Nanoscale Materials Stewardship Program (NMSP) Voluntary Submittal Package

for

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

Prepared for:

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July 25, 2008

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Executive Summary

The Synthetic Amorphous Silica and Silicates Industry Association (SASSI) [1] is pleased to provide to the United States Environmental Protection Agency (US EPA) this data submission package for synthetic amorphous silica (SAS, CAS No. 7631-86-9) under the voluntary basic program of the Nanoscale Materials Stewardship Program (NMSP). SASSI recognizes the importance of the NMSP program and its aims to "gather existing data and information from manufacturers, importers, processors, and users of existing chemical nanoscale materials," to "identify and encourage use of risk management practices in developing and commercializing nanoscale materials," to "encourage the development of additional test data," and to "encourage responsible development of nanoscale materials." (US EPA, 2008). This submission package was prepared with the assistance of Gradient Corporation.

SASSI's data submission focuses on synthetic amorphous silica (SAS), a form of silicon dioxide (SiO_2) that is intentionally manufactured, and hence differs from other classes of amorphous silica (*i.e.*, naturally occurring amorphous silica such as diatomaceous earth, which contains some crystalline silica). There are essentially two main polymorphs of SAS that are described according to their manufacturing process: wet process silica (CAS # 112926-00-8, precipitated silica or silica gel) and thermal process silica (CAS # 112945-52-5, pyrogenic silica). Inhalation exposure to SAS in occupational settings is associated with only transient and reversible pulmonary effects in humans and animals. SAS is distinct from and contrasts with crystalline silica, for which elevated exposures have been associated with increased risk for pulmonary diseases such as silicosis, tuberculosis, chronic obstructive pulmonary disease (COPD), and lung cancer. For SAS, available epidemiological studies do not support adverse health impacts from SAS exposure in occupational settings (ECETOC, 2006).

SAS is a component of a diverse range of products, *e.g.*, fillers in rubber and tires, free-flow or anti-caking agents in powder materials, and liquid carriers in the manufacture of animal feed and agrochemicals. Many consumer products such as toothpaste, cosmetics, paints, and adhesives contain SAS. Worldwide production was estimated to be over 1.3 million metric tons in 2004 (Waddell, 2006).

[1] SASSI Member Companies: Rhodia, Inc., Cabot Corporation, PPG Industries, Inc., PQ Corporation, J.M. Huber Corporation, Evonik Industries, W. R. Grace & Co., and Wacker Chemical Corporation.

SAS has been in commerce for over sixty years , and it is SASSI's understanding, based on US EPA's Federal Register Notice (January 28, 2008) describing the NMSP, that the Agency seeks data on recently invented "engineered" nanoscale materials and also on other well-known substances that are nanostructured (US EPA, 2008). SAS is an existing substance already listed on the TSCA chemical inventory under the general CAS number for silicon dioxide (CAS No. 7631-86-9). In accordance with nanotechnology definitions currently in development by the International Organization for Standardization (ISO) Technical Committee (TC) 229 and the Organisation for Economic Co-operation and Development (OECD) Working Party on Nanotechnology (WPN), SAS would be considered a nanostructured material rather than a nanoparticle. [2] Thus, we present available information on exposure and health effects of SAS conforming to US EPA's basic NMSP.

This data submission was prepared to address the requirements of the basic NMSP program. Although SASSI appreciates the US EPA preference for submitters to use an optional data submission form, we have structured our own data submittal package, following US EPA's instructions that "participants may provide data in any format or on any form that they choose" (US EPA, 2008). Based on guidance provided in US EPA's "Concept Paper for the Nanoscale Materials Stewardship Program Under TSCA" and "Support Statement for an Information Collection Request (ICR)," we have organized information in this data submittal under four general categories: Material Characterization, Use and Potential Exposures, Hazard Assessment, and Risk Management (US EPA, 2007). In addition, in this submittal, SASSI has endeavored to address the suggestions and questions posed by EPA staff at a June 18, 2008 meeting at EPA offices in Washington, DC, with EPA and SASSI representatives.

Importantly, this submission primarily addresses manufactured SAS used in a number of well-established applications, rather than modified forms of SAS that may be found in some end-user products.

This submission presents available information from the peer-reviewed literature and official review documents to support three key conclusions regarding the properties and health effects of SAS:

[2] As discussed in greater detail in Section 1 of this data submittal, materials characterization data show that, as placed on the market, SAS products typically consist of particles that are larger-sized aggregates and agglomerates rather than individual nanoparticles. Although nano-sized upon their formation during manufacturing, primary SAS particles rapidly form stable aggregates and more transient agglomerates, with final SAS products typically consisting of large agglomerates that do not easily break down unless strong force is applied. Since these aggregates and agglomerates retain the surface structure of nano-sized primary SAS particles, manufactured SAS can be viewed as a nanostructured material.

(1) Solid powder forms of manufactured synthetic amorphous silica (SAS) are nanostructured materials rather than nano-objects[3] or nanoparticles.[4] A nanostructured material has features which are on the nanometer length scale but overall do not have dimensions at the nanoscale. This general point will be substantiated by describing SAS morphology and discussing what is known about the size and properties of manufactured SAS. Colloidal forms of SAS (or Silica Sol), or SAS suspensions in liquid (typically water), wherein SAS can exist as discrete nanoparticles, are not covered in this submission.

(2) The health effects of SAS have been reviewed in recent years, and all the available data on worker populations and animal studies support the fact that SAS is a non-toxic substance with characteristic health impacts that are similar to other low-toxicity, biologically inert dusts.

(3) Industrial hygiene practices regarding the control and handling of SAS are grounded in over 60 years of manufacture and use, and collected exposure data and worker experience do not indicate any adverse worker health impacts (ECETOC, 2006).

Overall, it is the conclusion of SASSI that SAS is a substance that does not pose any unique toxicity due to its nanostructure or other physical-chemical properties. Even in the populations with the potential for elevated SAS exposures, namely occupationally-exposed workers, evidence for adverse health effects is limited and relates primarily to general effects similar to those of other nontoxic, inorganic dusts. Based on available studies on health effects, SAS presents little (if any) health risk when handled properly.

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[3] ISO/TS 27687 (ISO, 2007) defines a nano-object to be a material with one, two, or three external dimensions at the nanoscale.

[4] ISO/TS 27687 (ISO, 2007) defines a nanoparticle as a particle with all three external dimensions at the nanoscale.

1 Material Characterization

Commercially available solid forms of synthetic amorphous silica (SAS) are nanostructured materials composed of micron-sized agglomerates rather than free nano-sized particles. In this section, we describe what is known about the chemical and physical properties of different forms of SAS during their manufacture and use. For the purposes of the NMSP submission, this section focuses on the size characterization of SAS. Specifically, we summarize studies that support the fact that commercial powder forms of SAS are large particles in the micron size range.

1.1 Sources, Manufacturing and Properties of Synthetic Amorphous Silica

Silica is the common name for silicon dioxide (SiO_2), which is composed of two of the most abundant elements on earth, oxygen and silicon. Indeed, silicon accounts for about 28% of the mass of the earth's crust (IARC, 1997). There are two general classes of silica, amorphous and crystalline silica, and both of these forms can be either naturally occurring or man-made. All forms of silicon dioxide fall under the generic CAS No. 7631-86-9, and they are all included in the US EPA TSCA inventory under this CAS number. However, to differentiate between these structural forms of silica, new CAS numbers have been generated in recent years for pyrogenic silica (112945-52-5) and for precipitated silica and silica gel (112926-00-8). [5]

Table 1-1 lists the general physical and chemical properties of silica and in Figure 1-1, the various classes of silica and associated CAS numbers are provided. Table 1-2 gives many of the commercial product trade names for the three major forms of solid SASs. The distinction between crystalline and amorphous forms of silica is an important one, because exposure to the crystalline form has been associated with a number of pulmonary health effects, including silicosis and possibly lung cancer, while studies of amorphous silica have not established evidence for adverse chronic health effects (ECETOC, 2006).

[5] As discussed in US EPA (1990), although new CAS numbers have been issued to differentiate the multiple physical forms of amorphous silica, these CAS numbers have not been added to the TSCA Inventory. As explained by US EPA (1990), this is because these CAS numbers were not issued in response to any TSCA review and/or registration activities. Furthermore, since the different physical forms of amorphous silica do not differ in their basic chemical composition, US EPA does not consider the different physical forms of amorphous silica to be separately reportable under TSCA.

Table 1-1 Summary of General SAS Identity and Physical and Chemical Properties (from OECD, 2004)

CAS Number:	7631-86-9 (Silica) 112945-52-5 (Silica, amorphous, pyrogenic) 112926-00-8 (Silica gel, precipitated)
Chemical Name:	Silicon dioxide
Molecular formula:	SiO_2
Molecular Weight:	60.08 g/mol
Substance type:	Inorganic
Physical state:	Solid, amorphous
Degree of Purity:	>95 %
Melting point (° C)	approx. 1700
Boiling point	Not applicable
Bulk density (g/L)	50-320
Vapor pressure	none
Water solubility (mg/L)	Approx. 15-68 at 20 °C
Partition coefficient n-octanol/water (log value)	Not applicable
Henry's law constant	Not applicable
Particle Size	Depends on form of Silica, See Table 1-3

Table 1-2 Registered Trade Names ® for Various Forms of SAS (ECETOC, 2006)

Silica Form	**Trade names ®**
Pyrogenic Silica	Aerosil, Cab-O-Sil, HDK, Cab-O-Sperse
Precipitated Silica	Acematt, Agrosil, Baysical, BS, Ciptane, Durosil, Elfadent, Gomasil, OK, HK, TS, TK, Flo-Gard, Hi-Sil, Huberderm, Huberpol, Hubersil, Hubersorb, Lo-Vel, Microsil, Neosyl, Neosil, Orasil, Perkasil, Eheosil, Rhodaxane, Rhoximat, RxCipients, San-sil, Sident, Silcasil, Silene, Siloa, Sipernat, Sorbosil, Sylowhite, Tixosil, Ultrasil, Vulkasil, Wessalon, Zeo, Seocal, Zeocopy, Zeodent, Zeofoam, Zeofree, Zeolex, Zeopharm, Zeopol, Zeosil, Zeosyl, Zeothix, ZS
Silica Gel	Chillgarde, EP, ES, Daraclar, Gasil, Lucilite Sorbsil, Silcron, Silica, Sil-Proof, Syloid, Sylodent, Sylojet, Syloblanc, Trisyl, Quantum, Britesorb

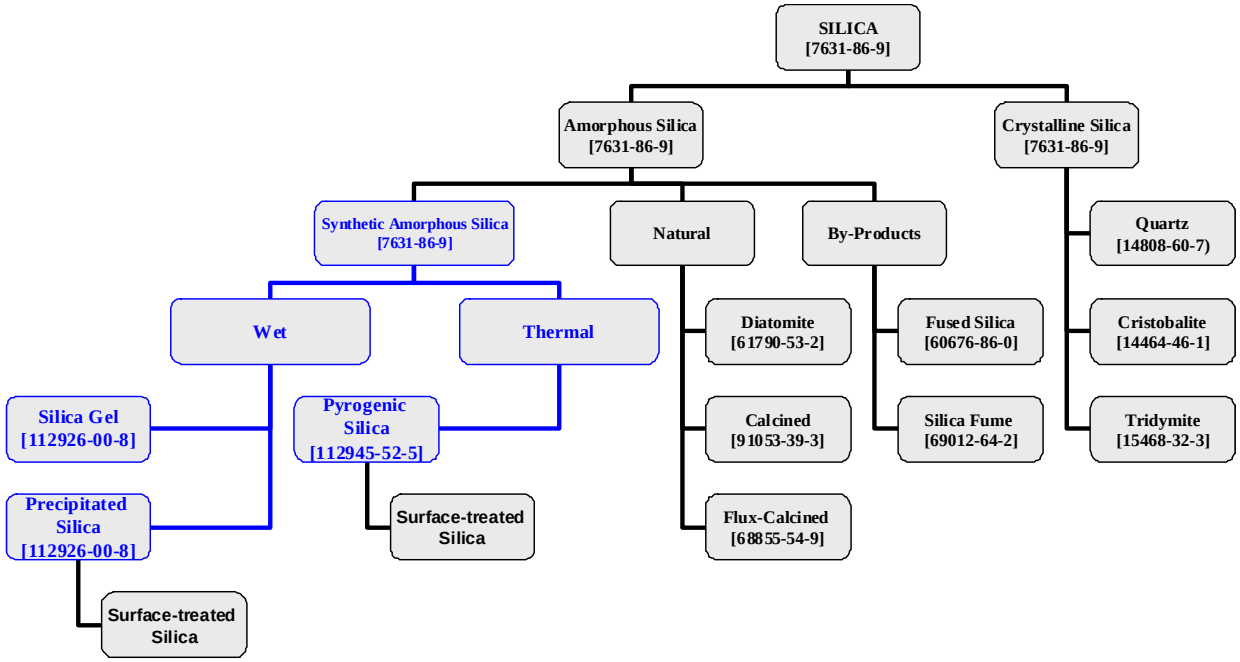


Figure 1-1 Polymorphs of Silica (adapted from ECETOC, 2006)

The building block of silica is the SiO_4 tetrahedron shown in Figure 1-2, which typically contains 4 oxygen atoms at the corners of a regular tetrahedron with silicon at the center. The siloxane (Si-O) bond length is only 0.162 nm, resulting in a bond with partial ionic character and high stability (Bergna and Roberts, 2006). The polymorphisms of silicas are based on different linkages of the tetrahedral $[SiO_4]^{4-}$ units. The crystalline silicas (quartz, tridymite, and cristobalite) form three-dimensional highly organized networks where the 4 oxygen atoms are shared with adjacent groups, with quartz being the most stable at room temperature. In contrast, the bulk structure of amorphous silica is determined by random packing of $[SiO_4]^{4-}$ units, resulting in a non-periodic structure as shown in Figure 1-3 (Bergna and Roberts, 2006).

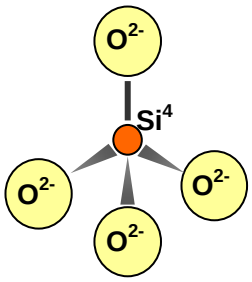
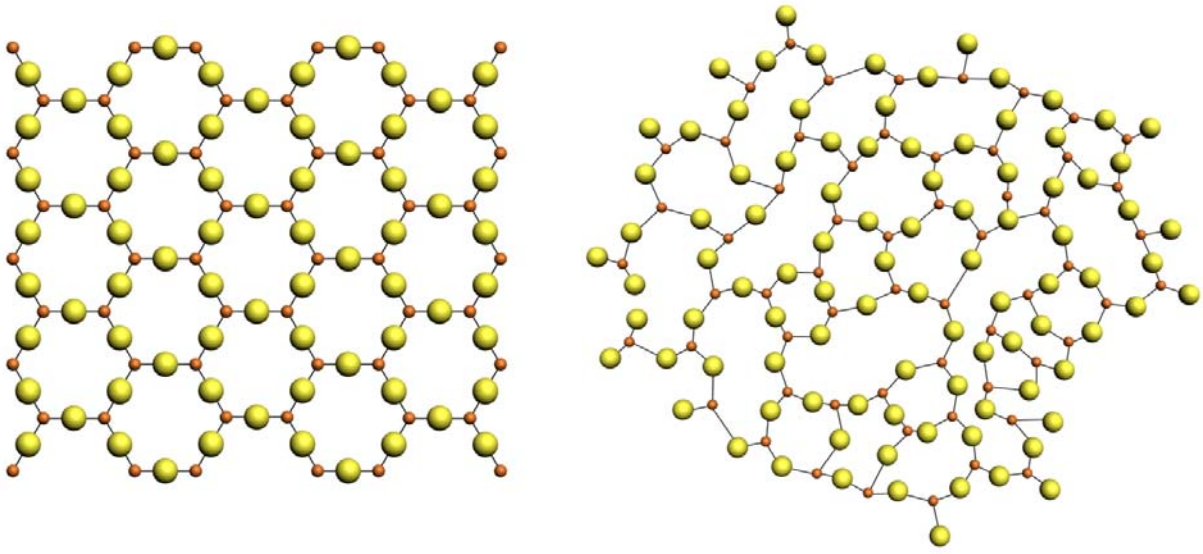


Figure 1-2 The Silica Tetrahedron



(a) **(b)**

Figure 1-3 Structural Differences Between Crystalline and Amorphous Silica (a) cross-sectional view of crystalline silica demonstrating the regular and periodic order and (b) cross-section of amorphous silica showing no regular order beyond the fundamental base of the tetrahedron

As shown in Figure 1-1 in blue, the two types of SAS that are covered in this submission are classified by their manufacturing process, *i.e.*, wet process silica (precipitated silica or silica gel) and thermal process silica (pyrogenic silica). There are other specific SAS varieties that are not covered in this submission. These include colloidal silica (silica sol), which encompasses stable dispersions of SAS in a liquid medium (typically water), and surface-modified SAS that is chemically treated to modify its surface characteristics (*e.g.*, to render the silica hydrophobic).

The two basic forms of SAS are characterized by their manufacturing process. Thermal or pyrogenic silica (also referred to as fumed silica, but distinct from fused silica or silica fume) is manufactured *via* a combustion process that involves volatile chlorosilanes and/or methylchlorosilanes being fed into a burner together with a mixture of hydrogen and air (Figure 1-4). The structural properties of pyrogenic silica are largely determined during manufacturing by adjusting the feed rates of hydrogen, air, and silanes into the burner (Bergna and Roberts, 2006). The specific surface area and particle size are primarily determined by the flame temperature (Bergna and Roberts, 2006). This

manufacturing process has been studied and described extensively in the literature (for *e.g.* see Roth, 2007; Tsantilis and Pratsinis, 2004; Ulrich, 1984; Wooldridge, 1998).

The mixture of volatile chlorosilanes and/or methylchlorosilanes, hydrogen, and air is combusted in a reaction chamber with temperatures that range from 1200 to 1600 °C. This flame produces silicon dioxide molecules which immediately nucleate and begin colliding to form SiO_2 nuclei. At this point in the process, coagulation rates are very rapid. Thus nuclei collide and rapidly sinter and coalesce into spherical primary particles. After some time, heat losses from the reactor cause a decrease in the temperature such that sintering and coagulation rates are approximately equal. At this point, the surface area (usually $<400 m^2/g$) and primary particles (typically ~5-50 nm) have reached their ultimate value. However, it should be noted that these primary particles do not exist outside of the reaction chamber due to rapid coagulation (Barthel *et al*., 1999). This is further demonstrated by Figure 1-5 which shows that coagulation results in the depletion of individual nanoparticles on the order of milliseconds (Ulrich, 1984). Moreover, because the decrease in reactor temperature is relatively slow, particles either completely coalesce or are sintered into much larger particles. Thus, coagulation continues and the sintering rate is sufficient that primary particles fuse upon collision to form stable silicon dioxide aggregates (~0.1 - 0.5 μm).

This process continues until reactor temperatures are decreased to the point where the sintering rate is effectively zero. Even though the collision rate has decreased significantly at this point, these aggregate clusters continue to collide, resulting in particles that are bound by Van der Waals forces and hydrogen bonding. These particles, known as agglomerates, typically range from ~0.5μm to >250 μm depending on how and at what point in the process they are measured (EC, 2007; IARC, 1997; IUCLID 7631-86-9; ECETOC, 2006). In the remaining steps of the process, silica agglomerates are filtered from the byproduct hydrochloric acid gas typically *via* baghouse filtration. The product is then heated to remove any residual hydrochloric acid. The resulting product is a fluffy white powder composed of stable micron-sized particles. Figure 1-6 shows a diagram of the thermal manufacturing process and Table 1-3 lists some of the properties of pyrogenic silica.

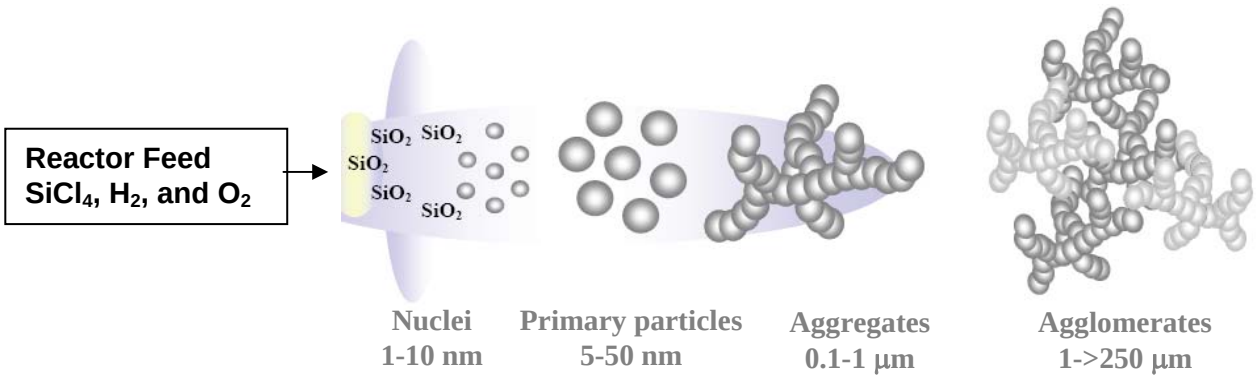


Figure 1-4 General Structure Development Sequence During SAS Manufacturing (from ECETOC, 2006)

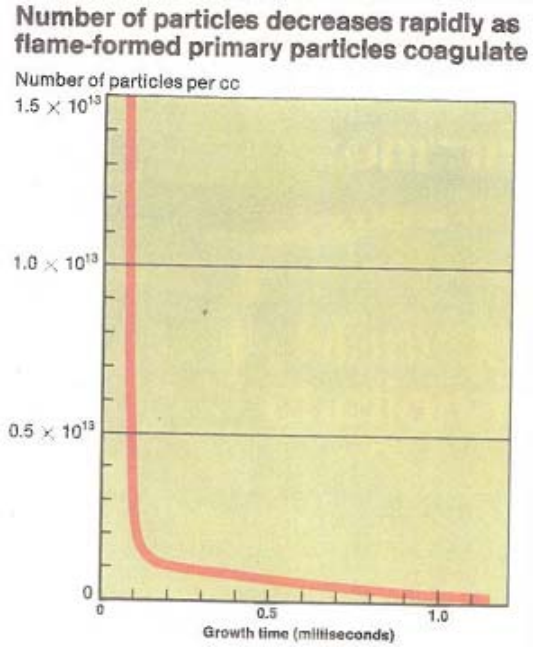


Figure 1-5 Depletion of the Small Particles Over Milliseconds

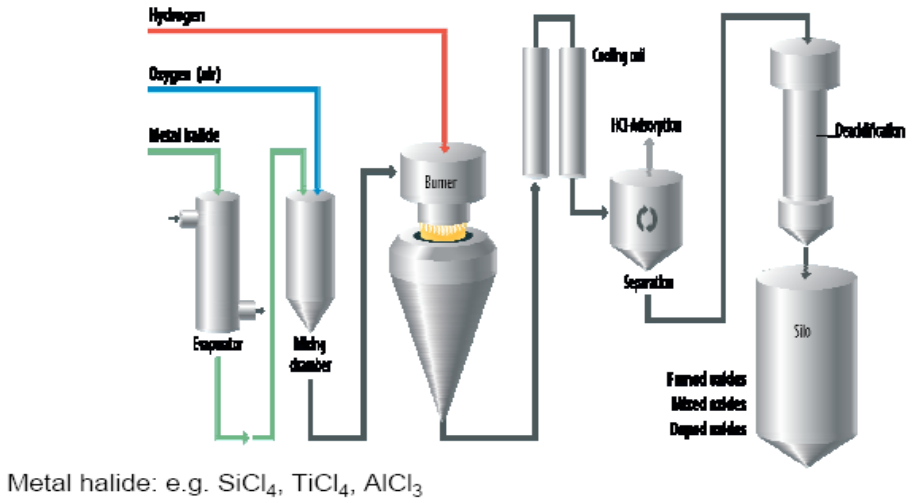


Figure 1-6 Typical Process Diagram for the Manufacture of Pyrogenic SAS (from Maier, 2008)

Synthetic amorphous precipitated silica and silica gels are manufactured *via* a wet process that involves an alkali metal silicate solution (or water glass) and acids, typically sulfuric acid. The process steps, as shown in Figures 1-7 and 1-8 for precipitated and silica gel, respectively, involve precipitation, filtration, washing, drying, milling, and granulation, followed by packing and shipping of the product. The size of the primary particles and the amount of aggregation and agglomeration are determined by the reaction conditions such as the pH, temperature, concentration, and amount of stirring. Silica gels are generally manufactured under acidic conditions with primary particles in the range of 1-10 nm that quickly adhere to form aggregates ranging from 1-20 μm upon drying. On the other hand, precipitated silica products are manufactured under neutral/alkaline conditions with primary particles in the range of 5-100 nm, aggregates ranging from 0.1-1 μm, and agglomerates ranging from 1-250 μm.

After precipitation, the various silica products are filtered *via* different methods (*e.g.* filter press, membrane filter press, or belt/drum filter) depending on the product being manufactured. At this stage, the product is also washed to remove any salts. The product is then dried either by plate, belt, or rotary drum. Alternatively, spray dryers can be used. Lastly, the milling stage establishes the final particle size distribution (ECETOC, 2006). Typical physical and chemical properties of precipitated silica and silica gel are given in Table 1-3. An overview of the manufacturing processes for various forms of silica is shown in Figure 1-9.

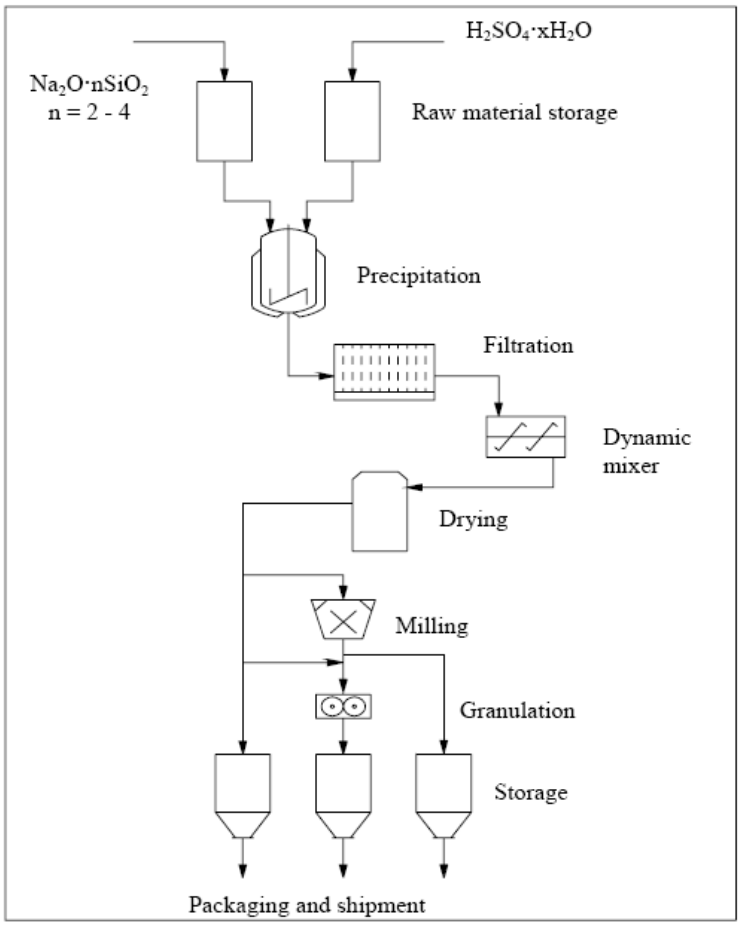


Figure 1-7 Manufacturing of Precipitated SAS (from ECETOC, 2006)

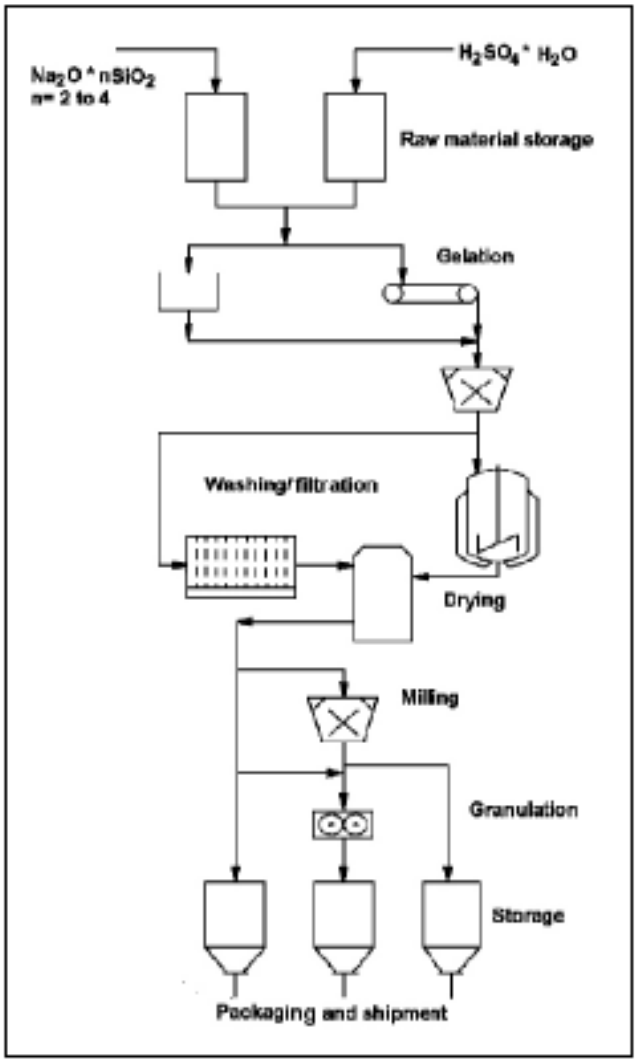


Figure 1-8 Manufacturing of Silica Gel (from EC, 2007)

Table 1-3 Typical Physical and Chemical Properties of Specific SAS Forms (from ECETOC, 2006)

Property (units)	Pyrogenic	Precipitated	Gel
Purity, % SiO_2 (by weight)	>99.8	>95	>95 (dry)
Color	white	white	white
Specific surface area (BET, m^2/g)	50-400	30-500	250-1,000
Loss on drying (% by weight)	<2.5	5-7	2-6
pH	3.6-4.5	5-9	3-8
Tapped (bulk) density (g/L)	30-250	30-500	500-1,000
Ignition loss (% by weight)	<2	3-14	2-15
Particle size			
Primary particle (nm)	5-50	5-100	1-10
Aggregate (μm)	0.1-1	0.1-1	1-20
Agglomerate (μm)	1-250*	1-250*	NA
Porosity			
Mean pore size (μm)	None	>0.03	0.0001-1
Pore size distribution	None	very wide	narrow
Specific gravity (g/cm^3)	2.2	1.9-2.2	1.8-2.2
Structure, DBP absorption (ml/100g)	250-350	80-320	80-350

* Agglomerate particle size is typically 100 μm

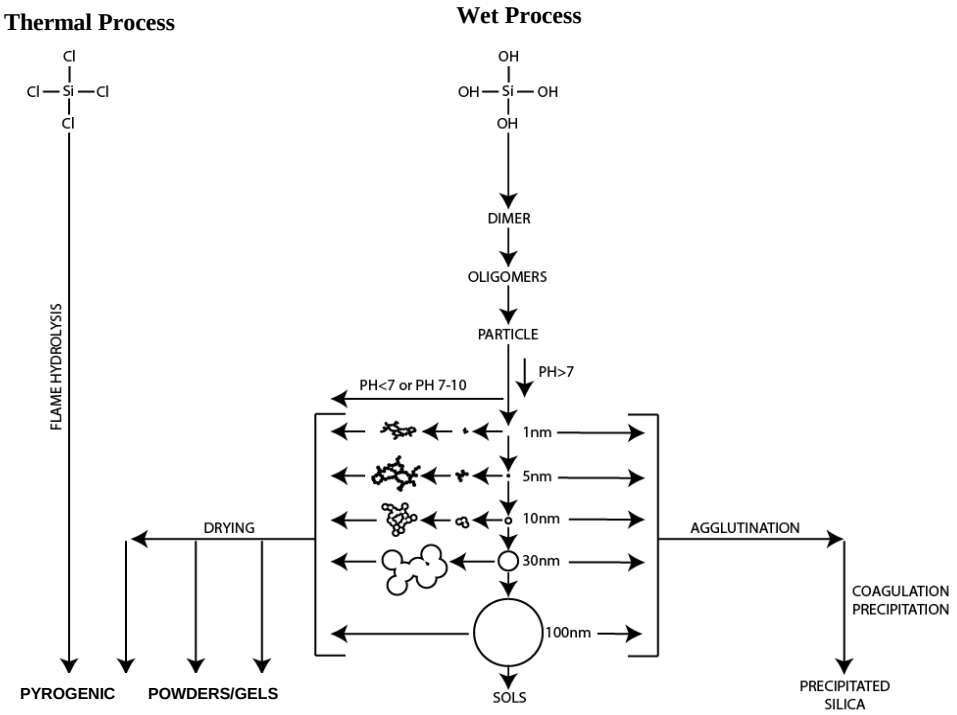


Figure 1-9 Overview of Silica Product Manufacturing Processes (from Bergna and Roberts, 2006)

The manufacturing process, feedstock, and reaction conditions (*e.g.*, flow rates, temperature, and pH) determine the different forms of SAS and their uses in a number of different products. SAS has gained usage as a reinforcing agent in silicone rubber products such as elastomers, as a thickening agent and for inhibiting separation of pastes and ointments (toothpaste), as a carrier of fragrances and flavors, as a functional pigment and flattening agent in paints and paper products, as an anti-caking agent in food products, as an excipient in pharmaceuticals, and as a semiconductor polishing agent in chemical mechanical planarization (Bergna and Roberts, 2006; ECETOC, 2006). Some of the applications of specific forms of SAS and related critical properties are listed in Table 1-4.

Table 1-4 Some Applications of Synthetic Amorphous Silica Forms

Form of SAS	Application	Important Properties
Gels	Desiccant, adsorbent	Porosity
	Paints: matting	Aggregate size
	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size
Precipitated	Rubber reinforcement	Particle size, surface area
	Free-flow, anti-caking agent	Aggregate size, porosity
	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size
	Paints: matting	Aggregate size
Pyrogenic	Rubber reinforcement	Surface area, purity, structure
	Heat insulation	Aggregate size, purity
	Rheology control (liquid systems)	Surface chemistry, aggregate/agglomerate size
	Chemical Mechanical Planarization	Aggregate size/agglomerates size, purity
	Anti-caking	Particle size, surface area

Solid forms of SAS, including pyrogenic and precipitated silicas and silica gels, are white, fluffy, or powdery amorphous forms of silicon dioxide (SiO_2). Furthermore, these industrial solid forms of SAS are characterized as high purity substances consisting of 95-99.8% SiO_2 with only trace amounts of other metal oxides, sulfates, and/or chlorides present. Pyrogenic silica is the purest form of SAS (>99.8% SiO_2) (ECETOC, 2006).

Given that SAS consists of a relatively unreactive hydrophobic siloxane unit (Si-O-Si) and hydrophilic silanol groups (Si-OH), the solubility of SAS depends on the number of silanol groups per unit surface area (per nm^2). For wet process silica gels, the concentration of silanol groups range from 5 to 8 SiOH/nm^2 and for pyrogenic silica, the number is much lower due to the thermal process, ranging from 1.25 to 2.5 SiOH/nm^2. In general, synthetic amorphous silica is much more soluble than crystalline silica. The saturation concentration in water averages about 120 mg/L compared to 5 mg/L for crystalline silica (ECETOC, 2006). Furthermore, the saturation concentration increases with increasing specific surface area of the SAS (or decreasing particle size). The solubility of SAS has implications for its toxicity, as more soluble forms of silica will be removed from the lungs at a much faster rate. Studies simulating the dissolution behavior of SAS in the lungs under physiological conditions show that total dissolution occurs within one day and that dissolved SAS is likely to be rapidly removed from the lungs (ECETOC, 2006). Also of note, dissolved silica is rapidly excreted from the body via urine. Details from these studies can be found in section 2.3.2 of the ECETOC report (2006).

Other key properties of specific forms of SAS are listed above in Table 1-3. Depending on the manufacturing process, SAS forms differ across several physical and chemical properties, including size and surface area. In addition, the loss on drying, a measure of the amount of physically bonded water, differs for pyrogenic SAS, which has the lowest water content (2.5% or less), and wet process SAS (2-15%). The tapped density describes the weight of the bulk product in powder form. Typical values range from 50 g/L for milled SAS products to 600 g/L for granulated or very dense products. Lastly, porosity is an important characteristic of many SASs. The International Union of Pure and Applied Chemistry (IUPAC) distinguishes between micropores (diameters d = 2 nm), mesopores (d = 2–50 nm), and macropores (d > 50 nm). Pyrogenic SAS is characterized as having no or very small pores (microporous), whereas precipitated and silica gel can be either mesoporous, macroporous, or microporous.

1.2 Particle Size Characteristics of SAS

As discussed below, based on a considerable body of research on the manufacturing process of SAS and materials characterization data, solid forms of manufactured SAS are known to consist predominantly of particle aggregates and agglomerates that generally have sizes exceeding 100 nanometers and ranging up to hundreds of microns. Indeed, solid forms of SAS (precipitated, pyrogenic, and silica gel) belong to the family of industrial aciniform aggregates (IAA), aciniform meaning "clusters of grapes". These IAAs are of significant commercial importance, as some 15 million metric tons are produced worldwide each year (Gray and Muranko, 2006). IAAs have in common the fact that aggregates are formed from primary particles that collide and are chemically bonded, resulting in stable entities. As described in the previous section, these aggregates can further adhere to each other forming larger, but more weakly attached agglomerates that are held together by hydrogen bonding and Van der Waals forces. Figure 1-10 illustrates the differences between a primary particle, an aggregate, and an agglomerate for aciniform compounds. Due to nucleation and condensation, particle growth occurs during the manufacturing of all solid forms of SAS (pyrogenic, precipitated, and silica gel) and thus the aggregates are the smallest and most stable entity for these forms of SAS. The aggregate size for most solid SAS ranges from about 0.1 to 1 μm. Although primary particles exist for solution-based SAS (silica sol) these particles quickly agglomerate upon drying. Thus, solid powder forms of commercial SAS do not exist as easily dispersible nanoparticles (*i.e.*, particles with a diameter of <100 nm). Surface-modification of SAS, which typically renders the product hydrophobic, tends to enhance agglomeration resulting in larger clusters of particles.

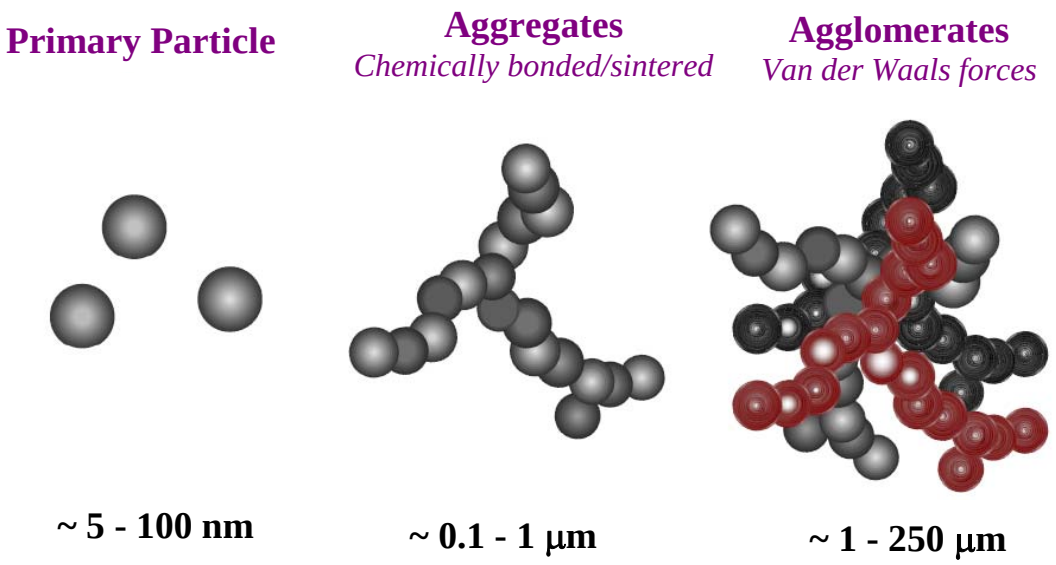


Figure 1-10 Agglomerate of Industrial Aciniform Aggregates (IAA) Showing the Primary Particle, Aggregate, and Agglomerate Structures (adapted from Maier, 2008)

As described in the ECETOC report (2006), particle size distributions have been characterized under typical SAS handling conditions (filling, shipping, and storage of SAS products). These conditions involve handling dry powder SAS at high concentrations. The sizing methods used to assess distributions of particle dimensions were non-destructive (*i.e.*, low shearing) methods, such as dry sieving and Fraunhofer laser light diffraction. By the dry-sieving method, no particles were found to pass through a mesh size of 90 μm and 35-83% of particles were found to pass through a mesh size of 125 μm. Using the Fraunhofer laser light diffraction method, pyrogenic SAS samples were estimated to have an average aerodynamic diameter of ~200 μm. Furthermore, the respirable fraction (portion of particles that can penetrate into the lungs, *i.e.*, below 10 μm aerodynamic diameter) for pyrogenic SAS comprised <1% by weight. These results support the fact that during manufacturing and handling of SAS products, worker are not exposed to particles in the nano-sized range.

These results are consistent with the findings of Gray and Muranko (2006) who reported that aggregates are the smallest separable entity for manufactured SAS, even for conditions of severe mechanical processing. In a series of experiments, which included mechanical processing *via* uniaxial compression, elastomer mixing, or ultrasonication, Gray and Muranko (2006) provided data that showed no release of primary SAS particles. Furthermore, the researchers observed that, although there can be

fracture of the largest and most complex aggregates under the high energy conditions of their experimental methods, this resulted in only modest reductions in the size of the largest aggregates.

In a similar study, Sauter *et al*. (2006) reported on dispersion of Aerosil 200V, a pyrogenic silica, in liquid using ultrasonic treatment or treatment *via* a rotor-stator system (*i.e., via* mechanical mixing). Due to the high tendency for these particles to agglomerate, the researchers found that very high energies were required (~10 GJ/m^3 = 10^{10} J/m^3) to obtain modest size reductions (from ~180 nm to ~120 nm). Interestingly, despite a similar amount of energy applied, the rotor-stator system was not able to achieve the same size-reductions that the ultrasonic treatment achieved. Importantly, and consistent with the findings by Gray and Muranko (2006), the authors found that the energy applied *via* either ultrasonic treatment or mechanical mixing (rotor-stator) was not strong enough to break apart agglomerates into primary particles. Additional studies of pyrogenic silica particle size distributions using various different particle sizing and dispersion techniques confirm that this product exists as a white fluffy solid composed of agglomerate sizes ranging from 10 to 90 μm without dispersion treatment (Barthel *et al*., 1999).

Similarly, in a recent study, Ma-Hock *et al*. (2007) provided additional findings confirming that SAS consists primarily as larger-sized (>100 nm) aggregates and agglomerates. For two types of hydrophobic pyrogenic SAS (e.g., surface-treated SAS) with differing surface areas (Aerosil R104, SA ~150 m^2/g and Aerosil R106, SA ~250 m^2/g) and an unspecified amorphous silicon dioxide "nanopowder," Ma-Hock *et al*. (2007) reported a range of primary particle sizes of 5 to 50 nm based on transmission electron microscopy (TEM) pictures, noting that the particles were suspended in ethanol for analysis. However, when the researchers attempted to obtain more quantitative primary particle size distributions using an ultrafine particle analyzer (UPA), they were unable to obtain primary particles because the primary particles are fused together forming aggregates. In addition, based on particle size distribution measurements made using both a Scanning Mobility Particle Sizer (SMPS) and an Optical Particle Counter (OPC) across the three SAS products as aerosolized at high energy using a dry powder brush feed aerosol generator or a nebulizer system, the researchers demonstrated a high degree of aggregation and agglomeration. Indeed, for the silicon dioxide sample, the researchers found substantial intersampling variability in the particle size distribution as measured by the SMPS because SiO_2 does not form a stable suspension. Ma-Hock *et al*. (2007) reported that median count distributions ranged from 0.20 μm to 0.45 μm, with a reported mass fraction of between 0.13 and 0.74% of the aerosolized SAS particles having diameters of less than 100 nm. These measurements thus confirmed that the main mass

fraction of aerosolized SAS particles consists of stable aggregates or agglomerates, even under the high dispersive energy typical of a brush dust feeder and nebulizer.

Scanning electron microscope (SEM) images as well as transmission electron microscope (TEM) images of various forms of SAS confirm the stable aggregated and agglomerate state of these products (Figures 1-11 to 1-16).

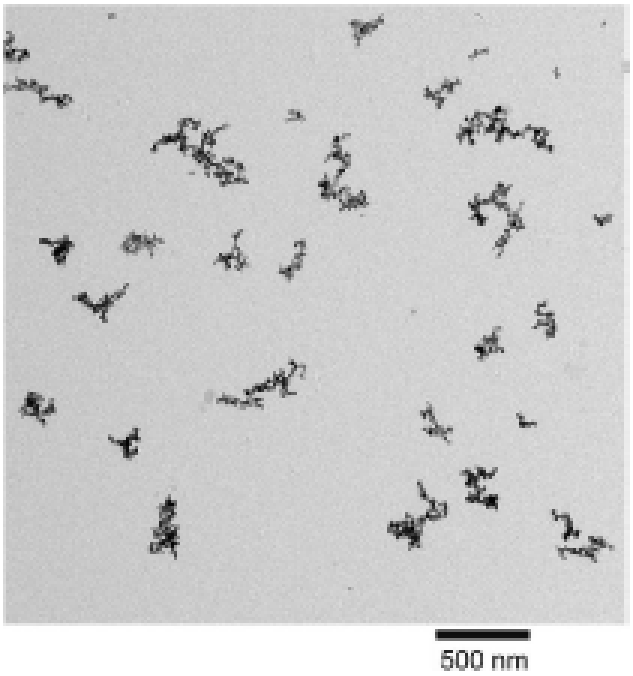


Figure 1-11 TEM of Precipitated Silica (Z1165) Showing Aggregate Structure (from Gray and Muranko, 2006)

Figure 1-12 TEM of Pyrogenic Silica (from Bogdan and Kulmala, 2006)

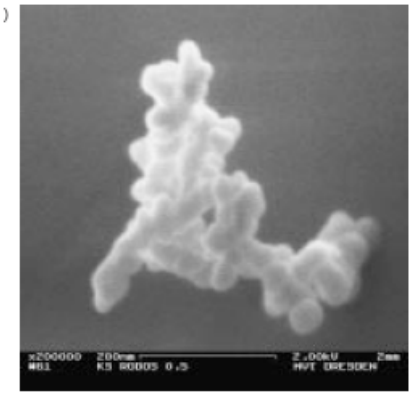


Figure 1-13 Electron Micrograph of a Pyrogenic Silica Aggregate (from Sheka *et al.*, 1999)

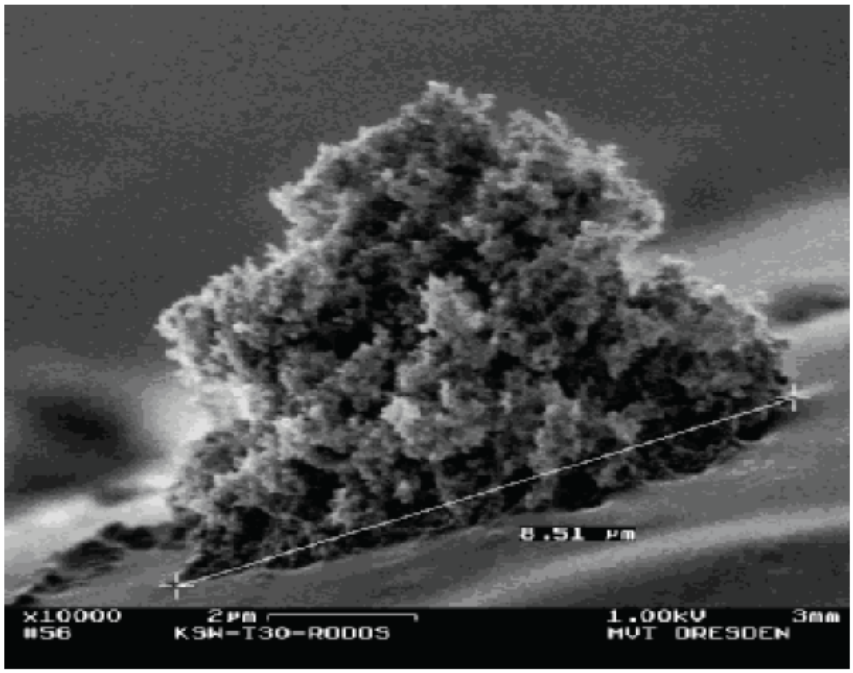


Figure 1-14 SEM of Pyrogenic Silica agglomerate (from ECETOC, 2006)

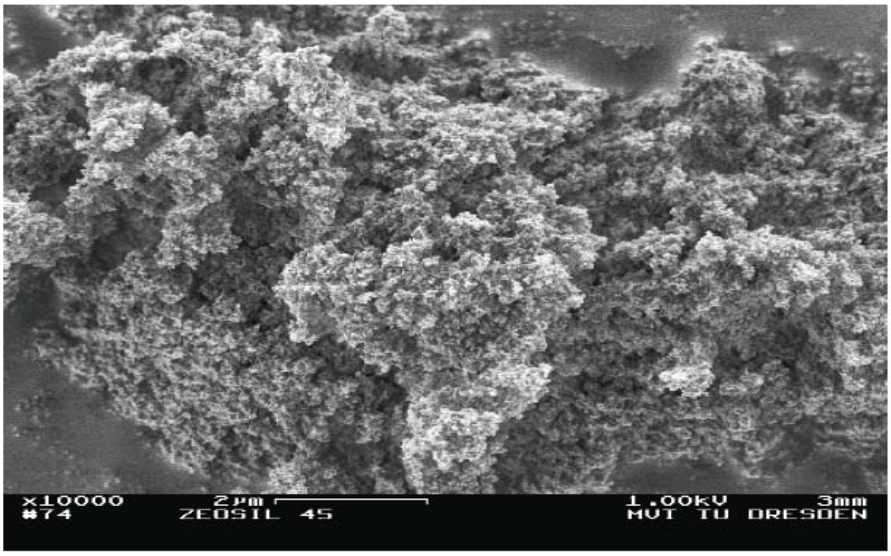


Figure 1-15 SEM of Agglomerated Precipitated Silica (from ECETOC, 2006)

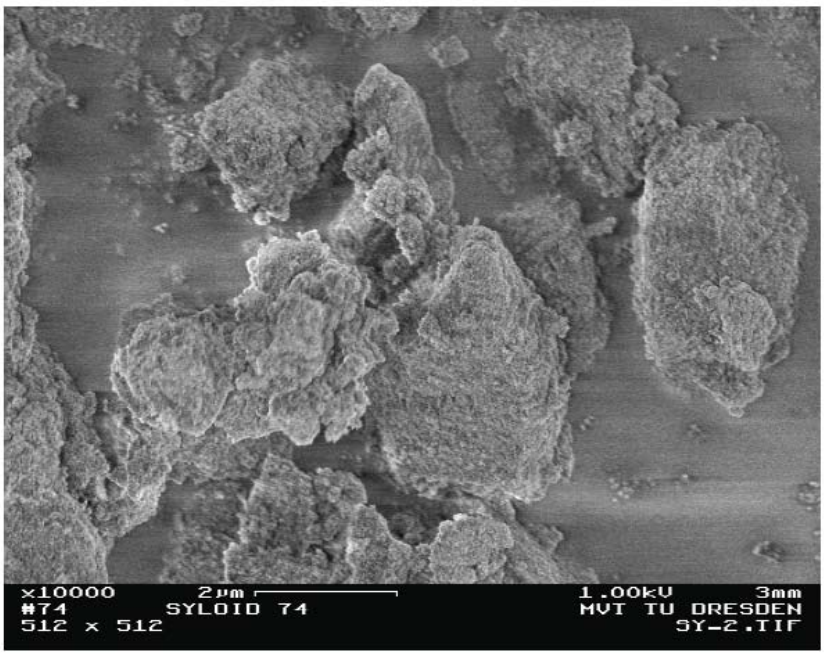


Figure 1-16 SEM of Silica Gel Aggregates (from ECETOC, 2006)

One of the concerns that has been raised for nanostructured materials is the possibility of disaggregation of the aggregates or agglomerates following deposition in the lungs and the subsequent release and potential translocation of any nano-sized units. Maier *et al*. (2006) tested whether disaggregation of samples of a commercial nanostructured titanium dioxide product (AEROXIDE TiO_2 P25, 20 nm primary particle size) occurred when mixed with dipalmitoyl phosphatidyl-choline (DPPC), the main surface-active component in lung surfactant. Like SAS, TiO_2 is a nanostructured industrial aciniform aggregate, which exists as highly aggregated and agglomerated particles. The authors calculated the energies needed to break apart aggregates and agglomerates of TiO_2, and assessed the particle size distribution of TiO_2 P25 in a pulmonary liquid model (PLM) that consisted of a DPPC dispersion.

Using computer-based molecular simulations, Maier *et al*. (2006) determined that 10 joules per square meter (J/m^2) of energy were required to break the oxide bonds between TiO_2 primary particles (*i.e.*, to break apart an aggregate) and 1 J/m^2 would be needed to break the weaker hydrogen bonds between aggregates (*i.e.*, to break apart an agglomerate), an order of magnitude difference. Importantly, the interaction energy between TiO_2 and the DPPC bilayer was calculated to be only 0.05 J/m^2, 200 times weaker than the energy needed to break apart the chemical bonds between primary particles in an

aggregate and 20 times weaker than interaggregate hydrogen bonds. Thus, based on their modeling simulations, the researchers concluded that DPPC does not promote the disaggregation of either TiO_2 agglomerates or aggregates.

To test their modeling calculations, Maier *et al*. (2006) also determined particle size distributions for TiO_2 P25 dispersions in DPPC using light-scattering methods (static laser scattering), finding TiO_2 particle sizes in the general range of about 0.8 to 100 μm no matter the TiO_2 concentration, the DPPC concentration, and the contact time. For these dispersions where TiO_2 P25 was added to the PLM with gentle shaking by hand, no particles in the ultrafine size range (*i.e.*, <100 nm) were observed. For some experiments where the TiO_2 P25 suspensions in PLM were treated with ultrasonication, a small signal corresponding to an additional particle fraction with aggregate sizes of about 100 nm was observed. As discussed by Maier *et al*. (2006), however, this particle fraction corresponded not to individual primary particles, but to smaller aggregates of 4 to 6 primary particles across. Lastly, a small Zeta potential (2.6 mV) was measured for TiO_2 in DPPC, much smaller than needed to disperse aggregates and so supporting an increased tendency towards agglomeration. Overall, these data thus support the conclusion that surfactants in the lungs or other biological fluids cannot break apart either aggregates or agglomerates which may become inhaled and deposit on lung surfaces.

Similar studies of disaggregation of SAS agglomerates in biologically-relevant fluids are not currently available. However, because SAS forms aggregates and agglomerates with similar bonding structures (*i.e.*, strong oxide bonds between primary particles, and weaker hydrogen bonds between aggregates), experiments using SAS would be expected to yield similar results. In addition, the results from Gray and Muranko (2006) and Sauter *et al*. (2006) support the fact that even under very high dispersion energy conditions (unlikely to be encountered in most exposure settings) there is only a very modest reduction in the size of SAS agglomerates.

1.3 Conclusion: Manufactured SAS Is Neither a Nanoparticle Nor a Nano-object

In this section we have presented information demonstrating that SAS is neither a nanoparticle nor a nano-object, consistent with nanotechnology terminology and definitions in development by the International Organization for Standardization (ISO) Technical Committee (TC) 229 and the Organisation for Economic Co-operation and Development (OECD) Working Party on Nanotechnology (WPN). Indeed, due to the nature of the manufacturing processes, SAS is typically found to be a highly

aggregated and agglomerated material whose external diameter is typically in the micron (μm) range not the nano-range. Moreover, the primary particles which give SAS its nanoscaled features are strongly bound to each other making it very unlikely that they will be found as independent entities in the final product. Thus, SAS falls under the category of a nanostructured material, consistent with the ISO and OECD definitions of nanostructured materials as having either an internal or surface structure on the nanoscale. Importantly, the human exposure potential, and SAS fate and behavior inside the body (*e.g.*, as to lung dosimetry, translocation potential, ability to pass through cell pores, *etc.*) will be dictated by either its aerodynamic diameter or its physical diameter rather than by its internal nanostructure. Because both SAS aggregates and agglomerates have diameters that lie outside the nano-region, they will behave similarly to respirable or inhalable-sized particles.

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2 Uses and Potential Exposures

Having been produced commercially for over sixty years, manufactured SAS has numerous applications in a variety of commercial and consumer products, including numerous food and pharmaceutical applications. In this section, we briefly summarize information related to the worldwide production and uses of manufactured SAS. In addition, we summarize what is known regarding potential exposures to SAS, focusing on occupational exposures where there is the greatest potential for human exposure. Importantly, due to the physical and chemical properties of powdered forms of SAS as described in the previous section, human exposure to SAS particles is expected to be largely in the form of micron-sized aggregates and agglomerates, thus concerns about nano-sized particle exposures do not apply to SAS.

2.1 Production and Uses

2.1.1 Production

Worldwide production of SAS was estimated to be almost 1000 kilotonnes (kt) in 1992 (ECETOC, 2006)and over 1300 kt (1.3 million tons)in 2004 (Waddell, 2006). The bulk of the production is for precipitated SAS products (800 kt). More recent production numbers for western Europe for 2000 also indicate a much greater production of precipitated SAS (286 kt), compared to pyrogenic SAS (72 kt) and silica gel (35 kt) (ECETOC, 2006). The current trend in annual sales (1997-2000) for Western Europe shows that sales for pyrogenic and precipitated SAS are increasing, whereas sales for silica gel have remained steady from 1997 to 2000 (ECETOC, 2006).

2.1.2 Uses

Forms of SAS have been in commerce since the 1950s and are used in a wide range of industrial applications and products. A summary of some of the major applications is provided below. For more details, refer to the ECETOC Report (2006).

As previously mentioned, precipitated silica is produced in much greater quantities than other forms of SAS. The primary use of precipitated silica is for the reinforcement of elastomer products like

tires, shoe soles, and mechanical rubber goods (seals, mats, belts, *etc.*). For tires, silica in tread compounds leads to significant improvements in rolling resistance and wet traction of tires without compromising tread wear (Bergna and Roberts, 2006). Precipitated silica is currently widely used in Europe and there is increasing demand in North America and Asia to cut fuel consumption and CO_2 emissions (Bergna and Roberts, 2006).

Pyrogenic silica (also known as fumed silica) is mainly used to improve mechanical strength, provide thermal stability, and reduce permeability of gases and liquids of silicone rubber. The higher surface area of pyrogenic silica yields higher transparency of the silicone rubber, which is important for certain applications such as medical tubing. Precipitated silica is also used in silicone products (Bergna and Roberts, 2006).

Both pyrogenic and precipitated silicas are widely used as carriers for liquids and semi-liquids or as free flow agents in powdered products (cosmetics, salts, and foods), particularly for hygroscopic and caking substances. For example, untreated pyrogenic silica has been cleared by the U.S. Food and Drug Administration (FDA) for use as a direct food additive in a number of different food products including grated cheese, dried eggs, dried egg yolks, and flavorings oils, and in materials that come into contact with foods during manufacturing, packaging, preparing, or transporting. In addition, SAS provides pastes and ointments with the desired consistency and prevents separation of the various ingredients, and thus has number of pharmaceutical and cosmetic applications. For these applications, the absorption capacity, kinetics of absorption, good flowability, and low dust content (good mechanical stability) are key characteristics (ECETOC, 2006). Figures 3-1 to 3-3 show use patterns in Western Europe in 1996 and, although somewhat dated, they provide a general sense of the wide range of products and applications for SAS and their commercial importance.

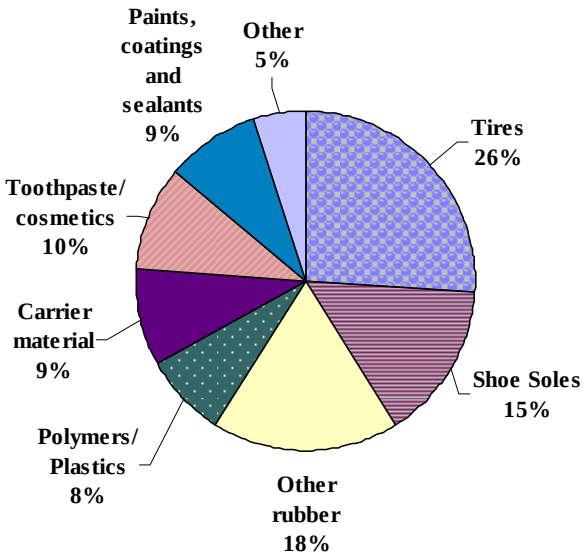

Figure 2-1 Uses of Precipitated Silica in Western Europe (1996, total production 231 kt, adapted from ECETOC, 2006)

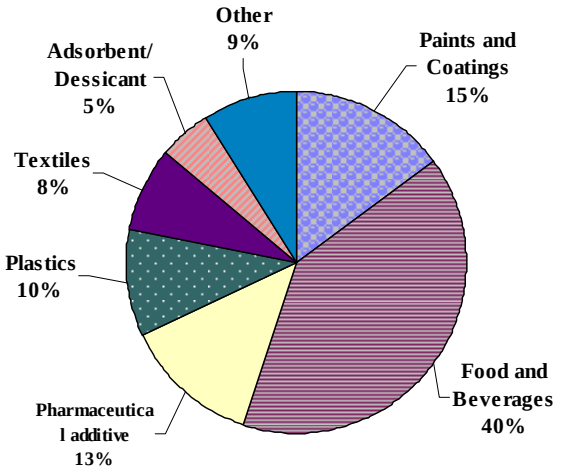

Figure 2-2 Uses of Silica Gel in Western Europe (1996, total production 20 kt, adapted from ECETOC, 2006)

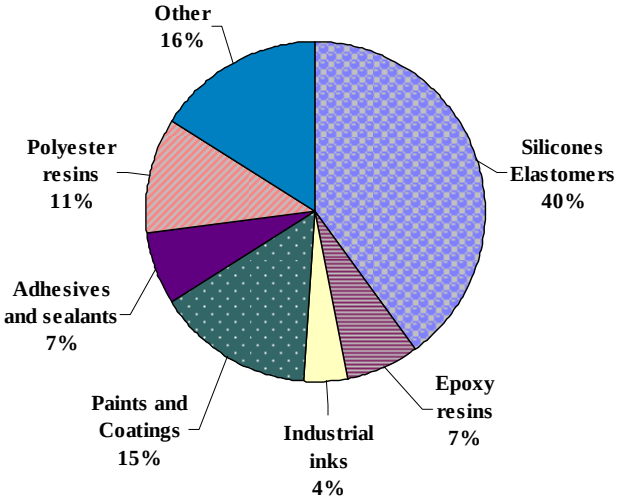

Figure 2-3 Uses of Pyrogenic Silica in Western Europe (1996, total production 46 kt, adapted from ECETOC, 2006)

2.2 Potential Exposures

2.2.1 Emissions, Distribution, and Environmental Fate

SAS can be released into the environment during the manufacturing process. Based on Western European production numbers, the amount of SAS released to air was estimated to be about 0.44 kt per year and the amount released to water was estimated to be 2.1 kt per year (ECETOC, 2006). Similarly, emissions of SAS into aquatic environments during use were estimated from Western European consumption data to be about 104 kt per year (ECETOC, 2006).

Based on the chemical properties of SAS, the relatively low water solubility (~114-151 mg/L) and low vapor pressure ($<10^{-3}$ Pa for Aerosil R972), released SAS will likely be distributed mostly to soil/sediment, less so to water, and negligibly to air (ECETOC, 2006).

Table 2-1 summarizes some of the environmental fate parameters for SAS. In general, SAS is an inert substance that is not expected to undergo any chemical transformations in soil, air, or water, except for dissolution in water. In fact, all forms of silica once dissolved in water are indistinguishable. The

dissolved silica is in the form of silicic acid, a bioavailable form of silica essential for aquatic organisms. Silica also accumulates in plants and plays a role in structural support to the cell walls. Silica has also been shown to be an essential nutrient in animal species, playing a role in bone development and associated with other structural components such as connective tissue, cartilage, and skin (ECETOC, 2006).

Silicic acid in the oceans comes from weathering of continental and oceanic crusts. Marine organisms such as diatoms take up the silicic acid to build their skeletons. When these organisms die, part of their skeleton dissolves and the remaining portions settle into the sediment. Similarly, dissolved silica in rivers results from weathering of rocks (ECETOC, 2006). The flux of naturally occurring dissolved silica in Western Europe has been estimated to be about 4,400 kt per year, thus the estimated release from manufacture and use of SAS is only about 2.4% of the naturally occurring silica present in European waterways (ECETOC, 2006).

Table 2-1 Environmental Fate (from OECD, 2004)

Photodegradation	stable in water and air
Stability in Water	stable: ion exchange processes possible
Stability in Soil	stable: silicates = soil components; ion exchange processes possible
Biodegradation	not applicable, inorganic substance
Bioaccumulation	not bioaccumulating due to inherent substance properties

2.2.2 Non-occupational Exposures

Most non-occupational exposures to silica are likely from ingestion of silica dissolved in water and from naturally-occurring silica or synthetic additives in food. In public water supplies, the median concentration of silica was 7.1 mg/L (based on the 100 largest US cities, ECETOC, 2006). Average daily intakes from food are estimated to range from 43 to 107 mg/day. Foods naturally high in silica include grains such as oats, barley, and rice (ECETOC, 2006). SASs are also widely used in a variety of food products such as beverage mixes, salad dressings, sauces, soups spices, and others (up to 2% by weight) as an anti-caking agent or thickener (see section 2.1.2). SAS is also commonly found in various pharmaceuticals contributing to overall oral exposures.

Although non-occupational exposure pathways are likely negligible, it is important to emphasize the scientific evidence indicating the excessive nature of the forces required to break apart SAS agglomerates and aggregates (see Section 1.2). It is thus highly unlikely that individual nano-sized SAS particles will be released during use of a consumer product, not only because SAS aggregates and agglomerates are typically contained within product matrices (*e.g.*, when used as a filler in rubber) but also because the nano-sized primary particles are tightly bound within larger-sized aggregates that are in turn held within robust agglomerates.

2.2.3 Occupational Exposures

Occupational exposures to SAS occur during production, packaging, and shipping of SAS products as well as during use. Only a few studies have measured occupational levels of SAS. These results are summarized in Tables 2-2 and 2-3. Total dust concentrations have been greatly reduced in recent years. For example, measured concentrations were as high as 199 mg/m^3 in 1959, but measurement data show substantial reductions down to ~40 mg/m^3 between 1974 and 1982. Between 1984 and 1986, measured levels were further reduced to between 2 and 4 mg/m^3 (IUCLID 7631-86-9). More contemporary concentrations measurements are even lower (see Table 2-3).

An on-going German monitoring and morbidity study of workers exposed to SAS has collected over 1,000 measurements of inhalable and respirable dust levels in SAS manufacturing plants (Table 2-3). Overall mean dust concentrations were 1.2 mg/m^3 (inhalable) and 0.3 mg/m^3 (respirable), values that are well below the German MAK standard of 4 mg/m^3 and US workplace standard of 6 mg/m^3 (ECETOC, 2006).

Table 2-2 1982-1996 Data on Occupational Exposures in SAS Manufacturing Plants (IARC, 1997)

SAS Form, region (job category)	Concentration (mg/m^3)	Comment
Precipitated SAS, France (production)	0-10.5 total 0-3.4 respirable	
Precipitated SAS, US (production)	<1.0-10 total	
Pyrogenic SAS, Europe- 9 plants (filling, packing, bagging, and mixing)	0.61-6.5 total 0.2-2.1 respirable	Personal samples, range of medians
Precipitated SAS and SAS gel, Europe- 9 plants (filling, packing, cleaning, blending)	1.0-8.8 total 0.5-2.1 respirable	Personal samples, range of medians

Table 2-3 Contemporary Levels of Inhalable and Respirable Dust in Five SAS Manufacturing Plants (from ECETOC, 2006)

Plant	Inhalable (mg/m^3)		Respirable (mg/m^3)	
	AM	GM	AM	GM
1	0.17-1.14	0.13-0.81	0.07-0.26	0.05-0.19
2	0.38/0.35	0.03/0.35	0.07/0.33	0.06/0.27
3	0.41-2.52	0.36-2.02	0.19-1.08	0.15-0.62
4	0.42-3.15	0.24-2.06	0.15-0.64	0.10-0.49
5	0.23-1.55	No data	0.10-0.34	No data

AM= arithmetic mean, GM= geometric mean

2.3 Conclusion: Information on SAS Uses and Potential Exposures Indicates a Low Exposure Potential to Nano-Sized SAS Particles

In this section we emphasized the long history of SAS use in numerous commercial and consumer products and thus its commercial importance. Consumers are likely to be exposed mainly *via* ingestion of natural and synthetic forms of silica and less likely to be exposed *via* inhalation or dermal contact. Occupational exposures, on the other hand, will include potential inhalation and dermal exposures. However, contemporary measurements in SAS manufacturing plants show that levels of inhalable and respirable SAS have decreased substantially and are well-below occupational health standards (see Section 4.1). Importantly, evidence of safe manufacture and use, coupled with data regarding the size distribution of solid forms of SAS (Section 1), have shown no indication of exposure to nano-sized SAS particles that would result in adverse health impacts.

3 Hazard Assessment

Available health effects data for manufactured SAS indicate very low, if any, toxicity in worker populations. In addition, over 60 years of use in commercial and consumer products provides compelling evidence of safety. In this section, we summarize the current state of knowledge on the health effects of SAS.

3.1 Epidemiological and Case Studies of SAS Health Effects

Because SAS have generally been considered to be of low toxicity, only a few quantitative epidemiological studies have been published examining the effects of occupational exposures. Occupational exposures to SAS occur during production, handling, and use in a variety of industries. Packing, weighing, reprocessing, and cleaning job categories are associated with the highest exposures, but engineering controls and use of personal protective equipment serve to reduce worker exposures (IARC, 1997).

Section 9 of the ECETOC report (2006) and Section 3 of the OECD SIDS (2004) provide detailed summaries of the available epidemiological studies of workers exposed to SAS. Also, a recent review of health hazards associated with inhalation of amorphous silica was conducted by Merget *et al*. (2001). In this review, Merget *et al*. (2001) concluded that "epidemiological studies do not support the hypothesis that amorphous silicas have any relevant potential to induce fibrosis in workers with high occupational exposure to these substances." However, Merget *et al*. (2001) did find that the data were too limited to rule out risk associated with chronic bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema.

To address these data gaps, a large worker monitoring and morbidity study is currently underway to assess the health status of workers exposed to SAS compared to unexposed controls in five German manufacturing plants, three manufacturing pyrogenic SAS, and two manufacturing precipitated SAS. A total of 397 current workers with at least 1 month's exposure and with complete data are participants in the study (out of 510 eligible workers). In addition, 178 former workers with at least one month of exposure between 1980 and 1994 are included in the study, along with 210 unexposed control workers.

For each of the exposed and unexposed workers in the study, the following data were collected: 1) demographic and background information (*e.g.,* smoking and medical history) *via* questionnaire; 2) atopy (*via* skin prick test and IgE titers); 3) spirometric data and reversibility; 4) carbachol bronchial provocation data; and 5) chest radiographs (ECETOC, 2006).

As reported in the ECETOC report (2006), preliminary results indicate that chronic bronchitis prevalence was slightly higher in the exposed group, but still within a normal range. There were also differences in spirometric measurements between exposed and control subjects, but these differences may be explained by the more prevalent smoking habits among the exposed workers. Obstruction or restriction was no different across plants, and bronchial hyperresponsiveness was within normal ranges. Lastly, chest radiographs showed no evidence of increased risk of pneumoconiosis of exposed subjects compared to controls and no significant pleural thickening. A detailed report is in preparation, with additional statistical analyses and testing of differences between exposed and control workers while accounting for potential confounders. Overall, preliminary results do not show health risks from SAS exposures in these workplace settings (ECETOC, 2006).

The ECETOC report (2006) also summarizes results from a limited company study of 143 German workers in a pyrogenic SAS manufacturing plant in which medical records from 1959 to 1985 were evaluated. Pulmonary symptoms (cough, sputum, and shortness of breath) as well as abnormalities in lung pathology or function were found in 54 workers, but there was no evidence of silicosis. An additional study evaluated chest x-rays of 215 workers in a German pyrogenic manufacturing plant collected from 1947 to 1959. Concentrations in the bagging area were found to range from 2 to 7 mg/m^3 with much higher exposure concentrations taken near a filling nozzle (15 – 100 mg/m^3). No lung pathologies were observed in any of the x-rays.

In addition, summaries of studies of workers exposed to precipitated silica can be found in the ECETOC report (2006). In one US study, 165 workers in 2 manufacturing plants were evaluated. Cumulative indices were developed based on exposure concentrations and duration. The authors found that respiratory symptoms correlated with smoking but not with SAS exposure, and there was no evidence of pulmonary function and chest radiograph abnormalities associated with SAS exposure. In a separate study, company health records of 78 employees employed for between 1 and 16 years (average of 4.75 years) were examined. Exposures ranged from 0.3 to 204 mg/m^3. Annual x-ray evaluations found no evidence of silicosis or other pulmonary disease. However, symptoms of mechanical irritation

of the skin, eyes, nose and throat from dust exposures were reported. Lastly, a study in France of 150 workers exposed to precipitated silica for an average of 12.2 years evaluated effects on pulmonary function and chest x-rays. As in previous studies, x-rays did not show any signs of pneumoconiosis or fibrosis. A small, non-significant decrease in some of the pulmonary function measures (but not all) was observed in the exposed workers (ECETOC, 2006).

In conclusion, there is no evidence from occupational exposure studies of adverse pulmonary effects from SAS exposure. Specifically, there is no evidence of lung cancer or other chronic pulmonary diseases (*e.g.*, silicosis) in workers exposed during the manufacturing of SAS. For studies that assessed respiratory symptoms and pulmonary function, any effects were typically correlated with smoking and not SAS exposure (ECETOC, 2006). The long manufacturing history of SAS with no evidence of adverse health outcomes coupled with the current low measured levels of exposure to workers, support the low potential risk of adverse effects associated with manufactured SAS.

3.2 Experiments in Laboratory Animals

SAS toxicity has been studied *via* various different routes of administration (oral, dermal, inhalation, intravenous, and intratracheal) in different animal species (rats, mice, rabbits, dogs, and monkeys). A summary of the *in vivo* and *in vitro* toxicity results for acute (oral, inhalation, and dermal), repeated dose (oral and inhalation), genetic toxicity (*in vitro* and *in vivo*), carcinogenicity, and reproductive effects are give in Table 3-1. Results of key studies are briefly summarized below. Detailed summaries are provided in both the ECETOC report (2006) and OECD SIDS (2004).

Table 3-1 Summary of Toxicological Data (from OECD, 2004)

Test	Endpoint/Findings
Acute Oral Toxicity	LD_{50} >3300 mg/kg (limit test)
Acute Inhalation Toxicity	LC_0 >140 - >2,000 mg/m^3 (Maximum concentrations technically feasible)
Acute Dermal Toxicity	LD_{50} >5000 mg/kg (limit test)
Primary Irritation (skin, eye)	Not irritating
Sensitization	No data available*
Repeated Dose Toxicity (inhalation)	inflammatory reaction in the lung: NOEL(5 d) = 1.0 mg/m^3
Repeated Dose Toxicity (inhalation)	inflammatory reaction in the lung (rat) NOAEL(13 wks) = 1.3 mg/m^3
Repeated Dose Toxicity (oral)	no substance-related abnormalities in rat: NOAEL(6 months) = ~9000 mg/kgbw
Genetic Toxicity *in Vitro*	
A. Bacterial Test (Gene mutation)	not mutagenic
B. Non-Bacterial In-Vitro Test (Gene Mutation)	not mutagenic
C. Non-Bacterial In-Vitro Test (Chromosomal Aberration)	not mutagenic
Genetic Toxicity *in Vivo*	not mutagenic
Carcinogenicity (inhalation)	inconclusive
Carcinogenicity (oral)	not carcinogenic in rat and mouse
Reproductive Toxicity	no effects (limited study in rat)
Developmental / Teratogenicity	no adverse effects in rat, mouse, rabbit and hamster

*Sensitization has not been seen in worker populations

3.2.1 Acute Exposures

Acute effects of SAS exposure have been studied in rats (oral and inhalation studies) and rabbits (dermal studies and eye irritation studies). A large number of oral mortality studies have been conducted in rats using various forms of SAS (pyrogenic, precipitated, gel, and sol). Detailed results can be found in ECETOC (2006; Table 27). No differences were observed in LD_{50} values across different types of SAS. Overall, no deaths occurred and there were no signs of toxicity after oral administration of SAS of up to 5,000 mg SiO_2/kg bw. Only at extremely high doses of SAS (10,000 and 20,000 mg SiO_2/kg bw) were animal deaths observed (ECETOC, 2006).

Dermal studies of different SAS types in rabbits showed only slight erythema (redness of the skin) with intact or abraded skin and oedema (swelling) with abraded skin, which was completely reversible in 5 days. There was no indication of systemic adverse effects. In general, animal tests showed no toxicity *via* the dermal route (ECETOC, 2006).

Inhalation studies have been conducted for various forms of SAS (see Tables 29 and 30 in ECETOC, 2006 providing details for hydrophilic and hydrophobic SAS, respectively). Inhalation studies using hydrophilic forms of SAS have proven to be difficult to conduct due to the strong binding forces of the aggregates and the high tendency of the aggregates to form agglomerates. Thus, most inhalation tests have been conducted using lower test concentrations than the recommended concentration of 5,000 mg/m^3 for acute respirable dust inhalation testing (ECETOC, 2006).

The available acute inhalation testing data show differences in mortality and morbidity results for hydrophilic *vs*. hydrophobic forms of SAS. For studies conducted using hydrophilic SAS, no mortality was observed in all studies, except for one in which 1/10 animals died (exposures of 2,200 mg/m^3). These studies were generally conducted via nose-only exposure or whole-body exposure with concentrations ranging from 139 to 2,200 mg/m^3 over exposure durations of 1 to 4 hours. Respiratory irritation was observed only in a study of rats exposed to 2,200 mg/m^3 for 1 hour. Studies conducted at lower concentrations showed no clinical effects.

A higher respirable dust concentration can be achieved using hydrophobic SAS, which may be a possible explanation for the high mortality rates observed in some of the hydrophobic SAS studies compared to hydrophilic SAS studies. As shown in Table 30 of the ECETOC report (2006), mortality rates were high at concentrations of about 2,100 mg/m^3 or greater. At necropsy, the rat lungs of the deceased animals showed severe redness. In another study, pre-death symptoms included closed eyes, wetness and redness around the nose and mouth, and respiratory distress. As discussed in the ECETOC report (2006), Degussa and Cabot found that SAS exposures at high concentrations occluded smaller bronchioles and extravasation of blood was observed, which may be indicative of suffocation rather than a direct toxic effect of the substance.

Furthermore, ECETOC (2006) reports that most of the acute inhalation studies for which particle size data were available described test samples that were significantly different from commercially available SAS products in terms of the particle size distributions. This is largely attributed to the methods of dispersing the powdered forms of the product for effective delivery. Dispersal of SAS powders results in a reduction in the size fraction yielding particles with mass median aerodynamic diameters (MMAD) below 10 μm (*i.e.*, in the respirable range). Most commercial powder forms of SAS (>99%) have MMAD greater than 10 μm. Furthermore, particle size determinations have shown that 99% of the particle fraction of most SAS powders exceed a MMAD of 90 μm, a particle size likely to

only reach the upper airways, if inhaled at all (see section 1.2). Thus, the relevance of these acute inhalation studies to actual human exposures is questionable (ECETOC, 2006).

Skin and eye irritation has been tested in rabbits (ECETOC, 2006; Tables 31 and 32) and results have demonstrated that SAS is largely non-irritating to the skin and eyes. While some mild effects (*e.g.*, redness) were observed, these effects were readily reversible. However, case reports of occupational exposures have described dryness and eczema resulting from chronic dermal contact of SAS. These reactions may be avoided by using skin care products (ECETOC, 2006; OECD, 2004). For sensitization no experimental data are available. However, based on its structure and physico-chemical properties, SAS is not expected to cause skin sensitization. In addition, there is long record of medical surveillance in worker populations that shows no evidence of skin sensitization (OECD, 2004)

3.2.2 Subchronic and Chronic Exposures

To assess effects from repeated exposures to SAS *via* oral, dermal, and inhalation routes of exposures, toxicity studies have been conducted for rats, rabbits, guinea pigs, mice and monkeys. Oral studies in rats confirm the absence of any toxic effects from ingestion. For example, chronic administration of SAS at a concentration of up to 5% in the diet to mice and rats caused no microscopic changes or neoplasms (ECETOC, 2006 Table 33). One dermal study was available in which the researchers found no effects from dermal exposure for intact and abraded skin of rabbits using concentrations of up to 10,000 mg/kg bw (ECETOC, 2006 Table 34). Numerous inhalation studies have been conducted in rats, guinea pigs, rabbits, and monkeys and across a variety of SAS forms (pyrogenic, precipitated, and silica gel). Exposure concentrations have ranged from 0.5 to 150 mg/m^3. These studies suggest that SAS causes transient increases in markers of inflammation and cell injury. In addition, in some studies, there was evidence of an inflammatory response, focal fibrosis, and granulomatous nodule formation, but the studies with a recovery period found that these pulmonary effects were not persistent. Importantly, in contrast to crystalline silica exposure, SAS exposure did not induce irreversible or progressive lung injury, and there was no evidence of lung tumors (ECETOC, 2006).

The repeated dose inhalation studies are summarized in the ECETOC report (2006, Tables 35 and 36 for hydrophilic and hydrophobic SAS, respectively). NOAELs have been determined based on these inhalation studies and range from 0.5 to 10 mg/m^3 depending on the SAS product used in the study. However, it is important to emphasize, as discussed in the ECETOC report (2006), that many of the

"adverse" effects that these NOAELs are based on reversible effects in the post-exposure recovery period.

3.2.3 Genetic and Reproductive Toxicity

SAS has been found to be non-mutagenic using several *in vitro* test systems (*e.g., Salmonella typhimurium* and *Escherichia coli*). In addition, in mammalian cells, neither point mutations nor chromosomal aberrations have been detected, and no genotoxicity was observed in *in vivo* studies (ECETOC, 2006).

Studies carried out in rats, mice, hamsters and rabbits have demonstrated no toxic effects on male and female fertility and no teratogenic effects or developmental abnormalities in progeny. The NOEL for maternal and fetal toxicity was >1600 mg/kg for silica gel and >500 mg/kg for pyrogenic silica (ECETOC, 2006).

3.3 IARC's 1996 Evaluation of Silica

The International Agency for Research on Cancer (IARC) offers a well-established paradigm for ranking potential cancer risk. For IARC, *sufficient* human evidence consists of epidemiology data that show: "A positive relation between exposure and cancer observed, with chance, bias, and confounding ruled out with reasonable confidence" (IARC, 1997). If chance, bias, and confounding cannot be ruled out with reasonable confidence, then IARC judges the human evidence to be less than sufficient, *i.e.*, *limited or inadequate*. If some positive associations have been reported, but such associations are neither consistent nor of sufficient quality, then IARC turns to animal evidence to assess the potential for carcinogenicity. Similarly in animals, *inadequate* evidence for IARC consists of evidence from studies that "cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available" (IARC, 1997). Based on its evaluation of the human and animal data, IARC assigns agents to the following carcinogenic classifications:

Group 1: The agent is carcinogenic to humans.

Group 2A: The agent is probably carcinogenic to humans.

Group 2B: The agent is possibly carcinogenic to humans.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

Group 4: The agent is probably not carcinogenic to humans.

It should be appreciated that within the context of the IARC rankings, the dose (or exposure level) is still crucial to assessing possible hazard. That is, even Group 1 carcinogens, which include relatively common substances such as alcoholic beverages, aflatoxins (natural contaminants of peanuts and other crops), asbestos, smokeless tobacco products, benzene, birth-control pills, formaldehyde, sand, soot, sunlight, and wood dust (IARC, 2008) would not normally be considered a serious hazard in the absence of sufficient, prolonged exposure.

In its 1996 evaluation of silica, IARC classified *amorphous* silica as a Group 3 carcinogen based on *inadequate* evidence in humans and *inadequate* evidence of increased tumors in animals.

3.4 Conclusion: Animal and Human Health Effects Data Show Little Evidence of Toxic Effects from Exposure to SAS

The health effects database that includes both animal and human studies indicates that adverse health impacts from SAS exposure are minimal, if any. Such a conclusion is supported by the recommendation in the recent OECD SIDS Initial Assessment Report (OECD, 2004) that SAS is "currently of low priority for further work" based on the low exposure potential to humans. As was described in detail in Sections 1 and 2, the physical characteristics as well as the available worker exposure data support the conclusion that exposure to respirable SAS is low and that there is no evidence of health hazards from current manufacture and use of these SAS products.

3.5 Environmental Effects

The effects of SAS on various micro-organisms, as well as aquatic and terrestrial organisms, have been investigated. In addition, the effects of SAS on ecosystems have been examined. Details can be found in the ECETOC report (2006). In general, there is no evidence of acute toxicity of SAS to organisms in the environment, except for the desiccant effects on insects exposed *via* direct contact with SAS. In fact, silica plays a critical role in many biological systems. For example, it forms the skeleton or shells of diatoms, radiolarians, and sponges, provides structural strength to plant stems, and is used by

plants to form needles that are used for protection. Silicon is essential for growth and development of diatoms and thus dissolved silica influences the phytoplankton populations in fresh and marine waters along with a number of other controlling factors (other nutrients such as phosphorus and nitrogen, light, temperature, *etc.*) (ECETOC, 2006). Importantly, the quantities of silica released into the environment are negligible compared to the natural flux of silica, particularly in aquatic environments (ECETOC, 2006).

As described in greater detail in the ECETOC report, ecotoxicity testing has been conducted for SAS using a variety of aquatic and terrestrial species and microorganisms. Aquatic toxicity tests conducted in accordance with OECD guidelines using good laboratory practices (GLP) have reported LC_{50} and EC_{50} values in fish and crustaceans were greater than 10,000 mg/L and 1,000 mg/L, respectively (ECETOC, 2006; Table 25). In many of the tests, the concentrations exceeded the limit of solubility of the product being tested, thus true concentrations were often not available. Tests for various micro-organisms including *Escherichia coli, Proteus sp., Pseudomonas aeruginosa, and others* have observed the mortality of gram-negative bacteria such as *Escherichia coli* in 6 hours to 3 days when in contact with SAS, whereas gram-positive bacteria were more resistant. Lastly, tests have been conducted in terrestrial organisms in relation to the use of silica as a biocide. Mortality of insects was observed at low humidity and when water was not available, probably due to the dehydration effects of the silica *via* contact. Ingestion routes were not toxic to the insects tested. Details are provided in the ECETOC report (2006; Table 26).

In conclusion, the amount of SAS released into the natural environment is negligible compared to the natural flux of silica in the environment (see Section 2.2.1). In laboratory experiments, SAS was not toxic to most organisms, although desiccant properties of SAS are likely responsible for observed mortality in tested insects. In general, SAS poses little to no risk of adverse ecological effects.

4 Risk Management

Industrial hygiene practices regarding the control and handling of SAS during manufacture and use are grounded in a considerable history. In this section, we summarize the current risk management practices that ensure the safety of SAS manufacturing and use.

4.1 Occupational Standards

Regulations and occupational guidelines for various forms of silica vary somewhat across different countries. In general, separate exposure limits have been adopted to distinguish between the different forms of silica and, in particular, to distinguish between amorphous and crystalline forms. Table 4-1 provides a list of selected occupational exposure limits for amorphous forms of silica (including SAS) that have been established for protection of workers.

These workplace exposure limits and standards are generally based on total dust determinations, but some countries have established separate limits for the respirable fraction [6] and consider amorphous silica to have similar toxicity to other low solubility, low toxicity dusts. For example, the National Institute for Occupational Safety and Health (NIOSH), consistent with its recognition of amorphous silica as a low-toxicity nuisance dust, recommends an allowable 8-hour time weighted average (TWA) of 6 mg/m^3. The current OSHA Permissible Exposure Limits (8-hour TWA) are 20 mppcf and 80 $mg/m^3/\%SiO_2$. [7] In 1980, OSHA changed the PEL for SAS to 6 mg/m^3, however this PEL was vacated on June 30, 1993. In 1991, the American Conference of Governmental Industrial Hygienists (ACGIH) established TLV-TWA for various forms of amorphous silica, recommending a TLV-TWA of 10 mg/m^3 for precipitated silica based on the default TLV for "particulates not otherwise specified" (Haber and Maier, 2002). However, due to insufficient data, in 2006 ACGIH withdrew all of the TLVs established for the various forms of amorphous silica (however, the values remain in the ACGIH records for a period of 10 years after withdrawal). In Germany, the MAK value for synthetic amorphous silicas, including

[6] The respirable fraction constitutes the inhaled particles that penetrate to the alveolar region of the lung and is defined by the measured mass fraction of total aerosol that has a 50 % cutoff of 4 μm (the aerodynamic diameter).

[7] mppcf = millions of particles per cubic foot of air; Based on available information, the expression "80 $mg/m^3/\%SiO_2$" means 80 mg/m^3 divided by the numerical percentage of crystalline silica ($\%SiO_2$). Note: 20 mppcf is considered to be equivalent to 6mg/m^3. See http://www.cdc.gov/niosh/npg/pdfs/2005-149.pdf .

pyrogenic, precipitated, and silica gel, was set at 4 mg/m^3, based on a LOAEL in rats of 6 mg/m^3 (Haber and Maier, 2002).

Table 4-1 Occupational Exposure Limits for SAS and Amorphous Silicas (adapted from ECETOC, 2006)

Type of silica / Country	TWA (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	-	Ministry of Interior, 2001
UK	6	2.4	HSE, 2005
US	6		NIOSH, 2005 [8]

[8] http://www.cdc.gov/Niosh/npg/npgd0552.html

4.2 Safe Handling Practices and Procedures

As with all nuisance dust exposures, SAS occupational control measures mainly involve assuring proper ventilation to maintain dust levels below occupational standards as listed in Section 4.1. As discussed in Section 3.2.3, levels of silica dust have decreased substantially over the years due to process changes and more stringent control. When exhaust ventilation is not possible, the use of appropriate respirators may be warranted depending on the exposure concentrations. In addition, suitable gloves, as well as use of barrier lotions, are recommended when handling SAS to prevent excessive drying of the skin. Protective clothing and eye protection may also be warranted for workers with repeated or prolonged exposures (ECETOC, 2006).

If adverse effects occur upon exposure to SAS, standard first aid measures are recommended. In the event of skin or eye contact with SAS, flushing with plenty of water is warranted. SAS may cause dryness and cracking of the skin that may result in redness, swelling, and itching. Medical treatment may be required if this occurs. Use of a protective skin cream barrier and avoiding direct skin contact with SAS are recommended safety measures (ECETOC, 2006).

In areas where SAS dust is generated, appropriate ventilation should be used. If workers experience trouble breathing, subjects should be moved to areas with fresh air and medical treatment should be sought if symptoms persist. SAS is not expected to cause any adverse effects from ingestion. Precautionary measures for SAS ingestion involve drinking plenty of water and seeking medical attention for any symptoms that develop (ECETOC, 2006).

Proper storage of SAS includes tightly closed containers and a dry, cool, and well-ventilated storage area. SAS does not pose a hazard as a result of fire or spillage. Lastly, SAS is not considered a hazardous waste and can be disposed in a landfill or *via* incineration. However, disposal of SAS to soils, waterways, sewers, and drains should be avoided.

Although most manufacturers of SAS do not have medical surveillance programs specifically to address any health impacts from exposures to fugitive SAS dusts, several companies have annual checkups which incorporate pulmonary function and chest x-rays as part of their general health surveillance program for workers.

4.3 Conclusion: Current SAS Exposure Standards and Work Practices are Protective of Health

Occupational standards have been established to protect workers from exposures to potentially high concentrations of particles. The limits set for SAS dusts are similar to those for other non-toxic nuisance dusts. Under conditions that restrict dust exposures to levels below occupational standards, SAS is not expected to be a hazard to worker populations, because the long track record of workers' exposures has demonstrated no adverse health hazards from workplace exposures to SAS. Moreover, the accumulated data on SAS suggest that the internal nanostructure of SAS does not give rise to unanticipated health hazards.

5 Summary Conclusions

In this submission SASSI has presented information to support three key points regarding the safe manufacture and use of SAS substances and products containing SAS. These key points include:

(1) Solid powder forms of manufactured synthetic amorphous silica (SAS) are not nano-objects or nanoparticles, but rather nanostructured with features which are on the nanometer length scale, but overall do not have dimensions at the nanoscale. This conclusion was supported by presenting a large body of studies that have characterized SAS particle size during the manufacturing process. These studies demonstrate the strong bonding of SAS particles into stable aggregates and agglomerates with dimensions in the micron range.

(2) Consumer exposure is mainly *via* ingestion of naturally-occurring and synthetic additives to foods and dissolved silica in water. Workers, on the other hand, will be exposed to SAS *via* inhalation and dermal contact. Current worker exposure data show that levels in manufacturing plants have decreased substantially in recent years and are well-below regulatory standards. Given that exposure are low, and supported by studies in worker population and in animals, SAS can be considered a non-toxic substance having characteristic health impacts that are similar to other low-toxicity, biologically inert dusts. In addition, there is no evidence that SAS is harmful to ecological systems.

(3) Safe industrial hygiene practices of SAS control and handling are in place to ensure that SAS exposure levels meet regulatory and occupational standards. A long worker exposure history has shown no evidence of adverse health impacts and collected exposure data indicate levels of exposure that are well-below health-protective regulatory standards.

Overall, SAS is a substance that does not pose any unique toxicity due to its nanostructure or other physical-chemical properties. Over 60 years of manufacture and use of SAS has shown that SAS presents little (if any) health risk when handled properly.

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