentration of 50 mg SiO_2/m^3 for 13 weeks, followed recovery for 3 or 8 months. Additional rats were exposed to crystalline silica (cristobalite) at 3 mg/m^3. Lung burden of silica significantly increased during exposure and declined rapidly during the recovery period to non-significant level at 32 weeks. After 13 weeks of exposure, changes in BAL fluid content compared to controls included increases in total cells from 2.89 to 16.9 × 10^7, neutrophils from 0.26% to 55%, protein from 0.26 to 1.59 µg/ml, lactate dehydrogenase (LDH) from 11.7 to 1,808 nmol/min/ml, and β-glucuronidase from 0.53 to 29.2 nmol/min/ml. The percentage of alveolar macrophages decreased from 98.5 to 42.6 while the percentage of lymphocytes and viable cells remained unchanged compared to controls. Significant increases in terminal transferase dUTP nick-end-labelling (TUNEL)-staining were detected in macrophages and terminal bronchiolar epithelial cells, representing fragmented DNA that could lead to cell death and be the possible source of the increased LDH levels in BAL. A HPRT assay of alveolar cells isolated from the SAS exposed animals was negative and the authors concluded that the induced persistent inflammation alone was not sufficient to induce genotoxic effects. Additional properties such as particle biopersistence and direct cytotoxicity were considered necessary. All parameters returned to control levels after 8 months of recovery (Johnston *et al,* 2000).

Male Sprague-Dawley rats, Hartley guinea pigs were exposed to Cab-O-Sil, referred to as silica F by the authors, at a concentration of 0 or 6.9 mg SiO_2/m^3 for 12 months, and Cynomolgus monkeys (*Macaca fascicularis*) for 13 months. Rats were killed after 3, 6 and 12 months and guinea pigs after 12 months. Monkeys were killed at termination of exposure. Rats exhibited interstitial fibrosis was but this was also seen in control animals. Effect of exposure was greater in monkeys that exhibited large numbers of macrophage and monocyte cell aggregates in the walls of respiratory bronchioles, alveolar ducts, and around venules and arterioles. Reticulin fibres and significant amounts of collagen and early nodular fibrosis were also present. In monkeys, lung volume was measured by means of pulmonary function tests, including forced expiratory vital capacity (FVC), inspiratory capacity (IC), residual volume (RV) and total lung capacity (TLC). Respiratory mechanics were evaluated using dynamic lung compliance(CL), average flow resistance (RL), forced expiratory flow at 75% or 90% of vital capacity (FEF_{75}, FEF_{90}), lung closing volume (CV), single-breath nitrogen washout (N_2), volume of isoflow (VISFL) and

diffusing capacity of the lung for carbon monoxide (DLCO). SAS exposure decreased FVC, IC, TLC, CL, FEF_{75} and $FEF_{90,}$ and increased RL and CV. There were no effects on lung hydroxyproline levels (Groth *et al,* 1981). The authors also tested precipitated SAS and SAS gel according to similar protocols (below).

Wistar rats, Saranac guinea pigs and New Zealand White rabbits were exposed to pyrogenic SAS, referred to as Dow Corning Silica by the authors, at an average concentration of 53 mg SiO2/m3 for variable durations. Control animals did not receive sham exposures (Schepers *et al,* 1957a,b,c).

Rats were exposed for up to 12 months and killed intermittently to assess the effects of exposure. The spontaneous death rate was very high, i.e. 74% by 12 months of exposure. Silica was cleared to the lymphatics, with associated formation of parenchyma nodules consisting of chromophobic macrophages, plasma cells, reticulum and collagen. Foamy macrophages accumulated in the alveoli and alveolar ducts, with apparent fusion to form giant cells. Over time, giant cells degenerated and focal emphysematous lesions were apparent. An additional group of rats was exposed for 6 months to the SAS, removed from dust exposure, and then evaluated for up to 12 months to assess recovery from exposure. The spontaneous death rate was 44%. During recovery there was rapid and virtually complete disappearance of pulmonary lesions at 12 months recovery. Also at 12 months post exposure there was an almost complete resolution of emphysematous symptoms indicating its focal nature and reversibility. Lungs from both groups of rats contained 1.5 mg SiO_2 after 3 months of exposure, which remained constant during exposure and subsided to 0.3 mg SiO_2 during recovery (Schepers *et al,* 1957a).

Different protocols were used to assess the response of guinea pigs to chronic inhalation of SAS. In the first experiment, guinea pigs were exposed for up to 24 months and killed every 2 months. In the second experiment, one group of guinea pigs (n = 19) was exposed for 12 months and another group (n = 18) for 24 months. After variable times of recovery, animals were killed and their lungs evaluated. In the third experiment, guinea pigs (n = 4) were exposed to SAS for 12 months, allowed to recover for 1 month, and then re-exposed for 1 day. Following 4 months of exposure, large vacuolated cells aggregated at the alveolar ducts/terminal bronchioles junction and infiltrated alveolar walls. With time, cellular masses atrophied, and adjacent alveoli expanded creating emphysematous lesions. Alveolar walls were replaced by reticulum and fibrotic bundles of collagen. During recovery, cellular aggregation and infiltration subsided, but the focal fibrosis of alveolar walls and the stenosis of alveolar ducts and bronchioles persisted. Emphysematous lesions decreased in the upper lobes, but tended to progress in the lower lobes. In the re-exposure experiment, the reactions of the lungs were less than those observed in naive animals without previous exposure. The average total silica content in the lungs was 2.8 mg at the end of 12 months, peaked at 8.2 mg at the end of 24 months, and decreased to 0.6 mg by 12 months after the end of exposure (Schepers *et al,* 1957b).

Rabbits were exposed for up to 12 months. The 2 (out of 10) animals that survived were used to assess recovery from exposure. None of the deaths could be ascribed to the inhaled SAS. Most premature deaths were attributed to complications from cardiac punctures. In exposed animals, cellular masses filled alveolar spaces and infiltrated alveolar walls. Cellular nodules, consisting primarily of macrophages, were evident in perivascular tissues. Abundant reticulum was observed in association with the nodules, along blood vessels, and in the alveolar walls. Collagen deposition also was evident. Emphysema and dilation of alveolar ducts occurred after only 10 and 11 days of dust exposure. In the 2 rabbits allowed to recover in room air, cellular reactions and emphysema regressed but minor focal alveolar wall collagen remained (Schepers *et al,* 1957c).

The value of the above three Schepers studies is limited because SAS concentrations were extremely variable. Standard deviations from mean values ranged from ± 24.7 to 84.7 mg/m^3, and it would not be appropriate to link the observed effects to any specific dose. For each species, few animals were available for examination, and therefore the findings are based on limited observations.

Precipitated

Male CD rats were exposed (nose-only) to hydrophilic, precipitated SAS (Zeofree 80) at concentrations of 0, 10 or 100 mg SiO_2/m^3 for 3 days. Additional rats were exposed to crystalline silica (cristobalite, 10 or 100 mg/m^3 and quartz Min-U-Sil, 100 mg/m^3). Animals were killed 1, 8, 30, or 90 days post exposure. Exposure to 10 mg/m^3 induced changes in BAL fluid content compared to controls, including increased percentages of granulocytes, LDH, proteins and N-acetyl glucosaminidase (NAG), by 145%, 200%, 175%, and 150% of control values, respectively. Exposure to 100 mg/m^3 increased the percentage of granulocytes, LDH, protein and NAG by 152%, 350%, 275%, and 200%, respectively. For both concentrations, all parameters returned to normal by 8 days post exposure (Warheit *et al*, 1995).

In a short-term inhalation study, male and female Wistar rats were exposed to Zeosil 45 at concentrations of 0 (control), 1.16, 5.39 or 25.2 mg SiO_2/m^3 for 5 days. Additional rats were exposed correspondingly and allowed to recover for 1 or 3 months. Crystalline silica (25 mg SiO_2/m^3, Min-U-Sil 5) was used as positive control. The MMAD of the SAS aerosol was 2.83 to 3.27 µm and 2.08 µm for crystalline silica (Note: i.e. the aerosols were potentially 100% respirable). There were no deaths or exposure-related abnormalities other than slightly decreased breathing in treated animals. Besides standard clinical observation and histopathological inspection, the most sensitive cell and biochemical parameters for the elucidation of an inflammatory tissue reaction were applied, including white blood cell count, viability and cell differentiation as well as determination of biochemical parameters in the BAL fluid. At the highest concentration (25.2 mg/m^3), SAS induced treatment-related effects reflecting

inflammation of lung tissue, associated with a slight morphological tissue reaction (hypertrophy, partial hyperplasia of the bronchiolar epithelium). The effects disappeared during recovery (apart from slight effects after 3 months in males only), showing clear signs of reversibility. However, recovery was not observed after exposure to crystalline silica. Effects at 5.39 mg/m^3 included very slight increases in the relative neutrophil count with concomitant decrease in the relative macrophage count the day after exposure. There were no morphological tissue changes. No effects were noted at the lowest concentration of 1.16 mg/m^3. The NOEL was 1 mg/m^3 (nominal) (Arts *et al*, 2003).

Fischer 344 rats exposed to precipitated SAS (product name not available) at a concentration of 30 mg SiO_2/m^3 for 8 days, showed an influx of cells into lung tissues, which returned to normal by 12 days recovery. Silica also produced increases in total cells and polymorphonuclear neutrophils (PMNs) obtained by lavage. These increases returned to normal on day 5 post exposure. There was no effect on lung weight, lung protein content, lung DNA content or lung hydroxyproline content. Exposure to SAS also increased the levels of BAL protein, lipid phosphorus and saturated dipalmitoyl-phosphatidylcholine, which returned to normal after 5 days recovery (Low *et al*, 1985; Hemenway *et al*, 1986).

Wistar rats were exposed to Sipernat 22S at a concentration of 34.9 mg SiO_2/m^3 for 13 weeks. Additional animals were sham exposed to air, and to crystalline silicas (quartz) at 58.5 mg/m^3 as positive control. The MMAD was not determined, but there was a wide range for the geometric agglomerate/aggregate size distribution (1 - 120 μm). Animals were killed immediately after the exposure and at 13, 26, 39 and 52 weeks post exposure. In males, the total silicon content of lungs and tracheobronchial lymph nodes was approximately 0.5 mg (1.1 mg SiO_2) immediately after exposure, declined at 13 weeks (0.1 mg Si, 0.21 mg SiO_2), increased again at 26 weeks (0.5 mg Si, 1.07 mg SiO_2) (no explanation given by authors), and became undetectable by 39 weeks of recovery. In females, the silicon content of lungs and lymph nodes was approximately 0.4 mg (0.86 mg SiO_2) immediately after exposure and then declined steadily to below detection by 39 weeks (silicon content data read from Figure 3 of publication). In both males and females, lung collagen content increased immediately after exposure, but returned to control levels by 52 weeks post exposure. In both males and females, alveolar macrophage accumulation occurred at 0, 13 and 26 weeks recovery, but was no longer significant by 39 weeks (Reuzel *et al,* 1991).

Mice (strain not stated) were exposed to air with or without precipitated SAS dust (source and concentration not given) for 1 year. An increased incidence of primary lung tumours was reported in those silica-exposed mice still alive at 600 days (21.3% in silica-exposed *versus* 7.9% in controls). Hyperplasia of the tracheobronchial lymph nodes was reported, but there was no evidence of lung fibrosis. An increased incidence of pneumonia was also apparent in dust-exposed mice when compared to controls (Campbell, 1940). The value of the Campbell study is

limited due to poorly controlled experimental conditions, and deficiencies of experimental techniques, study design, and reporting, which do not permit the assessment of tumorigenic effects. IARC (1997), in its evaluation, remarked that *"*The Working Group noted the inadequate description of the test material and the exposure conditions*."* Another deficiency is the absence of measurements of particle concentrations and size. In addition, the authors only sampled tissues with tumours for microscopy. Therefore, pneumonia could have been present in animals without obvious lung tumours; thus, the actual incidence of infection, both in exposed and control animals, could have been much higher.

Sprague-Dawley rats, Hartley guinea pigs and Cynomolgus monkeys (*Macaca fascicularis*) were exposed to Hi-Sil, referred to as silica P by the authors, at a concentration of 0 or 6.9 mg SiO2/m3 for up to 18 months. Rats were killed after 3, 6 and 12 months of exposure and guinea pigs and monkeys after 10 to 18 months of exposure. Rats and guinea pigs exhibited small numbers of macrophage and monocyte cell aggregates. Interstitial fibrosis was observed in rats but was also seen in some controls. In monkeys, large numbers of macrophage and monocyte cell aggregates were found in the walls of respiratory bronchioles, alveolar ducts, and around venules and arterioles. Reticulin fibres and some collagen were present. In monkeys, lung volume was measured by means of FVC, IC, RV and TLC. Respiratory mechanics were evaluated using RL, CL, FEF 75%, FEF 90%, CV, N2 washout, VISFL and DLCO. SAS exposure caused significant decreases in TLC and FVC; ventilatory performance and mechanical properties were unaffected. There was no effect on lung hydroxyproline levels (Groth *et al,* 1981).

Wistar rats were exposed to a Hi-Sil 233 at an average concentration of 126 mg SiO_2/m^3 for 15 months. Rabbits and guinea pigs were exposed to the same concentration for 12 and 24 months, respectively. Control animals did not receive sham exposures. Of all three species, subgroups of animals exposed to SAS for varying durations were removed from exposure and evaluated for clearance (elimination) of dust from the lungs. Viral pneumonic disease affected both exposed (mortality rate 24.6% in the main study and 33.3% in the clearance group) and control rats (mortality rate 37.3%). Observations from all three species were pooled. Lung weights increased with dust exposure but returned to normal after exposure ceased. Macrophages accumulated in alveoli, bronchioles and lymphoid tissue at different levels according to species. Epithelial proliferation was minimal, and appeared more related to infection than particle exposure. Mild deposition of reticulin fibres occurred in alveolar walls, but there was no evidence of collagen formation. Almost all observed changes were reversible and paralleled lung clearance of particles (Schepers, 1981). The value of the study is limited because of problems with infectious disease in the rats and (wild) monkeys, and the lack of reporting of important details such as particle concentrations during the actual dust generation, particle size, techniques used to assess particle effects, animal and tissue sampling.

Rhesus monkeys (*Macaca mulatta*) were exposed to precipitated SAS (product not stated) at a concentration of 15 mg SiO_2/m^3 for up to 12 months. Control monkeys did not receive sham exposures. One monkey was killed at 3 months of exposure, 1 monkey at 6 months, and the remaining 3 monkeys after 12 months of exposure. The animals showed infiltration of macrophages into the alveolar regions, which subsided in the 3 monkeys exposed for 12 months. With prolonged exposure, degeneration of alveolar septa led to the confluence of adjacent alveoli, alveolar wall sclerosis, and pulmonary emphysema. Tracheobronchial lymph nodes became enlarged, but did not appear fibrotic. There was no evidence of pulmonary fibrosis or necrosis (Schepers, 1962). The value of the study is limited because of problems with infectious disease in wild monkeys; the observations were based on few animals and the appearance of the lungs from control monkeys was not discussed. The relationship between emphysema and exposure was not explained.

Gel

In a short-tem inhalation study, male Wistar rats were exposed to hydrophilic SAS gel (Syloid 74) at 0.94, 5.13 or 25.1 mg SiO_2/m^3 for 5 days. Additional control and treated rats were allowed to recover for 1 or 3 months (cristobalite as positive reference was included in the study with precipitated SAS by Arts *et al*, 2003 above). The MMAD was between 1.57 and 1.71 µm, and apparently increased to 2.8 to 2.9 µm on day 4 and 5, due to a shortened tube connecting exposure chamber and measurement apparatus (Note: i.e. the aerosol was potentially 100% respirable). There were no deaths or exposure-related abnormalities. Besides standard clinical observation and histopathological inspection, the most sensitive cell and biochemical parameters for the elucidation of an inflammatory tissue reaction were applied including white blood cell count, viability and cell differentiation as well as determination of biochemical parameters in the BAL fluid. At the highest concentration (25.1 mg/m^3), SAS induced treatment-related effects in the lungs (changed differential cell counts, biochemical parameters in broncho-alveolar lavage, increased weight of lungs and tracheobronchial lymph nodes, and histopathological changes), reflecting inflammation. The effects had disappeared after 1 month recovery, but after 3 months, a slight increase in lung collagen content (without histopathological changes) was noted. After 1 day of exposure to 5.13 mg/m^3, the percentage of relative neutrophils was slightly increased, with a concomitant decrease in the percentage of macrophages. Clear signs of reversibility were observed. No effects were seen at the lowest concentration of 0.94 mg/m^3. The nominal concentration of 1 mg/m^3 was the NOEL (Arts and Kuper, 2003b).

Rats (male, Sprague-Dawley), guinea pigs (male, Hartley) and monkeys (male, Cynomolgus, *Macaca fascicularis*) were exposed to SAS gel (product name not available), referred to as Silica G by the authors, at a concentration of 9.4 mg SiO_2/m^3 for 12 months. Rats were killed after 3, 6 and 12 months and guinea pigs after 12 months. Monkeys were killed at the termination

of exposure. Both rats and guinea pigs exhibited small numbers of macrophage and monocyte cell aggregates. Interstitial fibrosis was observed only in rats but this was also seen in control animals. In monkeys, large numbers of macrophage and monocyte cell aggregates were found in the walls of respiratory bronchioles, alveolar ducts, and around venules and arterioles. Although reticulin fibres were present in the cell aggregates, collagen fibres were not. In monkeys, lung volume was measured by means of FVC, IC, RV and TLC. Respiratory mechanics were evaluated using RL, CL, FEF_{75}, FEF_{90}, CV, N_2, VISFL and DLCO. SAS exposure had no effect on lung volumes, but decreased CL, FEF_{75}, FEF_{90}, N_2 washout and increased RL. There was no effect on lung hydroxyproline levels (Groth *et al,* 1981).

Sol

CD rats were exposed by inhalation to SAS sol (Ludox) at concentrations of 0, 10, 50, or 150 mg SiO_2/m^3 for either 2 or 4 weeks. Groups of animals were killed immediately after the 2-week and 4-week exposures and 3 months after the 4-week exposure. At the end of the 4-week exposure, the average silicon content per lung was 489, 2,418 and 7,378 µg (1.1, 5.2, 16 mg SiO_2) at 10, 50 and 150 mg/m^3, respectively. The authors reported a concentration-dependence in the observed effects. Exposure to 10 mg/m^3 induced no changes in BAL fluid content compared to controls. Exposure to 50 mg/m^3 increased neutrophils and increased the labelling indices of epithelial, parenchymal and terminal bronchiolar cells. Exposure to 150 mg/m^3 increased the levels of neutrophils, LDH, protein content, alkaline phosphatase, and the labelling indices of epithelial, parenchymal, and terminal bronchiolar cells, and decreased the *in vitro* phagocytic capacities of alveolar macrophages. After the 3-month recovery period, all biochemical parameters had returned to control values as had cell proliferation, with the exception of animals exposed to 150 mg/m^3 where neutrophil numbers had largely recovered but were still significantly above control (Warheit *et al,* 1991, 1995).

CD rats were exposed to SAS sol (Ludox) at concentrations of 0, 10, 50 or 150 mg SiO_2/m^3 for 4 weeks. Animals were killed immediately after exposure and following 10 days and 3 months recovery. At the end of the 4-week exposure, the average silicon content in both lungs was 631, 2,560 and 7,520 µg (1.4, 5.5, 16 mg SiO_2) at 10, 50 and 150 mg/m^3, respectively. The silicon content decreased rapidly during recovery. Exposure to 10 mg/m^3 had no effect. Exposure to 50 mg/m^3 or 150 mg/m^3 produced transient increases in alveolar PMNs and Type II cell hyperplasia. Particles were apparent in alveolar macrophages and tracheobronchial lymph nodes. By 3 months post exposure, the particle content of alveolar macrophages had decreased, with an apparent increase in the tracheobronchial lymph nodes. Further, after 3 months recovery, 1/10 and 9/10 animals exhibited minimum nodular alveolar macrophage aggregates; 1/10 and 3/10 animals showed silicotic nodular-like lesions, at 50 and 150 mg/m^3, respectively. Collagen fibre deposition was minimal in these lesions. The nodules consisted of the incorporation of intra-

alveolar epithelioid cell granulomas into the interstitium and were not due to interstitial fibroblast proliferation. There was no evidence alveolar lipoproteinosis (Lee and Kelly, 1992, 1993).

Hydrophobic

There follows a discussion of the data on repeated inhalation toxicity of hydrophobic SAS (Table 36). All studies were conducted with pyrogenic SAS.

Table 36: Toxicity of hydrophobic pyrogenic SAS following repeated inhalation

Type/ Product name	Species, strain	Number of animals/ group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
Cab-O-Sil N70TS	Rat, CD	40 M, 40 F 20/sex, control	6 h/d, 5 d/wk, 4 wk	0, 60 on d 1, 30 thereafter	Deaths after 1 d at 60 mg/m^3 due to acute pulmonary haemorrhage with bronchiolar plugs. Active interstitial/ alveolar inflammation occurred and changed from diffuse reactions to more localised consolidative lesions. During post exposure, active inflammation less prominent, but some fibrosis and collagen apparent in the interstitium	Cabot, 1983	3b
Aerosil R974	Rat, Wistar	10 M, 10 F	6 h/d, 5 d/wk, 2 wk	0, 31, 87, 209	Signs of respiratory distress in all test groups. Body weight gain and food consumption reduced at 87 and 209 mg/m^3. No adverse change in haematological parameters. Changed liver and kidney weights at 87 and 209 mg/m^3, not associated with histopathological changes. Concentration-related increase in absolute/relative lung weight. Lungs of several animals/all groups pale, spotted, swollen and spongy, and occasional small haemorrhages. Lungs of animals in all test groups showed increased cellularity, accumulation of alveolar macrophages, alveolar oedema and early granulomata. NOAEL < 31 mg/m^3.	Degussa, 1986c	1d
Aerosil R974	Rat, Wistar	70 M, 70 F	6 h/d, 5 d/wk, 13 wk	34.7	Lung collagen content increased immediately after exposure, and did not return to control levels during 52 wk recovery. Granuloma-like lesions, alveolar macrophage accumulation, cellular debris, and increased septal cellularity occurred at varying times post exposure	Degussa, 1987; Reuzel *et al,* 1991	1b

Table 36: Inhalation toxicity of hydrophobic SAS following repeated inhalation (cont'd)

Type/ Product name	Species, strain	Number of animals/ group, sex	Exposure regime, duration	Concentration (mg/m^3)	Result	Reference	CoR
HDK SKS300	Rat, Wistar	10 M, 10 F	6 h/d, 5 d/wk, 13 wk	0, 0.51, 2.05, 10.01	Most effects only observed in high dose group. Increase in aspartate-amino-transferase level and alkaline phosphatase (M). Significant increase in absolute/relative weight of lungs and tracheobronchial lymph nodes. Lungs with red appearance, white spot(s) on the lungs (F). Accumulation of alveolar macrophages with few polymorphonuclear cells, accompanied by bronchiolar-alveolar epithelial hyperplasia and interstitial inflammatory cell infiltrates in lungs. Lung draining mediastinal lymph nodes showed increased histiocytosis and macrophage aggregates in paracortex and/or germinal centres. No indication of increased birefringence, typical for interstitial fibrosis. Clear recovery of all effects. NOEL = 0.51 mg/m^3	Wacker, 1998a,b	1a
J-DCA TX104	Rat, not stated	M, number not stated	6 h/d, 5 d/wk, 12 months	0, 10, 50, 150	10 mg/m^3 had no effect. 50 mg/m^3 and 150 mg/m^3 produced white foci on lung surfaces and collections of foamy macrophages within the alveoli. Peribronchial lymph nodes enlarged	Dow Corning, 1972	4a
J-DCA TX104	Monkey, Cynomolgus	M, number not stated	6 h/d, 5 d/wk, 12 months	0, 10, 50, 150	10 mg/m^3 had no effect. 50 mg/m^3 and 150 mg/m^3 produced interstitial fibrosis, which did not resolve or progress during recovery. Peribronchial lymph nodes enlarged	Dow Corning, 1972	4a

CD rats were exposed to Cab-O-Sil N70TS (also known as TS720) at a concentration of 0 or 30 mg SiO_2/m^3 for 4 weeks. Initial exposure was to 60 mg/m^3, but after one day 9 male rats died from "acute pulmonary haemorrhage accompanied by bronchiolar plugs with emphysema", and the concentration was lowered to 30 mg/m^3. The aerosol particles had a mean MMAD from 0.23 to 0.37 µm. Animals were killed after 1, 2 or 4 weeks of exposure. Two additional groups of rats were killed 6 and 12 weeks after exposure. SAS caused an active interstitial/alveolar inflammation, which changed from a diffuse reaction to more localised lesions. During recovery, active inflammation became less prominent, but some fibrosis and collagen proliferation was apparent in the interstitium (Cabot, 1983). The value of the Cabot study is limited because of methodological deficiencies, as follows. The proportion of the chronic pulmonary lesions that may have been due to the initial severe injury relative to those induced by the subsequent lower dose level (60 mg/m^3 compared to 30 mg/m^3) cannot be determined from the data. The methods used to generate the SAS aerosol were not state-of-the art. The MMAD was very small, ranging from 0.23 to 0.37 µm. This is not in accordance with OECD guidelines of MMAD that prescribe a diameter of 1 to 4 µm for respirable dust. The techniques used for tissue preservation were not optimal and could have generated artefacts, while tissue sampling was not uniform. Furthermore, the authors made several claims that were not supported by the histological techniques used. Finally, some of the control animals also exhibited lung lesions.

Wistar rats were exposed to hydrophobic, pyrogenic SAS (Aerosil R974) at concentrations of 0 (control), or 34.7 mg SiO2/m3 for 13 weeks. Additional animals were exposed to crystalline silica (quartz) at 58.5 mg/m^3. The MMAD was not determined, but there was a wide range for the geometric agglomerate/aggregate size distribution (1 - 120 µm). Animals were killed immediately after the exposure and at 13, 26, 39 and 52 weeks post exposure. In males, the silicon content of lungs and tracheobronchial lymph nodes was approximately 1.1 mg (2.35 mg SiO_2) immediately after exposure, declined at 13 weeks to 0.4 mg (0.86 mg SiO_2), increased again at 26 weeks to 1.1 mg (2.35 mg SiO_2) (no explanation given by authors), and became undetectable by 39 weeks of recovery. In females, the silicon content of lungs and lymph nodes was approximately 0.7 mg (1.50 mg SiO_2) immediately after exposure and then declined steadily to below detection by 39 weeks (silicon content data read from Figure 3 of publication). In both males and females, lung collagen content was statistically increased immediately after exposure; both controls and exposed animals still showed elevated levels (≈ 10%) by 52 weeks post exposure. In males, exposure to Aerosil R974 caused granuloma-like lesions, alveolar macrophage accumulation, and increased septal cellularity with recovery at 26, 52, and 52 weeks post exposure, respectively. In females, exposure to SAS caused granuloma-like lesions, alveolar macrophage accumulation, cellular debris and increased septal cellularity, all of which returned to normal after 26, 26, 13 and 52 weeks of recovery, respectively (Reuzel *et al,* 1991).

Wistar rats were exposed to HDK SKS300 at concentrations of 0, 0.51, 2.05 or 10.01 mg $SiO2/m^3$ for 13 weeks. The mean MMAD was 2.8, 3.62 and 4.47 µm, respectively. At

10.01 mg SiO2/m^3, statistically significant increases were seen in total protein, LDH and NAG in lung lavage fluid. Additionally significant increases were noted in total cell number and absolute numbers of neutrophils, macrophages/monocytes and lymphocytes. These increases were reflected in a statistically significant increase in the relative number of neutrophils with a concomitant decrease in the relative number of macrophages/monocytes. At 2.05 mg SiO2/m^3, changes were limited to an increased relative number of neutrophils with a concomitant decrease in the relative number of macrophages/monocytes, without influencing absolute cell numbers. No such changes were observed in animals of the low concentration group (0.51 mg/m^3) or at the end of the recovery period in all groups. Silica (measured as Si) was found in the lungs of all exposed animals in a concentration-related way; it was present in the tracheobronchial lymph nodes of animals exposed to 10.01 mg SiO2/m^3. By the end of the 13-week recovery period, silicon could still be detected in lungs and tracheobronchial lymph nodes of animals exposed to 10.01 mg SiO2/m^3. The silicon level in the lungs was decreased and the level in the lymph nodes increased, compared to the levels measured immediately after exposure (Wacker, 1998b). It is interesting to note that the incidence and severity of the histopathological changes observed in the lymph nodes of animals in the high concentration group had diminished (Wacker, 1998a).

Rats (strain not provided) and Cynomolgus monkeys (*Macaca fascicularis*) were exposed to J-DCA TX104 at concentrations of 0, 10, 50, or 150 mg/m^3 for up to 12 months. Animals were killed during the exposure (rats only at 2 weeks, 1, 3, or 6 months), at termination of exposure (both rats and monkeys at 12 months), or post exposure (rats at 14 months; monkeys at 14 or 24 months). In rats, mortality was dose related: 8% (control), 12% (10 mg/m^3), 26% (50 mg/m^3) and 33% (150 mg/m^3). In the surviving rats, 10 mg/m^3 had no effect, and 50 mg/m^3 and 150 mg/m^3 produced collections of foamy macrophages within the alveoli. In monkeys, 10 mg/m^3 had no effect, and 50 mg/m^3 and 150 mg/m^3 produced interstitial fibrosis, which did not resolve or progress during the recovery period (Dow Corning, 1972).

Summary: lowest-observed adverse effect levels

The effects of chronic inhalation of pyrogenic, precipitated, gel and sol SAS have been evaluated in mice, rats, guinea pigs, rabbits and monkeys exposed to concentrations ranging from 0.5 to 150 mg SiO_2/m^3. Although the value of some studies is limited, SAS exposure caused macrophage accumulation, reticulin fibre formation and nodule formation. Table 37 lists those subchronic and chronic inhalation studies that provide lowest-observed adverse effect levels (LOAELs). When available, NOAELs or NOELs were in the range of 0.5 to 10 mg/m^3. The difference in values may be explained by different particle size, and therefore the number of particles administered per unit dose. In general, as particle size decreases so does the NOAEL/LOAEL.

Table 37: Lowest-Observed Adverse Effect Levels (LOAELs) for SAS

Type/ Product name	LOAEL (mg/m^3)	Reference
Hydrophilic		
Pyrogenic		
Aerosil 200	50	Johnston *et al,* 2000
Aerosil 200	1.3	Reuzel *et al,* 1991
Cab-O-Sil	6.9	Groth *et al,* 1981
Cab-O-Sil M5	1.39	Arts and Kuper, 2003a
Dow Corning Silica	53	Schepers *et al,* 1957a,b,c
Precipitated		
Hi-Sil	6.9	Groth *et al,* 1981
Hi-Sil 233	126	Schepers, 1981
Precipitated	15	Schepers, 1962
Sipernat 22S	34.9	Reuzel *et al,* 1991
Zeosil 45	5.39	Arts *et al*, 2003
Gel		
Syloid 74	5.13	Arts and Kuper, 2003b
Hydrophobic		
Pyrogenic		
Aerosil R974	31	Reuzel *et al*, 1991
HDK SKS300	2.05	Wacker, 1998a,b
J-DCA TX104	50	Dow Corning, 1972

It is important to note that some of the studies are deficient in several aspects (see text above).

Also, importantly, the effects reported in the various other studies may not necessarily be adverse. The indices used by the investigators to assess the effects of silica exposure are established markers of inflammation and injury. However, what is not readily apparent is the functional or biological significance of the reported effects. Phrases such as “toxic effects” have been used without considering toxic significance. The importance of making this distinction is seen in the resolution of lung injury during recovery periods. For example, Reuzel *et al* (1991) reported that rats exposed to 1.3 mg/m^3 exhibited increases in lung collagen content and histological lesions, which resolved during the post exposure observation period. The inclusion of a post exposure

recovery phase was an important aspect of these studies. (The distinction between adverse and non-adverse effects in animal studies has been reviewed by ECETOC, 2002).

8.3.4 Other routes

The Task Force was aware of several earlier studies with sometimes unspecified silica, not necessarily SAS, applied by the intravenous, *i.p.* or intratracheal routes, which are not relevant for human health hazard assessment. Almost all of these have not been quoted (references listed in Section 11.2). Some of the reports contained limited useful information on the toxicokinetics of SAS (Chapter 7).

8.3.5 Summary and evaluation

The available repeated dose toxicity data confirm the absence of significant toxicity of SAS by the oral and dermal routes of exposure.

Numerous repeated dose inhalation toxicity studies have been conducted with hydrophilic and hydrophobic SAS in rats and some other animal species. The observed effects are physical in nature and are associated with the extremely small particle size and extremely high particle numbers administered. The alveolar SAS aerosol fraction is responsible for the toxicological effects that were observed. In contrast to the particle size distribution of SAS aerosols used in these repeated dose inhalation studies, only minor amounts (less than 1%) of the commercial products are respirable (alveolar fraction < 10 μm MMAD), as measured by method EN 481 (CEN, 1993). Therefore the existing inhalation tests do not represent the toxicological behaviour of the commercial hydrophilic and hydrophobic products.

Several SASs of different types (pyrogenic, precipitated and sols) have been evaluated in subchronic studies (up to 13 weeks), using airborne concentrations ranging from 0.5 to 150 mg SiO_2/m^3. The rat was the only species tested. Silica is cleared rapidly from the lungs during the post exposure period. A return to control levels is normally achieved within 8 months or less, depending on the exposure concentration, duration and SAS type. Morphology and clearance data indicate that SAS is most probably solubilised or effectively cleared to lymph node tissues. Subacute or subchronic exposure to SAS produces transient increases in inflammation, markers of cell injury, and lung collagen content. During the post exposure periods, most of the increases in markers of lung inflammation or injury decrease with a majority returning to control levels (Cabot, 1983; Low *et al,* 1985; Hemenway *et al,* 1986; Reuzel *et al,* 1991; Warheit *et al,* 1991, 1995; Lee and Kelly, 1992, 1993; Wacker, 1998a,b; Johnston *et al*, 2000; Arts and Kuper, 2003a,b; Arts *et al*, 2003). One investigator reported focal fibrosis and nodule formation at a dose

as high as 150 mg/m3, but there was no alveolar lipoproteinosis (Lee and Kelly 1992, 1993). All effects in rats are limited to the lung and there is no indication of systemic toxicity following repeated (subchronic) inhalation of SAS.

The effects of chronic inhalation of pyrogenic, precipitated and gel SAS have been evaluated in several animal species, including mice, rats, guinea pigs, rabbits and monkeys, using airborne concentrations from 10 to 150 mg SiO_2/m^3. SAS exposure caused macrophage accumulation, reticulin fibre formation, nodule formation, and some alterations in pulmonary function. Focal emphysematous lesions were noted in rats (Schepers *et al,* 1957a,b,c; Schepers, 1962). These lesions resolved during recovery (post exposure). In rabbits, similar lesions appeared after 10 and 11 days of exposure. Reversibility and early onset do not usually occur with emphysema, which brings this observation into question. With the exception of the study by Dow Corning (1972), there was no evidence of interstitial pulmonary fibrosis. In those studies that included a recovery period (Schepers, 1957a,b,c, 1981; Dow Corning, 1972), pulmonary effects diminished with time.

8.4 Genotoxicity

8.4.1 *In vitro*

Micro-organism gene mutation

Several SASs demonstrated no mutagenic activity in *Salmonella typhimurium* or *Escherichia coli* in the presence and/or absence of metabolic activation, using standard plate incorporation or spot test methods. SAS toluene extract also showed negative results in different test conditions. Negative results were also reported in yeast (*Saccharomyces cerevisiae*), without metabolic activation (Table 38).

Table 38: Mutagenicity of SAS in micro-organisms

Type/ Product name	Endpoint	Test system	Protocol	Metabolic activation [a]	Concentration tested (µg/plate)	Cytotoxicity	Result	Reference	CoR
Hydrophilic									
Pyrogenic									
Cab-O-Sil EH-5	Histidine reversion	*Salmonella typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Standard plate incorporation, agar plate	+ S9	≤ 10,000 [b]	None	Negative	Cabot, 1989a	1a
Cab-O-Sil M-5	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Not stated	+/– S9 (not defined)	5,000 [b]	None	Negative	Cabot, 1978	3a
Gel									
Silcron G-910	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Standard plate incorporation, agar plate	+/– S9	≤ 10,000 [b]	None	Negative	Mortelmans and Griffin, 1981; Prival *et al*, 1991	1b
Silcron G-910	Tryptophan reversion	*Escherichia coli* WP2	Standard plate incorporation, agar plate	+/– S9	≤ 10,000 [b]	None	Negative	Mortelmans and Griffin, 1981	1b
Syloid 244 [c]	Histidine reversion	*S. typhimurium*, TA1530, G-46	Spot test	– S9	Not stated	Not stated	Negative	US-FDA 1974	3a
Syloid 244 [c]	Forward mutation	*Saccharomyces cerevisiae* D3	Incorporation, agar plate	– S9	Not stated	Not stated	Negative	US-FDA, 1974	3a

Table 38: Mutagenicity of SAS in micro-organisms (cont'd)

Type/ Product name	Endpoint	Test system	Protocol	Metabolic activation [a]	Concentration tested (µg/plate)	Cytotoxicity	Result	Reference	CoR
Hydrophobic									
Pyrogenic									
Aerosil R972, toluene extract	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1537	Standard plate incorporation, agar plate	± S9	1,580 [b]	None	Negative	Degussa, 1983d	1d
		TA98		+ S9 + TCPO [d]	1,580 [b]	None	Negative		
Cab-O-Sil TS500, toluene extract	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Cabot, 1995j	1a
Cab-O-Sil TS530	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Cabot, 1994c	1a
Cab-O-Sil TS610	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Cabot, 1995b	1a
Cab-O-Sil N70TS [e]	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537, TA1538	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Cabot, 1994d	1a

Table 38: Mutagenicity of SAS in micro-organisms (cont'd)

Type/ Product name	Endpoint	Test system	Protocol	Metabolic activation [a]	Concentration tested (µg/plate)	Cytotoxicity	Result	Reference	CoR
Pyrogenic (cont'd)									
HDK VP KHD15 [f]	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Wacker, 1988a	1a
HDK VP KHD15 [f]	Tryptophan reversion	*Escherichia coli* WP2	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Wacker, 1988a	1a
HDK VP KHD50 [g]	Histidine reversion	*S. typhimurium*, TA98, TA100, TA1535, TA1537	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Wacker, 1988b	1a
HDK VP KHD50 [g]	Tryptophan reversion	*E. coli* WP2	Standard plate incorporation, agar plate	+/– S9	5,000 [b]	None	Negative	Wacker, 1988b	1a

[a] Induced by Aroclor 1254 from rat liver S9 mix
[b] Suspended in DMSO (dimethyl sulphoxide)
[e] Also known as FDA 71-48
[d] 1,1,1-Trichloropropene-2,3-oxide
[e] Also known as Cab-O-Sil TS720
[f] Current name HDK H2015EP
[g] Current name HDK H2050EP

Mammalian gene mutation and chromosomal aberration

SAS has been tested for gene mutation and chromosomal aberration in cultured mammalian cells (Table 39).

Table 39: Mutagenicity and chromosomal aberration of SAS in cultured mammalian cells

Type/ Product name	Endpoint	Test system	Exposure time (h)	Metabolic activation [a]	Concentration tested	Result	Reference	CoR
Hydrophilic								
Pyrogenic								
Cab-O-Sil EH5	6-Thioguanine resistance	Chinese hamster ovary (CHO) cells	5	– S9 + S9	10 - 250 µg/ml [b] 100 - 500 µg/ml [b]	No significant mutagenic activity	Cabot, 1990b	1a
Cab-O-Sil EH5	Chromosome aberration	CHO cells	16 2	– S9 + S9	38 - 300 µg/ml [b] 250 - 1,000 µg/ml [b]	No clastogenic activity	Cabot, 1990c	1a
Cab-O-Sil EH5	Unscheduled DNA synthesis (UDS)	Primary rat hepatocytes	18 - 20	+/– S9	0.3 - 1,000 µg/ml [b]	No genotoxic activity	Cabot, 1989b	1a
Gel					**Dose or concentration**			
Spherisorb 5 µ	Single cell gel/comet	Chinese hamster lung (V79) cells	3	NA [c]	17.2 - 137.9 µg/cm^2	Significant DNA migration ≥ 68.9 µg/cm^2	Zhong *et al*, 1997	2e
Spherisorb 5 µ	Single cell gel/comet	Human embryonic lung fibroblasts (Hel 299)	3	NA	17.2 - 137.9 µg/cm^2	Significant DNA migration ≥ 68.9 µg/cm^2	Zhong *et al*, 1997	2e
Spherisorb 5 µ	Micronucleus frequency	Chinese hamster lung fibroblasts (V79)	24	NA	20 - 160 µg/cm^2	Weak but significant induction of micronuclei	Liu *et al*, 1996	2e
Syloid 244 [d]	Chromosome aberration	Human embryonic lung cells (Wi-38)	24 [e]	– S9	1 - 1,000 µg/ml	Clastogenic activity not significant	US-FDA, 1974	3a

Table 39: Mutagenicity and chromosomal aberration in cultured mammalian cells (cont'd)

Type/ Product name	Endpoint	Test system	Exposure time (h)	Metabolic activation [a]	Concentration tested	Result	Reference	CoR
Hydrophobic								
Pyrogenic								
Cab-O-Sil TS500	Clastogenic activity	Chinese hamster ovary (CHO) cells	12 4	– S9 + S9	63 - 500 µg/ml [b]	No clastogenic activity	Cabot, 1995l	1a
Cab-O-Sil TS530	Clastogenic activity	Chinese hamster ovary (CHO) cells	12 4	– S9 + S9	63 - 500 µg/ml [b]	No clastogenic activity	Cabot, 1994e	1a
Cab-O-Sil TS610	Clastogenic activity	Chinese hamster ovary (CHO) cells	12 4	– S9 + S9	63 - 500 µg/ml [b]	No clastogenic activity	Cabot, 1995m	1a
Cab-O-Sil N70TS [f]	Clastogenic activity	Chinese hamster ovary (CHO) cells	12 4	– S9 + S9	42 - 333 µg/ml [b]	No clastogenic activity	Cabot, 1995n	1a

[a] Induced by Aroclor 1254 from rat liver S9 mix
[b] Suspended in DMSO (dimethyl sulphoxide)
[c] Not applicable
[d] Also known as FDA 71-48
[e] Presumably
[f] Also known as Cab-O-Sil TS720

SAS (hydrophilic Cab-O-Sil) did not increase the mutation frequency at HPRT locus in Chinese hamster ovary (CHO) cells with or without metabolic activation (Cabot, 1990b).

In a study with SAS (hydrophilic and hydrophobic Cab-O-Sil) on possible chromosomal aberration with CHO cells, there was no indication of clastogenic activity of SAS with or without metabolic activation (Cabot, 1990c, 1994e, 1995l,m,n). Negative results were also reported with SAS gel (Syloid) for induction of chromosomal aberrations in human embryonic lung cells (Wi-38) without metabolic activation (US-FDA, 1974).

SAS gel (Spherisorb) was tested in V79 cells for micronuclei induction. Crystalline silica (Min-U-Sil 5 and 10) served as positive control. A weak, but significant, dose-dependent induction of micronuclei was observed at high doses (80 and 160 µg SiO2/cm2) in the presence of high cytotoxicity (not quantified in the publication). In the absence of cytotoxicity, no micronucleus induction was observed. Experiments with crystalline silica pre-treated with simulated pulmonary surfactants showed that the cytotoxicity was reduced and no micronuclei induced (Liu *et al*, 1996). In such experiments using prolonged exposures, the culture medium quality may be compromised and consequently induce artificial effects. The observed micronucleus induction may be the result of a secondary or indirect effect of cytotoxicity and not due to the interaction of the SAS particles with the genetic material or the spindle apparatus. Moreover, the nature of the SAS tested and possible surface chemistry are not specified in the report or otherwise known to the Task Force.

When SAS (Cab-O-Sil EH5) was tested for the ability to induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes, it was concluded that exposure up to 1,000 µg/ml did not induce DNA repair, although high cytotoxicity was noted (Cabot, 1989b).

In two single cell gel/comet assays with SAS gel (Spherisorb), using Chinese hamster lung fibroblast (V79) and human embryonic lung fibroblast (Hel 299) cells, significant, dose-related DNA migration was observed in cells exposed to 68.9 or 137.9 µg SiO_2/cm^2 for 3 hours. Observations were similar in both cell lines although in the SAS treated V79 cells the tail length appeared to decrease at the highest dose. Concentrations were lower and exposures were shorter than in a micronucleus test with the same SAS. The test substance was autoclaved. No information on cytotoxicity was given (Zhong *et al*, 1997). The method seems more sensitive for crystalline silica than for SAS. The authors mention the genotoxic potential of silicic acid, but this seems somewhat contradictory as crystalline silica is more genotoxic then SAS. Furthermore, the authors do not indicate if they believe that the mechanism of action is different between SAS and crystalline silica. Finally, the nature of the SAS tested and possible surface chemistry are not specified in the report or otherwise known to the Task Force.

8.4.2 *In vivo*

The available studies on genotoxicity of SAS (gel) *in vivo* are summarised in Table 40.

Table 40: In vivo mutagenicity of SAS gel (Syloid 244) following oral administration (US-FDA, 1974)

Endpoint	Test system	Protocol	Dose (mg/kgbw)	Result	CoR
Gene mutation (host mediated)	Mice (host) + *S. typhimurium* TA 1530, G-46 (indicator)	*i.p.* injection of *S. typhimurium* cells collected 3 h after last administration	1 or 5 × 1.4 - 5,000	No mutagenic activity	2e
Mitotic recombination (host mediated)	Mice (host) + *S. cerevisiae* D3 (indicator)	*i.p.* injection of *S. cerevisiae* cells collected 3 h after last administration	1 or 5 × 1.4 - 5,000	No genotoxic activity	2e
Chromosome aberration	Male Sprague-Dawley rat bone marrow	Killed 6, 24, 48 h	1 × 1.4 - 5,000	Negative	2e
Chromosome aberration	Male Sprague-Dawley rat bone marrow	Killed 6 h after last administration	5 × 1.4 - 5,000	Negative	2e
Dominant lethal mutation	Sprague-Dawley rat	8 mated, killed 14 days after mating for uterus examination	1 × 1.4 - 5,000	Negative	2e
Dominant lethal mutation	Sprague-Dawley rat	8 mated, killed 14 days after mating for uterus examination	5 × 1.4 - 5,000	Negative	2e

No mutagenic or genotoxic activity was reported in two host-mediated assays with SAS gel (Syloid 244) in *Salmonella typhimurium* or in *Saccharomyces cerevisiae* injected *i.p.* into mice orally exposed to single or repeated doses of up to 5,000 mg SiO_2/kgbw (US-FDA, 1974).

Single or repeated oral dosage of rats with Syloid 244 did not induce significant increases of chromosomal aberrations in rat bone marrow (US-FDA, 1974).

Under the same exposure conditions using Syloid 244, in a test for dominant lethal mutations, fertility index, total number of implantations of corpora lutea, pre-implantation losses, and dead implants from treated animals were not significantly different from controls. No dose-related or time-related patterns were found (US-FDA, 1974).

8.4.3 Other studies

SAS (Sigma Chemical, not further specified) did not demonstrate significant apoptotic potential in human alveolar macrophages (hMA) at 80 µg SiO2/ml when compared to a positively apoptotic dose of 133 µg/ml of crystalline silica (Min-U-Sil 5). Involved mechanisms are interaction with scavenger receptor and interleukin-converting enzymes (ICE and IL-1β release). It is suggested that the fibrotic potential of a particulate depends upon its ability to induce apoptosis of alveolar macrophages (Iyer *et al*, 1996).

Cytotoxic and cell transforming effects of various crystalline (quartz, cristobalite) and amorphous forms of silica (biogenic, synthetic) were evaluated in SHE cells (Elias *et al*, 2000). Hydrophilic SAS (Aerosil OX50) was neither cytotoxic nor transforming. The authors hypothesised that the observed inactivity of the tested SAS is related to the absence of surface reactivity, which appears to be involved in the mechanisms of the pathogenicity of certain forms of silica.

8.4.4 Summary and evaluation

SAS is not a gene point mutagen *in vitro*, using *Salmonella typhimurium*, *Escherichia coli* or *Saccharomyces cerevisiae*. SAS does not induce gene mutations in CHO cells or chromosomal aberrations in cultured mammalian cells.

Although primary repair (UDS) tests with SAS were negative, weakly positive results (micronuclei) have been obtained in Chinese hamster lung cells as well as in a single cell gel/comet assay, albeit in presence of high cytotoxicity (which could have caused an artefact). No cell transformation or apoptotic potential has been demonstrated for SAS.

Cytogenetic tests in bone morrow, dominant lethal tests in rat and host-mediated assays using *S. typhimurium* or *S. cerevisiae*, were clearly negative, indicating that SAS is not genotoxic *in vivo*.

The above results demonstrate that SAS is non-genotoxic in a variety of *in vitro* and *in vivo* tests.

8.5 Chronic toxicity and carcinogenicity

SAS gel (Syloid 244) was administered to B6C3F1 mice and Fischer rats (40/sex/group/species) in the diet for 21 and 24 months, respectively. Dosage was 0, 1.25, 2.5 or 5.0% of diet in the control, low, medium and high groups, respectively (Takizawa *et al*, 1988).

In both male and female mice, there was a transient significant (although minor) decrease in growth rate at the higher doses between weeks 15 and 50. The high dose group exhibited the greatest mean survival rate but there was no significant difference in survival rates between groups. The mean haematocrit and mean corpuscular volume at 12 months in females was somewhat lower than controls, but there was no evidence of altered haematological profiles between any groups at 12 and 21 months. Abnormal atrophy or hypertrophy of the liver, spleen, heart, and brain was sporadic between groups but did not appear to be sex, dose or time related.

In male rats, there was a transient significant increase in growth rate at the lowest dose between weeks 15 and 50. In males the high dose group exhibited the greatest mean survival rate but there were no significant difference in survival rates between groups. In females there was an inverse relationship between dose and survival rate but differences were not significant between groups. There were some erratic variations in haematology and serum biochemistry in both males and females but there was no pattern associated with sex, dose or time. Significantly lower liver weights were observed for females in the 2.5 and 5.0% dosage groups at 12 and 24 months. There was no difference in spleen, heart and brain weights between treatments. The atrophy or hypertrophy of the organs observed in each group was not sex- or dose-related.

The authors concluded that no significant dose-related effects were seen at any dose level upon clinical laboratory examinations and that dietary administration of SAS, under the conditions of the experiment, resulted in no long-term toxic effects.

In mice, there was no significant increase in neoplastic or non-neoplastic lesions of the examined tissues, which included the lymphatic system, lungs, liver and kidney.

In rats, there was no significant increase in neoplastic or non-neoplastic lesions of the examined tissues, which included the lymphatic system, lungs, liver, adrenals, testes, mammary gland and prepuce.

Hydrophobic SAS (Aerosil R972) was administered to Wistar rats (20/sex/group) in the diet (100 mg/kg/d) for 24 months. No malignant tumours were observed. There were no differences in type and/or number of benign tumours compared to controls. No other organ lesions were reported (Degussa, 1969; CoR 3b).

No chronic dermal toxicity studies are available. The results of chronic inhalation studies in animals were discussed in Sections 8.3.3 and 8.3.5.

8.5.1 Summary and evaluation

Chronic administration of SAS at a concentration of up to 5.0% in the diet to mice and rats causes no alteration in survival rate, bodyweight, food consumption, behaviour, organ weights or blood chemistry. Similar administration did not cause gross or microscopic changes or neoplasms in any examined tissues.

8.6 Reproductive toxicity

8.6.1 Developmental toxicity and teratogenicity

Pregnant albino CD-1 mice were dosed daily by gavage with SAS gel (Syloid 244) suspended in water at 0, 13.5, 62.7, 289 and 1,340 mg SiO2/kgbw from day 6 to 15 of gestation. Similarly, albino Wistar rats were given doses of 0, 13.5, 62.7, 292 and 1,350 mg/kgbw. Pregnant Golden hamsters were also given SAS by gavage for 5 consecutive days beginning on day 6 of gestation at doses of 0, 16, 74.3, 345 and 1,600 mg/kgbw/d. Dutch-belted female rabbits injected with 0.4 ml of chorionic gonadotropin were inseminated artificially with approximately 2 × 107 motile sperm cells. From day 6 to 18 of gestation, the females were dosed by gavage with SAS at 0, 16, 74.3, 345 and 1,600 mg/kgbw/d. In all of these studies there were no compound-related maternal deaths or significant variations of maternal body weight gain. There were no significant differences in the number of corpora lutea (measured in rabbit only), percentage of implantation and/or resorption, and weight of live pups when compared to controls. The number of external, visceral or skeletal abnormalities in the test groups did not differ from controls (US-FDA, 1973a,b,c,d).

Female Wistar rats were dosed daily with hydrophobic SAS (Aerosil R972) in the diet at 0 or 500 mg SiO_2/kgbw for 8 or 17 weeks before mating with males (5 F/1 M) similarly exposed for

4.5 months (Section 8.3.1: Degussa, 1963). Treatment was continued during breeding. Parents were not affected by the treatment whatever the parameter considered. There were no treatment-related effects in the litter size or birth weights; no clinical, behavioural or gross anomalies were observed at birth (Degussa, 1965a,b). The development of the progeny was normal and no treatment-related changes were observed in the 4-week old pups of both generations (Lewinson *et al*, 1994). These studies are summarised in Table 41.

Table 41: Developmental toxicity studies with SAS

Type/ Product name	Species, strain, number	Exposure period	Dose (mg/kgbw/d)	Result	NOEL, maternal and foetal toxicity (mg/kgbw/d)	Reference	CoR
Hydrophilic							
Gel		**(Day of gestation)**	**Gavage**				
Syloid 244 [a]	Rat, Wistar	6 - 15	0, 13.5, 62.7, 292, 1,350	No findings	> 1,350	US-FDA, 1973a	2e
Syloid 244	Mouse, CD-1	6 - 15	0, 13.5, 62.7, 292, 1,340	No findings	> 1,340	US-FDA, 1973b	2e
Syloid 244	Rabbit, Dutch-belted	6 - 18	0, 16, 74.3, 345, 1,600	No findings	> 1,600	US-FDA, 1973c	2e
Syloid 244	Hamster, Golden	6 - 10	0, 16, 74.3, 345, 1,600	No findings	> 1,600	US-FDA, 1973d	2e
Hydrophobic							
Pyrogenic			**Diet**				
Aerosil R972	Rat, Wistar	8 or 17 wk, then mated with M exposed for 4.5 months	0, 500	No findings	> 500	Degussa, 1963a,b; Lewinson *et al*, 1994	3a

[a] Reported as FDA 71-48

8.6.2 Effects on fertility

Following daily dosing of Wistar rats with Aerosil R972 in the diet at 0 or 500 mg SiO_2/kgbw for 6 months, pathological examination and comparison of organ weights (testis and ovaries) revealed no abnormal or treatment-related effects (Lewinson *et al*, 1994).

8.6.3 Evaluation

High-dose or long-term oral administration of SAS did not induce developmental toxicity in several animal species. These data support the conclusion that SAS has no toxic effect on development.

With regard to male and female fertility, no adverse effects on reproductive organs were found following oral exposure for 6 months.

9. EFFECTS ON HUMANS

9.1 Short-term toxicity

No data were found concerning systemic effects in humans following oral or inhalation exposure to SAS.

9.2 Irritation and sensitisation

9.2.1 Skin irritation

SAS is known to cause dryness of the (unprotected) skin and mucous membranes, which may result in mechanical irritation (Section 9.3.1: Plunkett and DeWitt, 1962).

9.2.2 Eye irritation

SAS can cause mechanical irritation of the eye.

9.2.3 Skin sensitisation

A patch test with SAS gel (Ludox HS40) in human volunteers produced no skin reaction. The patch was applied for 6 days and, after 2-weeks of incubation, challenged for 48 hours (DuPont, 1970).

A single, non-confirmed case of dermatitis, attributed to allergy, following skin contact with hydrophilic SAS (Russian 'Aerosil A300') has been reported, probably a misinterpretation due to broken skin associated with the drying effect of SAS (Lyashchenko *et al*, 1989). However, approximately 50 years of cumulative experience in SAS production plants has not produced a single case of suspected contact allergy (Degussa-Hüls, 2000; Rhodia, 2000; Wacker, 2000; Cabot, 2001).

9.3 Epidemiological studies and case reports

9.3.1 Industries producing SAS

A descriptive report of a cross-sectional health survey of workers currently exposed to SAS, of workers who had left jobs where they were exposed to SAS and of unexposed controls in 5

German factories has been made available. In 3 factories, the exposure was to pyrogenic SAS and in 2 factories the exposure was to precipitated SAS. A study that links these findings with exposure data and other potentially confounding variables is in preparation. Eligible for inclusion were 510 currently exposed workers who had at least one month's exposure and 497 (95.7%) agreed to be studied. Of these, 397 had complete data sets and were the 'current' workers. Of 269 former workers with at least one month's exposure after 1980 and who had left employment before 1994, 178 were males with a complete data set and were included as 'left' workers. Another 210 unexposed control workers also participated. The following data were compared: (i) a physician-administered questionnaire covering demographic data, height, smoking, medical history and current respiratory symptoms, (ii) atopy, determined by skin prick tests and specific IgE titres, (iii) Spirometric data and reversibility, (iv) carbachol bronchial provocation test and (vi) chest radiographs. There were some differences between the proportion of women in the exposed and control groups both within and between factories. Techniques of spirometry were also slightly different.

The prevalence of chronic bronchitis was within expected ranges but somewhat higher in exposed subjects. There were minor differences between plants and between exposed and control subjects for the standard spirometric measurements. The maximal expiratory flow at 50% FVC (MEF_{50}) was almost effort-independent. Differences between plants were absent or smaller with this parameter. The authors assume that more pronounced smoking habits in the exposed group is responsible for the small differences. The percentage of subjects with obstruction or restriction was no different between plants. Bronchial hyper responsiveness was within expected ranges for the study group. Chest radiographs showed no increased risk of pneumoconiosis of exposed subjects compared to controls. Relevant pleural thickening in exposed or non-exposed subjects was not observed. The results do not demonstrate a health risk due to SAS exposure (Merget and Kappler, 2005).

Pyrogenic SAS

An in-house evaluation was made of the medical records (from 1959 to 1985) of 143 German workers manufacturing pyrogenic SAS (Aerosil, not further specified). The exposure period ranged from 1 to > 30 years. Fifty-four workers complained of pulmonary symptoms such as dry cough, sputum and shortness of breath or exhibited abnormalities in lung pathology or function. Of these 54 workers, 59% had a case history of disorders or of confounding exposure, 56% were smokers, and only 22% had neither. No cases of silicosis were observed (Degussa, 1988). The value of this study is limited. The concentration of SAS during the exposure period is unknown and no attempt was made to calculate cumulative exposure. No statistical analysis was conducted to correlate exposure, smoking habits or other influencing factors with respiratory symptoms or lung pathology.

The chest X-rays of 215 workers involved in the production of pyrogenic Aerosil (substance not further specified) in Germany were evaluated. X-ray data were collected from 1947 to 1959. The average duration of exposure was not calculated, but only 9 of the employees had been employed for more than 10 years. Airborne SAS concentrations measured in 1959 in the bagging room and production room ranged from 2 to 7 mg SiO_2/m^3. Levels were considerably higher at the filling nozzle (15 - 100 mg/m^3), but it is unclear if these exposures occurred in the breathing zone of the workers. None of the X-rays showed any evidence of lung pathology (Volk, 1960). The value of this study is limited. The concentration of SAS during the exposure period is unknown and no attempt was made to calculate cumulative exposure. It would be unusual to find no evidence of pathology amongst such a large number of X-rays and it can be concluded that the X-rays were of poor quality and/or were poorly interpreted.

Precipitated SAS

The medical records of 165 workers involved in the manufacturing of precipitated SAS (Hi-Sil and Silene) in two industrial facilities in the USA were reviewed with regard to their annual spirometry, chest X-ray, and most recent respiratory questionnaire. For each worker, the extent of exposure was expressed as a cumulative index based on quantity and duration of exposure. Workers were exposed for 1 to 35 years with mean exposure duration of 8.6 years. Total SAS concentrations were measured by personal airspace gravimetric monitoring and graded on a scale of 1 (minimal, < 1.0 mg/m^3) to 4 (maximum, up to 10.0 mg/m^3). Sputum production and dyspnoea were inversely correlated with the cumulative exposure index, while cough and dyspnoea correlated with mean pack-years of smoking but not SAS exposure. Linear regression analysis of yearly change of all pulmonary function variables, including FVC, forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, and maximum mid-expiratory flow (FEF_{25-75}) showed no correlation with the either the dose of SAS or total years of exposure. Among 44 workers with a mean exposure time of 18 years, yearly decline of FVC and FEV_1 were similar to the overall group. Eleven workers had minimal radiographic evidence of pneumoconiosis, but they also had prior occupational exposure in limestone mines or soda ash plants using limestone, which the authors noted contained crystalline silica. Of 143 workers with serial radiographs and exposure to only SAS, none had radiographic pneumoconiosis. The authors concluded that respiratory symptoms in SAS workers correlated with smoking but not with SAS exposure, while serial pulmonary function values and chest radiographs are not adversely affected by long-term exposure (Wilson *et al*, 1979, 1981).

Company health records were reviewed for 78 men employed in the manufacture of precipitated SAS (Hi-Sil and Silene) in the USA. Duration of employment ranged from 1 year to 16 years and 7 months (average of 4.75 years). The percentage of time/employee exposed to SAS varied from less than 30% (7 employees), 50 to 90% (31 employees) to up to 100% (40 employees). Total

SAS levels ranged from 0.3 to 204 mg SiO_2/m^3. Symptoms included mechanical irritation of (unprotected) skin, eyes, nose and throat from dry dust contact and thermal burns of skin and eyes from wet slurry. The workers did not exhibit silicosis or any other pulmonary disease based on annual X-ray examination (Plunkett and DeWitt, 1962).

Workers employed in the manufacture of precipitated SAS in France were examined using pulmonary function test and X-ray. A group of 150 exposed workers (no controls) of similar socio-economical level were selected. Each subject was exposed (≥ 6 h/d) for at least 5 continuous or discontinuous years. Overall, the mean duration of exposure was 12.2 years. The control group was exposed for a maximum of 3 continuous or discontinuous months. Absence of past exposure to pneumoconiosis agents, smoking habits and medical history were checked using a specific questionnaire. The FEV_1, FVC, peak expiratory flow (PEF), FEF_{25-75}, maximal expiratory flows at 25, 50 and 75% of the vital capacity (FEF_{25}, FEF_{50}, FEF_{75}) were measured using a spirometer and converted into the percentage of predicted value for each person after adjustment for age and sex. Pulmonary radiographic examinations were performed during the year of the survey or the year before or after. The mean age was 43.1 and 44.3 for the exposed and control groups, respectively. The same percentage of abnormal spirometric measurements was observed in both exposed and control groups. There was no difference in the distribution and type of dysfunctional measurements observed between exposed and non-exposed groups. Smoking did not affect the results. There were no significant differences in the mean percentage of the predicted pulmonary function values between exposed and non-exposed groups. A slight, statistically non-significant, decrease in the MEF_{25-75}, MEF_{25}, MEF_{50}, and MEF_{75} was observed in the exposed group. None of the X-ray exams showed signs of pneumoconiosis or fibrosis (Garnier, 1996).

9.3.2 Other industries or occupations

Respiratory parameters were examined among 41 workers exposed to precipitated SAS (substance not specified) in a French chemical plant synthesising amino acids and vitamins. A control group consisted of 90 workers in the same plant with equivalent socio-economic status. A dust exposure index was calculated for each worker using quantity (measured from individual samplers: total dust 0 - 10.5 mg/m3, respirable dust 0 - 3.4 mg/m3) and duration of exposure (mean 8 y, range 1 - 28 y). No differences between the two groups were observed for blood gases, chest radiographs and most of the respiratory symptoms (by questionnaire). The exposed group reported a higher incidence of asthma and associated symptoms. In the exposed group, a significant decrease was found in measures of forced expiratory flow. However, this finding was not correlated with the exposure index, and additional analyses showed that smoking status was more relevant than exposure status. When the authors compared the effects of smoking status on forced expiratory flow, smokers (both exposed and controls) experienced significantly reduced

flow when compared to their non-smoking counterparts. Furthermore, forced expiratory flow measures in non-smoking, exposed workers were no different from values in non-smoking, control workers. The authors noted a positive interaction (synergistic) between cigarette smoking and SAS exposure in the induction of small airway disease; that is, decrements in pulmonary function were more than additive in the smoking, exposed group than in the smoking, non-exposed and non-smoking, exposed groups combined (Choudat *et al,* 1990).

Workers at a silicone products manufacturing plant were surveyed; 29 of the 126 workers were personally interviewed. Personal concentrations of SAS (substance not specified) ranged from 0.15 to 10 mg SiO_2/m^3, with a mean of 1.7 mg/m^3 (total particulate; 8-h TWA). Of the 29 employees interviewed, 15 worked in the room temperature vulcanising rubber area. Ten of the 15 employees complained of upper respiratory tract irritation. Although the majority of the affected employees attributed exposure to catalysts as the source of their irritation, 4 (or 3) employees indicated that SAS dust was the problem. (Note: The summary states 4 workers, but the results indicate 3 workers). The remaining interviewed employees worked in the heat curable rubber compounding area, where potential exposure to SAS is greater than the room temperature vulcanising area. Although some workers complained about eye irritation, nausea, headaches, or rashes, none of the workers complained about upper or lower respiratory problems (McQuilkin and Daniels, 1981).

Constrictive *bronchiolitis obliterans* was described in an animal feed worker (female, non-smoking), who developed severe irreversible airflow obstruction after working in the production of animal feed for 2 years. The worker had been exposed to precipitated SAS (Sipernat 22) and synthetic silicates, micro-organisms, proteolytic enzymes, various organic compounds and volatile acids. Chest X-rays were negative for infiltrates, but showed evidence of hyper-inflation. Transbronchial biopsy tissue was unremarkable, but lung biopsy tissue showed some exudative pleural reactions and scattered pleural fibrosis. Silica particles were detected in biopsy specimens. (Spain *et al,* 1995). Throughout the text, the authors refer to silica as amorphous and synthetic silicates; however, Table I in the article shows that crystalline silica was also present.

9.3.3 Summary

There is no evidence of cancer or other long-term respiratory health effects (for example, silicosis) in workers employed in the manufacture of SAS. Respiratory symptoms in SAS workers have been shown to correlate with smoking but not with SAS exposure, while serial pulmonary function values and chest radiographs are not adversely affected by long-term exposure to SAS (Plunkett and DeWitt, 1962; Wilson *et al*, 1979, 1981).

9.3.4 Agency reviews and recommendations

American Conference of Governmental Industrial Hygienists

Cunningham *et al* (1998) tabulated the human studies (same as discussed above) that were used by the American Conference of Governmental Industrial Hygienists (ACGIH) in their considerations. In a series of evaluations (ACGIH, 1986, 1989, 1992), the committee established and revised threshold limit values (TLVs) for SASs, including precipitated silica and silica gel, for which the ACGIH committee established a TLV-TWA average of 10 mg SiO_2/m^3, for total dust containing no asbestos and < 1% crystalline silica. The ACGIH stated that these forms of amorphous silica "have relatively little adverse effect on pulmonary function and do not produce significant disease or toxic effect when exposures are kept under reasonable control." ACGIH (2005b) intends to withdraw the specific values to due to insufficient data (Section 5.2.3).

International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC, 1997) considered the available literature on occupational exposure to amorphous silica, including diatomaceous earth, SAS, silica fume and fly ash, and biogenic silica fibres. Thus, the literature base from IARC's monograph is not applicable for this review. Since there was insufficient evidence of carcinogenicity in experimental animals and very little epidemiological evidence, IARC concluded that "Amorphous silica is not classifiable as to its carcinogenicity to humans (Group 3)."

US Environmental Protection Agency

The US Environmental Protection Agency (EPA), in Section 5.8 (epidemiology studies of amorphous silica exposures) of its health assessment document (US-EPA, 1996), briefly reviewed some studies on precipitated SAS exposure (Wilson *et al,* 1981). The agency also relied on ACGIH (1992). The EPA concluded that there was not enough information to develop a concentration-response relationship and to establish a NOAEL.

9.4 Reproductive and developmental effects

No data were found concerning reproductive or developmental effects in humans following exposure to SAS.

9.5 Neurotoxicity

No data were found concerning neurotoxicity in humans following exposure to SAS.

9.6 Summary and evaluation

SAS is essentially non-toxic in humans via the oral, dermal and ocular routes of exposure. Although no data exists concerning systemic effects in humans, animal studies and experience (use of untreated SAS as a direct food additive) indicates that no oral toxicity is expected. Approximately 50 years of cumulative experience in production plants has not produced a single case of suspected contact allergy. SAS may cause mechanical irritation of the eye and is known to result in dryness and possibly cracking of the skin following repeated exposure. Both of these effects are easily avoided using standard personal protective equipment (Section 10.2.1).

To date, there is no evidence of cancer or other long-term respiratory health effects (for example, silicosis) in workers employed in the manufacture of SAS. Respiratory symptoms in SAS workers have been shown to correlate with smoking but not with SAS exposure, while serial pulmonary function values and chest radiographs are not adversely affected by long-term exposure to SAS.

The human health effects, including carcinogenicity, have been reviewed by a number of agencies and SAS has not been listed as carcinogenic or hazardous (ACGIH, 1992; IARC, 1997).

10. FIRST AID AND SAFE HANDLING ADVICE

10.1 First aid

10.1.1 First aid and medical treatment

Standard first aid measures should be employed if an adverse reaction to SAS exposure occurs. Supportive medical treatment, as indicated by the subject's condition, is recommended.

10.1.2 Skin and eye injuries

Repeated exposure to SAS may cause skin dryness or cracking. Application of a skin barrier cream may help to avoid contact of the skin with SAS. Clothing contaminated with SAS should be removed, and contaminated skin washed with plenty of water and soap. Seek medical attention if redness, swelling, itching or burning occurs.

Flush contaminated eyes immediately with a steady flow of water. Seek medical attention if redness, swelling, itching, burning or visual disturbances occur.

10.1.3 Inhalation

Appropriate exhaust ventilation should be provided at machinery and places where SAS dust can be generated. If coughing, shortness of breath or other breathing problems occur, move the subject to fresh air. Seek medical attention if symptoms persist. If necessary, restore normal breathing through standard first aid measures.

10.1.4 Ingestion

Health injuries following ingestion of SAS are not known or expected. If ingestion of SAS occurs, do not induce vomiting. If the victim is conscious, give several glasses of water to drink. Obtain medical advice if symptoms develop.

10.2 Safe handling

10.2.1 Safety at work

SAS should be handled in well-ventilated areas. Avoid raising dust. Take precautionary measures against possible build-up of electrostatic charge in presence of flammable or combustible gases, vapours, or liquids.

When handling SAS, use suitable gloves. Application of a lotion or barrier cream is also recommended to prevent drying of the skin. If repeated or prolonged skin contact is likely, protective clothing should be worn. Eye protection is also recommended.

General and/or local exhaust ventilation should be provided to maintain airborne SAS levels below the occupational exposure limit. If this is not feasible, use suitable respirator protection, depending on the air concentration of SAS. Respiratory protection should be used only as part of a complete respiratory protection programme, in accordance with national standards and current best practice.

10.2.2 Storage safety

SAS should be stored in tightly closed containers in dry, cool, well-ventilated areas. Keep SAS away from volatile chemicals.

10.2.3 Fire and extinguishants

SAS does not pose an unusual hazard in the case of a fire. All general extinguishing media are suitable. Unused SAS will not burn. Highly treated SAS will with a carbon content of > 5% may lead to development of CO and CO_2, and form slightly explosive mixtures with air.

10.2.4 Protection against fire and explosion

In case of fire, wear suitable protective equipment.

In the presence of flammable, combustible or explosive gases, vapours, or liquids, ensure that all containers are well grounded. Also, use inert gas when working with flammable, combustible or explosive gases, vapours or liquids.

10.3 Management of spillage and waste

Collect spilled SAS into suitable waste containers for disposal. Prevent generation of dust.

SAS is not a hazardous waste and, depending on local and national standards, it can be disposed of in a landfill or by incineration. Release of SAS into soil, drains, sewers and water courses should be prevented.

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11.3 Databases consulted

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APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

Code of reliability (CoR)	Category of reliability
1	Reliable without restriction
1a	Good laboratory practice guideline study (OECD, EC, EPA, FDA, *etc.*)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, *etc*.)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	Reliable with restrictions
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	Not reliable
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	Not assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated
4e	Documentation insufficient for assessment

APPENDIX B: SAS TYPES MENTIONED IN THIS REPORT

The following hydrophilic and hydrophobic SAS types mentioned in this report are listed with names of producers (Table B.1 and B.2). Current trade names are given in Section 2.1.

Table B.1: Hydrophilic SAS (without surface treatment)

Type/ Product name	**Producer**
Pyrogenic	
Aerosil A300	Degussa
Aerosil 150	Degussa
Aerosil 200	Degussa
Aerosil OX50	Degussa
Cab-O-Sil fluffy [a]	Cabot
Cab-O-Sil EH5	Cabot
Cab-O-Sil H5	Cabot
Cab-O-Sil M7D	Cabot
Cab-O-Sil M5	Cabot
Cab-O-Sil F2	Cabot
Pyrogenic (Dow Corning Silica)	Cabot
HDK N20	Wacker
HDK T30	Wacker
HDK V15	Wacker
Precipitated	
FK700	Degussa
Hi-Sil 190	Pittsburgh Plate Glass
Hi-Sil 233	Pittsburgh Plate Glass
Sident 9	Degussa
Sident 20	Degussa
Silene	Pittsburgh Plate Glass
Sipernat 22 [b]	Degussa
Sipernat 22S	Degussa
Sipernat D10	Degussa
Tixosil 375	Rhodia
Tixosil 53	Rhodia
Tixosil 63	Rhodia

Table B.1: Hydrophilic SAS (without surface treatment) (cont'd)

Type/ Product name	Producer
Precipitated (cont'd)	
TK 800	Degussa
TS100	Degussa
Ultrasil VN3	Degussa
Zeo 49	JM Huber
Zeofree 153	JM Huber
Zeofree 80	JM Huber
Zeosyl 113	JM Huber
Zeosyl 200	JM Huber
Zeosil 45	Rhodia
Wessalon S	Degussa
Gel	
Gasil	Ineos (former Crossfield)
Silica G	Unknown
Silcron G-910	Millennium Inorganic Chemicals
Spherisorb 5 µ	Phase Separations
Sylodent 700	Grace
Syloid 244 [c]	Grace
Syloid 74	Grace
Sylobloc K300	Grace
Syloid HC	Grace
Sol	
Ludox 5-20-30% SiO_2	DuPont
Ludox HS40	DuPont
Ludox TM50	DuPont
Positive Sol 130 M 26% SiO_2	DuPont

[a] Same as or very similar to Cab-O-Sil M5
[b] Probably lower bulk density compared to Sipernat 22S
[c] Also known as FDA 71-48

Table B.2: Hydrophobic SAS types (surface treated)

Type/ Product name	Producer	Treating agent
Pyrogenic		
Aerosil R809	Degussa	HMDS [a]
Aerosil R972	Degussa	DDS [b]
Aerosil R974	Degussa	DDS
Cab-O-Sil N70TS [c]	Cabot	PDMS [d]
Cab-O-Sil silane treated	Cabot	Unknown [e]
Cab-O-Sil ST20	Cabot	HMDS
Cab-O-Sil ST22 [f]	Cabot	HMDS
Cab-O-Sil TS500	Cabot	HMDS
Cab-O-Sil TS530	Cabot	HMDS
Cab-O-Sil TS610	Cabot	DDS
Cab-O-Sil TS720	Cabot	PDMS
D500	Degussa	Unknown
HDK SKS130	Wacker	HMDS
HDK SKS300	Wacker	HMDS
HDK SKS300 VI	Wacker	HMDS with vinyl function < 1%
HDK H15	Wacker	DDS
HDK H20	Wacker	DDS
HDK VP KHD15 [g]	Wacker	PDMS
HDK VP KHD50 [h]	Wacker	PDMS
J-DCA TX104	Dow Corning	HMDS

[a] Hexamethyldisilazane CAS 68909-20-6
[b] Dimethyldichlorosilane CAS 68611-44-9
[c] Also known as Cab-O-Sil TS720
[d] Polydimethylsiloxane CAS 67762-90-7
[e] Actual identity of this product remains unclear
[f] Previous name aminopropylsilane-treated pyrogenic SAS
[g] Current name HDK H2015EP
[h] Current name HDK H2050EP

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