FOREWORD **INTRODUCITON**

SYNTHETIC AMORPHOUS SILICA AND SILICATES

7631-86-9, 112945-52-5, 112926-00-8: Silicon Dioxide
1344-00-9: Silicic Acid, Aluminum Sodium Salt
1344-95-2: Silicic Acid, Calcium Salt

SIDS Initial Assessment Report

for

SIAM 19

Berlin, Germany, 19-22 October 2004

1a. Chemical Name:	Silicon dioxide (synthetic amorphous silica)
2a. CAS Number:	7631-86-9 (CAS No 112945-52-5 and 112926-00-8)
1b. Chemical Name:	Silicic acid, aluminum sodium salt
2b. CAS Number:	1344-00-9
1c. Chemical Name:	Silicic acid, calcium salt
2c. CAS Number:	1344-95-2
3. Sponsor Country:	United Kingdom Dr. Steve Robertson Environment Agency National Centre for Ecotoxicology & Hazardous Substances Isis House, Howbery Park, Wallingford OX10 8BD, UK Fax: +44 1491 828 556
4. Shared Partnership with:	Degussa AG, lead company
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	ASASP (Association of Synthetic Amorphous Silica Producers) [CEFIC Sector Group]
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	This category is sponsored by the UK under the ICCA Initiative and is submitted for first discussion at SIAM 19
7. Review Process Prior to the SIAM:	The industry consortium collected new data and prepared the updated IUCLID, and draft versions of the SIAR and SIAP. UK government peer-reviewed the documents and audited selected studies.
8. Quality check process:	
9. Date of Submission:	23 July 2004
10. Date of last Update:	
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7631-86-9 (Silica)[1)] 112945-52-5 (Silica, amorphous, fumed, crystalline-free) 112926-00-8 (Silica gel and precipitated silica, crystalline-free) 1344-00-9 1344-95-2
Chemical Name	Silicon dioxide (7631-86-9, 112945-52-5, 112926-00-8) Silicic acid, aluminum sodium salt (1344-00-9) Silicic acid, calcium salt (1344-95-2)
Structural Formula	SiO_2 / SiO_4 tetrahedron (base unit of the structure of the macromolecular network)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The similarity in the chemical structure, composition, production and processing as well as the similarity in physico-chemical properties and the available toxicological and health data, strongly suggest that the impact on the living organism and environment should not differ considerably between the category members: synthetic amorphous silica (SAS) [CAS No 7631-86-9] and synthetic amorphous silicates, Na-Al silicates (NAS) [CAS No 1344-00-9] and Ca silicates (CS) [CAS No 1344-95-2]. They all form fine powders of amorphous particles between 1 and 350 µm with high surface areas.

Human Health

Absorption, disposition, elimination: SAS forms [CAS No 7631-86-9] are rapidly eliminated from the lung tissue during and after prolonged inhalation exposure of experimental animals with no disproportionate disposition occurring in the mediastinal lymph nodes, whereas crystalline forms exhibit a marked tendency to accumulate and persist in the lung and lymph nodes. Intestinal absorption of SAS appears to be insignificant in animals and humans. There is evidence of ready renal elimination of bioavailable fractions.

Acute toxicity: Following inhalation exposure of rats to the highest technically feasible concentrations of 140 to ~2000 mg/m^3 SAS, no lethal effects were observed. Oral and dermal administration of SAS and amorphous silicates failed to cause mortality at the highest doses tested: LD_0 values ranged from 3300 to 20000 mg/kg in rats. No inhalation data are available for NAS [CAS No 1344-00-9] and CS [CAS No 1344-95-2] and no dermal data for CS. By analogy to SAS [CAS No 7631-86-9], and NAS, respectively, they are assumed to be void of significant acute hazards.

Irritation/Sensitisation: The tested silica/silicate materials [CAS No 7631-86-9; CAS No 1344-00-9] are not irritating to skin and eyes. It is assumed that these results also hold for SAS and CS for which corresponding studies are not available. No experimental data is available on sensitisation. There is no evidence of skin sensitisation in workers over decades of practical experience.

Repeated dose toxicity: The *inhalation* of respirable particles of SAS produces a time- and dose-related inflammation response of the lung tissue in animal studies. Thirteen-weeks exposure to an average concentration of 1.3 mg/m^3 of a pyrogenic SAS resulted in mild reversible pro-inflammatory cell proliferation rather than a pathologically relevant

[1] Note: Silicon dioxide (CAS No. 7631-86-9) is the general CAS No. which includes all forms of silicas (e.g. also crystalline and natural forms) (see family tree SIAR). Only the silica sub-classes, the synthetic amorphous silicas, are subject of this evaluation.

tissue change. Given the low-grade severity of this common lung-tissue response, 1 mg/m^3 can be established as NOAEL and LOEL (sub-chronic, 13 weeks). The LOAEL was 5.9 mg/m^3, the mid concentration, which produced clear signs of histopathological adverse effects (stimulation of collagen production, increase in lung weight, incipient interstitial fibrosis, slight focal atrophy in the olfactory epithelium). All these effects were reversible following discontinuation of exposure. No lung-tissue effects were observed following exposure of 5 days to 1 mg/m^3 of the same silica [NOEL (short-term)]. The LOAEL (5 d) was 5 mg/m^3.

In the absence of experimental data for NAS and CS, an effects profile similar to that of SAS is supposed to also hold for amorphous silicates, based on the assumption that the particle size and morphology rather than particle composition is the determinant of inflammatory response in the lung. This implies that synthetic amorphous silicates would not provoke a more severe pulmonary response under same test conditions.

After long-term *oral application in the diet (2 years)*, no adverse effects were demonstrable for SAS and CS only occasional growth depression or slight elevation of organ weights at the highest doses [NOAEL(chronic, oral) = approx. 2500 mg/kg bw/d)]. Following feeding of 0.625 to 10 % NAS in the diet for 14 d, no substance-related clinical and histopathological findings at any dose level were observed in rats and mice.

Medical surveillance reports failed to reveal significant pathological lung effects attributable to occupational long-term exposure to SAS and/or synthetic amorphous silicates: in particular, no signs of pneumoconiosis, silicosis and fibrosis were evident.

Mutagenicity: There is no evidence that SAS or CS induce mutations either *in vitro* or *in vivo* in standard methods. There was also no evidence for a mutagenic activity in an ex-vivo HPRT gene-mutation assay on isolated alveolar type-II cells after long-term inhalation exposure of rats to a distinctly noxious/inflammatory SAS concentration of 50 mg/m^3 (13 weeks). Likewise, based on structure analogy, no genotoxic effects are expected to occur from exposure to NAS for which corresponding studies were not located.

Carcinogenicity: Negative findings in a rat carcinogenicity model after comparative intra-pleural treatment with various types of materials (including a NAS) and the absence of a mutagenic potential underline that the cancerogenic potential of synthetic amorphous silicas/silicates can be considered as negligible.

Based on the negative results after long-term oral administration of SAS (up to 5 % in the diet given to rats and mice) and CS (up to 10 % in the diet given to rats), there is no evidence of a carcinogenic potential arising from ingestion of these amorphous minerals. Likewise, based on structure analogy, no cancerogenic effects are expected to occur from exposure to NAS for which a corresponding study is not available.

Reproduction: An early limited one-generation study on rats gave no evidence of adverse effects on *reproduction performance* at 500 mg SAS/kg bw/d, the highest dose tested (NOAEL). But the reliability is poor due to the small group size of animals.

Numerous subchronic studies as well as a dominant lethal study with a CS failed to demonstrate any histopathological changes or deleterious effects in the reproductive organs of treated animals. Furthermore, given the inherent physico-chemical properties and ubiquitous nature of this class of compounds, there is no structural alert to indicate a potential for reproductive and developmental toxicity. Therefore, based on the weight of evidence, prolonged exposure to synthetic amorphous silica, applied before and during pregnancy at high doses, is not expected to produce harmful effects on the reproductive performance or embryonic/foetal development in experimental animals.

Based on structure analogy, no impairment of fertility/reproductive performance is expected to occur likewise from exposure to NAS and CS, for which corresponding studies are not available.

The experimental data on *intra-uterine development* gained in four animal species (rat, mouse, hamster and rabbit) across all three types of synthetic amorphous silica and silicates allow the conclusion that there is no potential for adverse effects on embryonal/foetal development arising from oral exposure to these silica/silicates. The NOEL for maternal and developmental toxicity is the highest tested dose of 1600 mg/kg bw/d.

Environment

SAS, NAS and CS are solids in powder form which have a low water solubility, based on the sum of soluble SiO_2 and cations (water-soluble fraction): ≤70 mg/l (SAS), approx. 70 – 80 mg/l (NAS), and approx. 260 mg/l (CS) at 20 °C. They are not volatile and have no lipophilic character. These compounds will be distributed mainly into

soils/sediments and weakly into water and are expected to combine indistinguishably with the soil layer or sediment due to their chemical similarity with inorganic soil matter. The bioavailable forms of silica are dissolved silica [$Si(OH)_4$] almost all of which is of natural origin. The ocean contains a huge sink of silica and silicates where a variety of the marine habitat (diatoms, radiolarians, and sponges) is able to exploit this resource as a construction material to build up their skeletons. Based on the chemical nature of silica and silicates (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no photo- or chemical degradation is expected. Biodegradation is not applicable to these inorganic substances.

Studies on fish, Daphnia and algae using excess loadings of SAS or NAS showed no acute toxicity, although physical effects on Daphnia were observed in tests using unfiltered test medium. Test results, based on loading rates, are as follows: 96h LL_0 *(Brachydanio rerio)* = 10000 mg/l for SAS and NAS; 24h EL_{50} (*Daphnia magna)* >10000 mg/l for SAS; 72h NOEL (*Scenedesmus subspicatus)* = 10000 mg/l for NAS. Since SAS, NAS and CS have similar chemical structures and physico-chemical properties, the conclusion of low acute aquatic toxicity applies to the whole category.

There are no chronic aquatic toxicity data, but due to the known inherent physico-chemical properties, absence of acute toxic effects as well as the ubiquitous presence of silica/silicates in the environment, there is no evidence of harmful long-term effects arising from exposure to synthetic amorphous silica/silicates.

Tests have been conducted on the German cockroach and Grain weevil which demonstrate a lethal effect on these animals due to sorption of the lipid cuticle followed by dehydration. However, the validity of these studies could not be confirmed.

Exposure

The worldwide production in 1992 was estimated at around 100,000 metric tons *(pyrogenic SAS)*, about 800,000 metric tons *(precipitated SAS),* about 115,000 metric tons *(silica gels and sols)*. The European consumption in 2000 (including imports and excluding exports) was approx. 408,500 metric tons with 368,000 metric tons for SAS and 40,450 metric tons for silicate, respectively; in 2002 the overall consumption amount to about 481,050 metric tons.

SAS, NAS and CS are used in a wide variety of applications, including consumer products. They are used to thicken pastes and ointments, to maintain flow properties in powder products and as a carrier for fragrances or flavours and are present in cosmetics (especially toothpaste), pharmaceuticals and food. They are also used in animal feed, rubber and silicones (as fillers), paints (as pigments), lacquers (as flattening agents) and plastics (to prevent plastic films from sticking together and for thixotropy control). SAS is registered as a biocide in the EU and has been successfully employed against juvenile and adult store-product pests, predominantly exerting lethal activity on juvenile and adult forms by sorption of the cuticular lipid layer, thus causing dehydration of the insects.

Potential *occupational sources* of inhalation exposure to SAS dusts are the manufacture itself and various down-stream applications producing product that contain synthetic amorphous silica and silicates as auxiliary agents (production of rubber/silicons, paints/laquers, plastics, papers, cosmetics and pharmaceuticals, as well as animal feed and beverages). In a recent monitoring program in five silica production plants, 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).

The *general population* that may come into contact with finished, silica-containing articles is unlikely to be exposed to dusty silica/silicates, as the silica compounds are bound into the matrix of the article and not freely available.

Synthetic amorphous silica and silicates possess properties indicating a hazard for human health following inhalation. These hazardous effects appear to resemble those pulmonary tissue reactions known from exposure to respirable dust. Under practical occupational conditions, these materials tend to form agglomerated particle sizes which will not reach the peripheral area of the lung. This implies that the toxicologically relevant, respirable fraction will be much lower at the workplace than under experimental conditions where the powders are actively atomized shortly before exposure. The concentration of the toxicologically relevant particle fraction at the workplace is estimated to be at least 50 times lower than commonly applied in animal inhalation studies. This would allow estimating a higher workplace-relevant No-Effect-Level for total dust than found in animal studies.

With this in mind and due to the high standard of current control measures that are in place to minimise exposure (automatic and closed packaging operation equipped with local exhaust ventilation, standard protective working clothes, routine observance of occupational exposure level), it is assumed that occupational exposure to synthetic amorphous silica and silicates is low.

Emission to the environment may occur during production and use of SAS, NAS and CS although the potential amount of anthropogenic SAS released into the aquatic environment is estimated to represent only a small fraction of the dissolved silica naturally present in rivers.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in this category are currently of low priority for further work. They possess properties indicating a hazard for human health (repeated inhalation toxicity). Based on data presented by the Sponsor country, relating to 5 production plants in one country, which account for an unknown percentage of global production and relating to the use pattern in several OECD countries, the exposure to humans to respirable dust is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemicals in this category are currently of low priority for further work due to their low hazard potential.

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1 IDENTITY

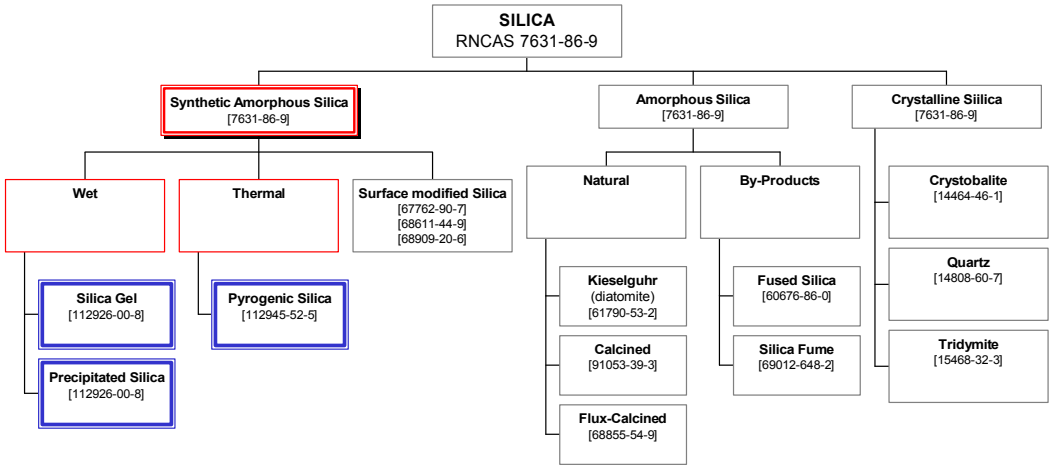
The data presented here are limited to **synthetic amorphous silica**[1)] (CAS No 112945-52-5 and 112926-00-8) abbreviated as **SAS**, and **synthetic amorphous silicate** species, **sodium aluminium silicate**, abbreviated as **NAS**, and **calcium silicate**, abbreviated as **CS**, which are produced or imported by the industrial companies indicated as members of the Consortium (see IUCLIDs 1.0.1.). In the generic product diagram (p. 5), the relevant silica types are highlighted. Chemical modifications of silica or silicates (i.e. hydrophobic silica) as well as crystalline silica or silicates are not part of this assessment. In exceptional cases, for the purpose of comparison and distinctive description of certain characteristics, findings of otherwise excluded silica/silicate types may be mentioned, for example if included in a comparative study. The silica types arising from the thermal production line will be further assigned as pyrogenic silica instead of *fumed* silica in order to avoid confusion with silica-containing *fume* dust which signify fly-ash materials arising from industrial combustion processes.

1.1 Identification of the Substance

CAS Number:	7631-86-9 (Silica) 112945-52-5 (Silica, amorphous, fumed, crystalline-free) 112926-00-8 (Silica gel and precipitated silica, crystalline-free)	1344-00-9	1344-95-2
IUPAC Name:	Silicon dioxide	Silicic acid, aluminum sodium salt	Silicic acid, calcium salt
Structure:	SiO_4 tetrahedron (base unit of the structure of the macromolecular network)		
Generic empirical formula:	$nSiO_2$	$nSiO_2 \bullet mAl_20_3 \bullet xNa_20$	$nSiO_2 \bullet mCa0 \bullet xNa_20$
Molecular Weight:	60.08g/mol (SiO_2)		
Synonyms:	Silica	Sodium aluminum silicate	Calcium silicate
Substance type:	Inorganic		
Physical status:	Solid, amorphous		
Degree of Purity:	>95 %	>95%	>95%

[1] Note: Silicon dioxide (CAS No. 7631-86-9) is the general CAS No. which includes all forms of silicas (e.g. also crystalline and natural forms) (see family tree SIAR). Only the silica sub-classes, the synthetic amorphous silicas, are subject of this evaluation.

Polymorphs of Silica



For further details see Figure 1 (wet process), IUCLID 7631-86-9, or CEFIC 2003.

1.2 Purity/Impurities/Additives

A. The technical forms "wet process" **silica** (precipitated silica and silica gel) or "thermal" = "pyrogenic" = "fumed" **silica** (silica by flame hydrolysis, are silica and plasma silica) are used for synthetic amorphous silica with high purity which are purposely produced under controlled conditions.

B. Precipitated synthetic amorphous **sodium aluminum silicates** (silicic acid, aluminum sodium salt) are non-stoichiometric amorphous forms of the precipitated synthetic reaction product of aluminum sulfate and sodium silicate with varying contents of sodium oxide, aluminum oxide and silicon dioxide. The content ranges of the oxides after ignition are described in Table 1.

C. Precipitated synthetic amorphous **calcium silicate** is a synthetic amorphous form of the reaction product of calcium chloride or calcium hydroxide with sodium silicate. The content ranges of the oxides (calcium oxide and silicon dioxide) after ignition are described in Table 1.

Table 1 Frame compositions of synthetic amorphous silica and silicates

	A	B	C
	SAS	**NAS**	**CS**
Parameter	**wt.%**	**wt.%**	**wt.%**
SiO_2	≥95	>42 – <85	>50 – <95
Na_2O	0.2 – 2.4	>0.2 – <22.0	<4.0
Al_2O_3	--	>0.2 – <36.0	--
CaO	--	--	>1 – <35.0
Sulfates as SO_3	0.2 – 3.0	< 1	n.a.
Fe_2O_3	< 0.05	< 0.1	< 0.1
Trace oxides	< 0.07	< 0.1	< 0.1

The typical limits of heavy metals for specific SAS and silicate products are in line with the quality requirements of DIN EN 71/3 (toys), BGVV Recommendation LII (Fillers for Commodities Made

of Plastic) and of quality requirements for direct food additive E551, E552 and E554 (2000/63/EU and 2001/30/EU).

1.3 Physico-Chemical Properties

See Table 2

1.4. Category Justification

A category approach, incorporating SAS and the synthetic amorphous silicates, is justified based on the similarities in chemical composition, physico-chemical, environmental and human health properties. The different category members are manufactured by slight chemical modifications to the same manufacturing process (see below Fig. 1; CEFIC 2003).

The same orders of water solubility, density, and the absence of a vapour pressure at ambient conditions along with the similarity in the chemical structure and composition allow us to conclude that these silicas and silicates will show the same or very similar environmental behaviour.

It is essential to recognise the physical differences and differences in the toxicological profile between SAS and synthetic amorphous silicates which are crystalline-free and crystalline silica. A number of types of SAS have been tested for subacute and subchronic inhalation toxicity. Transient increases in markers of inflammation and lung cell injury have been reported. In all studies with a post-exposure recovery period, the observed effects were clearly temporary. In marked contrast to crystalline silica, SAS did not produce persistent changes or progressive lesions resembling silicosis. During recovery following exposure, inflammatory markers rapidly decrease for SAS but remain elevated for crystalline silica. Unlike exposure to crystalline silica, SAS does not induce irreversible or progressive lung injury. Chronic inhalation of crystalline silica can produce lung tumours in rats, whereas this has not been demonstrated for SAS. These differences have also been seen in many epidemiological studies on workers with long-term exposure to either SAS or crystalline silica. Unlike those workers exposed to crystalline silica, workers exposed to SAS did not develop lung carcinomas, silicosis or chronic obstructive pulmonary disease. Read-across of results obtained with one compound is expected to be applicable to the other compounds.

The overview Table 2 below presents all experimental data in matrix form to document where data exist, and highlights where there are data gaps.

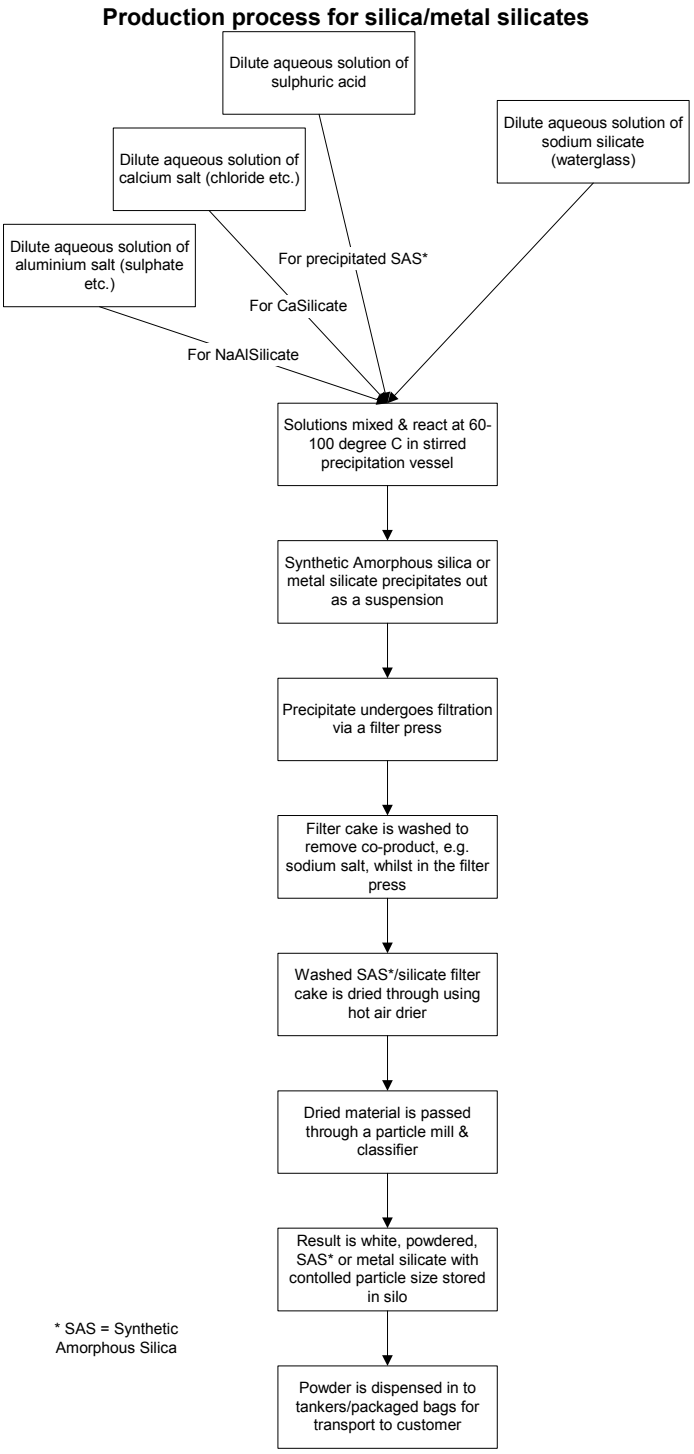


Figure 1: Scheme for the Production Process of Precipitated Synthetic Amorphous Silica and Silicates (CEFIC 2003)

Table 2 Summary of data for physico-chemical properties of synthetic amorphous silica (SAS) and silicates / interpolation in case of data gaps

	SAS [7631-86-9]	**NAS [1344-00-9]**	**CS [1344-95-2]**
PHYSICAL-CHEMICAL PROPERTIES			
Form	White powder		
Melting Point [°C]	approx. 1700 (m)* (Reliab. 4)	approx. 1700 **	approx. 1700 **
Boiling Point [°C]	no data, not applicable	no data, not applicable	no data, not applicable
Density [g/cm³] (m)*	approx. 2.2 at 20 °C	approx. 2.1 at 20 °C	approx. 2.0 at 20 °C
Bulk Density (tapped) [g/l] (m)*	50 - 320	220 – 300	230 - 300
Vapour Pressure (20 °C)	none	None	none
Partition Coefficient (log Pow)	not relevant (inorganic, non-lipophilic substance)	not relevant (inorganic, non-lipophilic substance)	not relevant (inorganic , non-lipophilic substance)
Water Solubility (Saturation) [mg/l] (m)*	approx. 15 - 68 at 20 °C (pH 5.5 - 6.6) (referring to SiO_2)	approx. 68 – 79 at 20 °C, pH ~9 (Sum of soluble SiO_2, Na and Al ions)	approx. 260 at 20 °C, pH ~9.7 (Sum of soluble SiO_2, Na and Ca ions)
pH (m)*	4 – 9	5 – 11	7 – 11
Particle Size (aggregates/agglomerates) [µm] (m)*	1 - 350	2 – 100	1 – 100
* *(m) = measured; ** read across from 7631-86-9* *References: see respective IUCLID*			
ENVIRONMENTAL FATE and PATHWAY			
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	not applicable, inorganic substance	not applicable, inorganic substance
Bioaccumulation	not bioaccumulating due to inherent substance properties		

.		**SAS [7631-86-9]**	**NAS [1344-00-9]**	**CS [1344-95-2]**
ECOTOXICOLOGY				
Acute/Prolonged Toxicity to Fish		96h LL_0=10000 mg/l (limit test)	96h LL_0 =10000 mg/l (limit test)	no data: analogy
Acute Toxicity to Aquatic Invertebrates		24h EL_{50} >10000 mg/l	no data: analogy	no data: analogy
Toxicity to Aquatic Plants, e.g. Algae		no data: analogy	72h NOEL= 10000 mg/l	no data: analogy
TOXICOLOGY				
Acute Oral Toxicity		LD_{50} >3300 mg/kg (limit test)	LD_{50} >5000 mg/kg	LD_{50} >5000 mg/kg
Acute Inhalation Toxicity		LC_{50} >0.14 - >2.0 mg/l (Maximum concentrations technically feasible)	no data: analogy	no data: analogy
Acute Dermal Toxicity		LD_{50} >5000 mg/kg (limit test)	LD_{50} >5000 mg/kg	no data: analogy
Primary Irritation (skin, eye)		not irritating	not irritating	no data: analogy
Sensitization		no data	no data	no data
Repeated Dose Toxicity (inhalation)		inflammatory reaction in the lung: NOEL(5 d) = 1.0 mg/m^3	no data: analogy	no data: analogy
Repeated Dose Toxicity (inhalation)		inflammatory reaction in the lung (rat) NOAEL(13 wks) = 1.3 mg/m^3	no data: analogy	no data: analogy
Repeated Dose Toxicity (oral)		no substance-related abnormalities in rat: NOAEL(6 months) = ~9000 mg/kgbw	Chronic: no data: analogy no gross signs of toxicity in rat and mouse, no death: NOAEL(14 d) >5000 mg/kgbw	No gross signs of toxicity in rat, no death NOAEL(2 years) = approx. 5000 mg/kgbw (Reliab. 4)
Genetic Toxicity *in Vitro*				
A.	Bacterial Test (Gene mutation)	not mutagenic	no data: analogy	not mutagenic (Reliab. 4)
B.	Non-Bacterial In-Vitro Test (Gene Mutation)	not mutagenic	no data: analogy	no data: analogy
C.	Non-Bacterial In-Vitro Test (Chromosomal Aberration)	not mutagenic	no data: analogy	not mutagenic (Reliab. 2)

	SAS [7631-86-9]	NAS [1344-00-9]	CS [1344-95-2]
Genetic Toxicity *in Vivo*	not mutagenic	no data: analogy	not mutagenic (Reliab. 2)
Carcinogenicity (inhalation)	inconclusive (Reliab. 3)	no data	no data
Carcinogenicity (oral)	not cancerogenic in rat and mouse	no data: analogy	not cancerogenic in rat (Reliab. 4)
Carcinogenicity (intrapleural)	no data: analogy	Not cancerogenic in rat	no data: analogy
Toxicity to Fertility	no effects in limited study in rat (Reliab. 3)	no data: analogy	no data: analogy
Developmental / Teratogenicity	no adverse effects in rat, mouse, rabbit and hamster	no adverse effects in rat, mouse, rabbit and hamster	no adverse effects in rat, mouse, and hamster

References of (eco)toxicological data are stated in respective chapters below.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The worldwide production in 1992 was estimated at around 100,000 metric tons *(pyrogenic silica)*, about 800,000 metric tons *(precipitated silica),* about 115,000 metric tons *(silica gels and sols)*. Most of this output is produced in Western Europe, North America and Japan; other origins (Ukraine, India) contribute to less than 5000 tons. Precipitated silicas have only been produced since the 1950s, but they have grown to become the most important group of silica products on the basis of production tonnage.

European production volumes for synthetic amorphous silicas and silicates for the year 2000 and 2002 are shown below (CEFIC Statistics):

Product Group	Production (t/a)	
year	2000	2002
Pyrogenic Silicas	72,000	73,900
Precipitated Silicas	285,500	337,100
Silica Gels	34,600	no data
Silicates	40,800	no data
Total	432,900	510,900*

** Note that there are data gaps for specific product types.*

The European consumption in 2000 (including imports and excluding exports) was approx. 408,500 metric tons with 368,000 metric tons for SAS and 40,450 metric tons for silicate, respectively (CEFIC Statistics). The respective total consumption in 2002 was 481,050 metric tons.

The consumption rates of SAS [CAS No. 112945-52-5 (pyrogenic) and CAS No. 112926-00-8 (silica gel, precipitated)] stated in the SPIN data base on the use of chemical substances in the Nordic Countries (www.spin2000.net) were too small (less than 2000 tons/a of either type) as to be representative of the total European consumption. Synthetic amorphous silica and silicates are presently used in a wide variety of industrial applications. They are often tailor-made to meet the requirements of various uses. In general, the synthetic amorphous silicas/silicates become an integral part of a product matrix, and thus the powder form no longer exists in most applications.

Consumer Use Products*:* Due to their inert nature synthetic amorphous silicas are used in cosmetics (especially tooth paste), pharmaceuticals and foods. Synthetic amorphous silica for pharmaceutical use meet the requirements of international pharmacopoeias, such as DAB 10, USP/NF XXIV/ 19, and the European Pharmacopoeia 2002. They provide thickening in pastes and ointments to inhibit the separation of components and maintain flow properties in powder products. They can also function as a carrier for fragrances or flavors. They are also used in beer and wine clarification.

Food additive grades of synthetic amorphous silica meet the requirements of the Joint Expert Committee on Food Additives of WHO/FAO and many other national requirements. Synthetic amorphous silica is registered in the European Union as Hydrated Silica E551 [Directive 95/2/EC and 96/77/EC].

Animal Feed*:* Synthetic amorphous silica and silicates serve as carriers and anticaking agents in vitamins and mineral premixes.

Rubber and Silicones*:* Synthetic amorphous silica and silicates are used as reinforcing fillers for many non-staining and colored rubber and silicones products. A new application for synthetic amorphous silica is in energy conserving automobile tyres (green tyres).

Paints*:* Synthetic amorphous silica and silicates are used as functional pigments in emulsion paints.

Lacquers*:* The most commonly used flatting agents in lacquers are synthetic amorphous silica.

Plastics*:* Plastic films often tend to stick to each other but this can be prevented by the addition of an synthetic amorphous silica as an anti blocking agent. Synthetic amorphous silica is also used in polyester and epoxy resins for thixotropy control. For polyethylene battery separators, precipitated SAS is used to generate the porosity of the separator to enable the sulphuric acid flow from electrode to electrode.

Paper*:* Small amounts of synthetic amorphous silica and silicates added to paper improve printability and opacity. Synthetic amorphous silica is also used in specially coated paper grades for ink jet printing, copying etc.

Insecticide: Synthetic amorphous silica types have successfully been employed against juvenile and adult store-product pests, predominantly exerting their lethal activity on juvenile and adult forms by sorption of the cuticular lipid layer, thus causing dehydration of the insects (Mewis and Ulrichs, 1999). Synthetic amorphous silica [CAS No. 112945-52-5] is also included in the list of notified biocides in Europe (EU Regulation 2003).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Emission to the environment may take place during production and uses of synthetic amorphous silica and silicates. At the production stage, the quantity emitted to the air is estimated to be 438 tons/year SiO_2, about 0.1 %, and the quantity emitted to the water 2.1 $x10^3$ tons/year SiO_2, about 0.5 % of the annual production in Europe (ASASP/CEFIC). Emissions of synthetic amorphous silica during the production stage are negligible compared to the potential emissions during uses. Emissions during applications were calculated on the basis of the quantities of silica consumed in EU in the different use categories (CEH Marketing Research Report, 1998) and the associated percentage of releases in the aquatic environment as proposed in the EURAM method (Hansen et al., 1999). This is a very conservative approach because the percentages of emission are very high. In this worst-case scenario, the amount of silica released into the aquatic environment represents approximately 33.5% of the silica used in EU (JACC draft No. 9). This percentage applied to the quantity of silica and silicate consumed in EU in 2002 (481 ktons) gives a quantity of 161 ktons of anthropogenic silica released into the environment.

This amount of synthetic amorphous silica introduced into the environment must be seen in the context of the natural flux of silica resulting from the weathering of silicate and aluminosilicate minerals by waters. The total flux of dissolved silica into the rivers in Western Europe is estimated to be 4374 ktons SiO_2/year (Treguet et al., 1995). That means, the potential amount of anthropogenic silica released into the aquatic environment represents at maximum only 3.7% of the dissolved silica naturally present into the rivers. This approach does not take into account any treatment before releases and neither the repartition of the released silica between the dissolved phase and the particulate phase in the aquatic environment. With regard to the low water solubility of silica and silicates a high fraction of the estimated releases will not be bioavailable.

2.2.2 Fate in the environment

Silicon oxides are the most abundant compounds in the earth's crust mass. They appear as complex silicate minerals in soils and sediments and as biogenic silica in organisms such as diatoms, radiolarians or silicoflagellates and in plants such as grass, rushes, rice or sugar cane.

Synthetic amorphous silica and silicates released into the environment are expected to be distributed mainly into soils and sediments, weakly into water and probably not at all in the air due to their physico-chemical properties, particularly low water solubility and very low vapour pressure.

Synthetic amorphous silica and silicates released into the environment are expected to combine indistinguishably with the soil or sediment due to their similarity with inorganic soil/sediment matter and will be subjected to natural processes under environmental conditions (cation exchange, dissolution, sedimentation).

Based on the chemical nature of synthetic amorphous silica and silicates (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no photo- or chemical degradation is expected. Biodegradation is not applicable to these inorganic substances.

The bioavailable form of synthetic amorphous silica and silicate is the dissolved form which exists exclusively as monosilicic [Si(OH)4] acid under environmental pH. In analogy to the general chemical reaction of weak acids and salts of weak acids with water, the water-soluble fraction of silica acts as a weak acid and, therefore, will tend to lower the pH value, while that of a silicate acts as a base tending to bind protons and, thus, raise the pH value by forming hydroxyl ions (compare

1.4, Tab. 2). But pH shifts which are measurable at high loadings under laboratory conditions are not expected to occur from the anthropogenic deposition in the aquatic environment of synthetic amorphous silicas and silicates due to low aquatic releases and sufficient natural buffer capacities. Finally, these materials are supposed to combine indistinguishably with the soil layer or sediment due to their chemical similarity with inorganic soil matter.

Dissolved silica can be actively assimilated by some marine and terrestrial organisms as normal natural processes mainly related to structural function.

2.3 Human Exposure

2.3.1 Occupational Exposure

In a comprehensive monitoring programme and morbidity study on workers in Germany (in progress), more than 1000 inhalable and respirable dust measurements were performed in synthetic amorphous silica-production plants (involved companies: Degussa, Wacker, Cabot). The measurements were carried out according to BIA-Kennzahl 7752 and 7490 (BIA-Arbeitsmappe Messung von Gefahrstoffen, Erich Schmidt, Bielefeld, 1989 / Loseblatt-Ausgabe). Overall the mean dust concentrations were 1.2 mg/m³ (inhalable) and 0.3 mg/m³ (respirable). The highest mean values were observed for job categories involved with packaging and loading operations (up to 3 mg/m³ inhalable and up to 1 mg/m³ respirable dust). Job categories include production, packaging and loading, quality control, and technical service.

All mean values of all job categories comply with the German MAK workplace threshold limit of 4 mg/m³ (inhalable dust). The results can be summarized as follows (Degussa 2004):

Plant	Number of job categories*)	Number of measurements [n]	Total and fine dust [mg/m^3]			
			Inhalable		Respirable	
			AM	GM	AM	GM
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

AM = arithmetic mean; GM = geometric mean

**)Job categories include production, packaging and loading, quality control, and technical service.*

A collection of historical exposure data for synthetic amorphous silica documented in IARC (1997, Tab. 16, p. 81) range from 0 – 10.5 mg/m^3 for total or respirable dust. The median respirable dust concentration obtained by personal sampling (1991 – 1996 and 1982 – 1996) is reported to have been from 0.2 – 8.8 mg/m^3. Some further historical data are given in Sec. 3.1.5 (Human studies) and IUCLID 7631-86-9, 5.10.

2.3.2 Consumer Exposure

There is potential for consumer exposure via a number of consumer products containing synthetic amorphous silicas/silicates, such as toothpaste, food and paints. However, in general the synthetic

amorphous silicas/silicates become an integral part of a product matrix, so the possibility of dust inhalation can be excluded in most applications.

An acceptable daily intake has not been defined. For use in food additives, limitations were set at 1% or quantum satis according to EU Directive 95/2/EC or 2% according to US regulation 21 CFR §172 480.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

Inhalation

SAS could be detected in lungs of rats only in relatively small amounts at the end of the exposure period of 13 weeks, on the average 0.2 mg in all animals of the 30-mg groups. Only one male rat exposed to 30 mg/m^3 showed a small amount of SAS in the regional lymph node. During the post-exposure observation period, no SAS could be recovered from any animal [Degussa 1987].

Exposure to 50 – 55 mg/m^3 (total dust) SAS, HDK V15, (approx. 30 mg/m^3 respirable) for 12 months of rats (initially: 5 h/d; 5 d/wk, after an unspecified time reduced to 2 d/wk or 3 d/wk because of treatment-related losses due to purulent bronchitis): After 3 days, about 0.25 mg and after 6 weeks 0.5 mg SiO_2 was found in the lungs. After 12-months exposure, about 1 % of administered total respirable dust was estimated to be still retained in the lung. The increase in lung deposition was rapid at the initial exposure, then low from 18 weeks to 12 months of exposure (6 weeks: 0.5 mg, 18 weeks: 1.2 mg, 12 months: 1.37 mg SiO_2). [note: The decline in the later deposition rate was probably also influenced by the reduction of the exposure frequency]. Mediastinal lymph nodes contained about 0.02 mg SiO_2 after 6 weeks and 0.13 mg SiO_2 after 12 months. After 5 months post-exposure, mean levels of SiO_2 were 0.16 mg/lung and 0.047 mg/lymph node, i.e. a reduction at some 88 % in the lung and more than 50 % in the lymph nodes [Klosterkoetter 1969].

After prolonged exposure of rats to high concentrations of SAS (Aerosil 150, pyrogenic) (lower unspecified exposure for 40 days, 40-50 mg/m^3 for subsequent 80 days), total deposition amounted to about 7.4 % (~435 µg in lung and lymph nodes) of respirable, theoretically deposited material (total ~5840 µg in lung and lymph nodes): overall elimination was high without accumulation in the lung: only 5-6 % (~300 µg) was found after 120 exposure days in the lung. On the other hand, transfer to mediastinal lymph nodes was substantial after prolonged exposure under these conditions with about 31 % of total deposit = 2.0 - 2.5 % (~135 µg) of the respirable, theoretically deposited material. The involvement of lymphatic elimination appears to be not relevant after short exposure periods (here up to 40 times), at least at lower body burden of SAS [Klosterkoetter 1963] [note: In other studies, higher retentions after 3 months were found (see Schepers et al., 1957, see below)].

During exposure of rats to 53 mg/m^3 (DOW silica, pyrogenic: 85 % from 1 – 10 µm, active dust exposure for 8 h/d and passive exposure for 16 h/d), for up to 12 months, the development of

pulmonary lesions was accompanied by a rapid increase in SAS in the lung, not seen in studies at lower exposure concentrations. Average lung content reached 1.5 mg SiO_2 (= approx. 10 % of lung ash) after exposure of 3 months, thereafter residing on a steady-state level. After 2 post-exposure months, levels subsided to about 0.3 mg SiO_2 per lung [Schepers 1957a, see also 3.1.5]. In guinea pigs, under identical conditions as mentioned above, average lung content reached 2.5 mg SiO_2 per lung after 12 months, about 4 % of lung-ash weight, clearly relatively lower than found in the rat. There was hardly any deposition of SAS in the lymphatic system, which was characteristic of the rat under identical test conditions [Schepers 1957b, see also 3.1.5].

Oral

After daily *oral administration* of 1500 mg/kg bw SAS (FK 700) as aqueous suspension to rats for one month, there was no accumulation of SiO_2 in the organism: the average SiO_2-content in liver was 1.5 µg, in kidney 6.4 µg and in spleen 5.3 µg. The corresponding control values were 1.8, 7.2 and 7.8 µg SiO_2, respectively [Degussa 1968].

In a similar experiment in 20 rats receiving 20 daily oral doses of 100 mg SAS (HDK V15) per animal (about 500 mg/kg bw) each, tissue values were slightly increased in liver and kidney: in liver 4.2 µg (control value 1.8 µg), in the spleen 5.5 µg (7.2 µg) and in the kidneys 14.2 µg (7.8 µg) [Klosterkoetter, 1969].

Other Route: subcutaneous

SAS (HDK V15), 10 mg *subcutaneously injected* in 0.3 ml water, was rapidly removed from the site of injection: mean recovery 24 h post-treatment 6.90 mg, after one month 0.65 mg (approx. 10 % left) and after two months 0.30 mg (less than 5 % left) [Klosterkoetter 1969]. Similar results were obtained in rats after subcutaneous application of 30, 40, and 50 mg AEROSIL 150 as suspension in water or in 0.5-% Tween or as dry powder (operative, subcutaneous): after 6 weeks 95 – 97 % of the substance was eliminated [Degussa 1964].

Studies in Humans

In vivo Studies: oral

In 12 human volunteers, no significant increased renal excretion of SiO_2 was found following single oral ingestion of 2500 mg (AEROSIL 175 and FK 700): To two groups of 5 m / 1 f persons (age 22 – 28), precipitated SAS was administered in two portions of 1250 mg (each suspended in 250 ml apple juice). The total urine was collected daily and analysed for the monomer SiO_2-content prior and after treatment. In 5/6 persons, the renal SiO_2 excretion was increased by 7 to 23 mg above the individual 3-day baseline levels ranging from 16 to 87 mg SiO_2/d. In 1/6 persons it was decreased (26 mg), the medium daily SiO_2 secretion of the following 3 days was increased by 4 to 20 mg (5/6 persons) and slightly decreased by 1/6 persons. Overall, increases were not unequivocally detectable [Degussa 1966].

Conclusion

Analytical data on the kinetics of silica deposition in the lung of experimental animals during and after prolonged exposure to silica are largely consistent. The initial uptake phase is characterized by relatively high deposition followed by a phase of low increase. Synthetic amorphous silicas are rapidly eliminated from the lung tissue, whereas crystalline silica exhibit a marked tendency to accumulate. No disproportionate deposition of synthetic amorphous silica occurs in the lymph nodes.

After oral ingestion, there is no accumulation of SAS in body tissues. Upon cessation of exposure, rapid elimination occurs. Intestinal resorption appears to be insignificant in animals and humans: In

the human test, the small apparent increases in the urine output of human volunteers were remarkably low as compared with the high dose of 2500 mg SiO_2 applied. SAS injected subcutaneously are subjected to rapid dissolution and removal.

There are no equivalent experimental data on synthetic amorphous silicates.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

There are no experimental data for synthetic amorphous silicates.

All acute *inhalation studies* performed with dry dust were hampered by the technical problem to achieve the recommended highest test concentration of 5 mg/l, apparently attributable to the high adhesive forces which caused rapid precipitation onto equipment walls. Therefore, the maximum attainable chamber concentrations were distinctly lower than envisaged.

Average dust concentrations of 139 mg/m^3 (range: 110 – 190 mg/m^3) for the pyrogenic SAS, Aerosol 200, and of 691 mg/m^3 (range: 650 – 725 mg/m^3) for the precipitated SAS, Sipernat 22 were obtained, with a respirable mass fraction of some 45 to 47 % accounting for particles with a mass median aerodynamic diameter (MMAD) of less than <5µm [Degussa 1983a; 1983b]. In either experiment, no clinically and pathologically meaningful effects were observed after 4-h exposure of rats (5 m, 5 f, each). In the latter study, animals showed signs of some discomfort and stress, and body weight of females was retarded for two days post-exposure.

In a further study, all ten rats (5 m, 5 f) survived when exposed to an average concentration of 2080 mg/m^3 pyrogenic SAS, Cab-O-Sil M5, (MMAD = 0.76 µm) for 4 hours. Clinical symptoms were nasal discharge during exposure, in a few animals crusty eyes and nose as well as alopecia at days post-exposure. No macroscopic organ lesions were noted but in one animal discoloration of the lungs was observed [Cabot 1981].

Dermal

Experimental data are available for SAS and NAS.

After acute dermal application of up to 5000 mg/kg bw of aqueous pastes of precipitated SAS and NAS (ZEO types) to the intact and abraded skin of rabbits for 24 hours under occlusive conditions, no signs of systemic or organ toxicity were noted. There were only very slight transient erythemas (Draize score 1) at the site of treatment in solitary animals (e.g. J.M. Huber, 1978a,b).

Oral

Experimental data exist for all three types of synthetic amorphous silicas and silicates.

The *acute oral* administration of various forms of SAS (aqueous suspension or gel) or silicates failed to produce signs of toxicity or deaths in treated animals with LD_{50} values greater than the top doses applied, either by gavage: >3100 – >20000 mg/kg bw [e.g. in mice: Cabot 1964; in rats: Degussa 1990; Rhone-Poulenc 1986; J.M. Huber 1973, 1978c; Litton Bionetics 1974] or in the diet for 24 hours [Degussa, 1979: LD_{50}(rat) >10,000 mg/kg bw.)].

Conclusion

Both the acute oral ingestion of and dermal exposure to high doses of synthetic amorphous silica and silicates will produce no systemic toxicity. The acute inhalation of dust may cause discomfort and stress as well as sign of local irritation to nasal, bronchiolar and ocular mucous membranes. The SAS dusts are considered as acutely non-toxic.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Experimental data are available for SAS and NAS.

The synthetic amorphous silica or silicates are not skin irritating in experimental studies on rabbits exposed to 0.19 g (one case) or 0.5 g of dry or moistened test item under occlusive conditions for 4 [Degussa 1991a] or 24 hours [e.g. Degussa 1978a; J.M. Huber 1973; Rhone-Poulenc 1992].

Studies in Humans

From occupational physicians, case reports for the working environment are available describing dryness or degenerative eczema of the skin in workers with chronic contact. These reactions may be avoided by skin care (e.g. Wacker 2000).

Eye Irritation

Studies in Animals

Experimental data are available for SAS and NAS.

All products tested as a powder (0.1 g) have shown no or only weak and transient irritating effects on the conjunctivae of the eyes of rabbits with the iris and cornea not affected at all (e.g. Degussa 1978b, 1991b; J.M. Huber 1978d,f).

Respiratory Tract Irritation

Studies in Animals

Within the scope of acute and repeated inhalation testing, irritating effects were noted in animals (see Sections 3.1.2 and 3.1.5).

Conclusion

Synthetic amorphous silica and silicates are not irritating to skin and eyes under experimental conditions, but may produce skin dryness following prolonged and repeated exposure.

3.1.4 Sensitisation

Studies in Animals

Skin

No experimental data are available on the synthetic amorphous silicas and silicates.

Studies in Humans

There is long experience in humans. Data collected from industrial hygiene surveillance over the last 50 years do not indicate any potential for skin sensitisation. As mentioned above, there are reports describing dryness or cutaneous irritation that may be misinterpreted as a sign of sensitisation or allergy. (e.g. Wacker 2000).

Conclusion

Medical surveillance records on workers gave no evidence of skin sensitisation over decades of practical experience. Given the inherent physico-chemical properties and ubiquitous nature of this class of compounds, there is no structural alert to indicate a sensitising potential.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

Several short-term repeated dose studies and numerous subchronic and chronic inhalation studies have been conducted with SAS of the pyrogenic, precipitated and gel types, using various animal species, mostly rat, but also mouse, guinea pig, rabbit and monkey (see IUCLID 7631-86-9). The exposure concentrations ranged between approx. 1 and 150 mg/m^3.

In a fully reliable and valid short-term inhalation study programme, three SAS were investigated in comparison to a crystalline silica as positive control compound: Wistar rats (10 animals per group and sex in the first part of the study, and 10 males per treated groups and 6 males in the control group in the second and third part of the study) were exposed to nominally 1, 5, and 25 mg/m^3 of each silica for 5 d, 6 h/d. Satellite groups were exposed correspondingly and kept for a recovery period of one and three months. (Note: Two out of the three tested SAS were only examined in males because they had proven to be more sensitive than females, as observed in the first study.) The mass median aerodynamic diameter of particle size distribution (MMAD) ranged from 1.5 – 3.5 µm, i.e. the aerosol was potentially 100 % respirable. The most sensitive parameters for the elucidation of an inflammatory tissue reaction were applied besides standard histopathological inspection: white blood cell count, viability and cell differentiation as well as determination of biochemical parameters in the bronchio-alveolar lavage (BAL) (TNO 2003a,b,c).

All tested SAS produced a similar effects profile: but the pyrogenic SAS (Cab-O-Sil) induced a more marked inflammatory reaction:

Generally, the *high exposure concentrations* (25 mg/m^3) induced dose-related effects which reflected an inflammatory response of the lung tissue, associated with a slight morphological tissue reaction (hypertrophy, partly hyperplasia of the bronchiolar epithelium). All observed changes disappeared or tended to disappear during recovery, showing clear signs of reversibility, while recovery was not observed for the crystalline silica.

For the *precipitated and gel types*, effects at the *mid exposure concentration* (5 mg/m^3) were confined to very slight increases in the relative neutrophil count with concomitant decrease in the relative macrophage count at the day after exposure. There were no morphological tissue changes. For the *pyrogenic type*, slight hypertrophy of the bronchiolar epithelium was noted also at the *mid-dose* level. No effects were noted at the *low-concentration levels of any SAS* tested (1 mg/m^3) (TNO 2003a,b,c).

In one comprehensive, fully reliable and valid 13-weeks study including recovery intervals of up to one year, effects of various SAS, Aerosil 200 (pyrogenic type), Sipernat 22 (precipitated type) and Aerosil R974 (hydrophobic, amorphous) and, furthermore, quartz (crystalline silica), were

investigated [Degussa 1987; Reuzel et al. 1991]. The primary particle size was calculated theoretically from electronmicroscopic photographs (range <6 – 45 nm). However, it is important to note that primary particles do not exist as individual free units, but only as aggregates and agglomerates. Because of technical problems, the aerodynamic aggregate/agglomerate size distribution in the test atmospheres was not determined. The approximate maximum of the geometric aggregate/agglomerate size distribution of Aerosil 200 was estimated to be at 10 µm, based on normal photograph technique. Reliable analytical data on the factual experimental particle size distribution in the test chamber are not available and technically difficult to obtain (Degussa 1987, p. 13; Reuzel et al. 1991; see also IUCLID, 6.1, IARC, 1997).

Aerosil 200 was examined at 1.3, 5.9 and 31 mg/m^3 (average of analytical values), Sipernat at 35 mg/m^3 for 6 hours/day, 5 days/week. Ten male and ten female rats were sacrificed directly after termination of exposure, 50 others were saved for examinations at 13, 26, 39, and 52 weeks post-exposure.

Dose-related changes caused by inflammatory reactions and irritation of the tissue were observed in the lung of animals exposed to Aerosil 200. Associated lesions only partly recovered during the one-year post-exposure period at the top exposure level. The level of 1.3 mg/m^3 induced only slight changes, which generally recovered quickly (cellular infiltration, stimulation of collagen production and increase in lung weight). There were no signs of silicosis at any exposure level. Focal interstitial fibrosis was not noted directly after the exposure period of 3 months, but appeared with a delay in the 30-mg rats, and to a lesser degree, in the 6-mg group. Treatment-related, microscopic changes in the nasal region were occasionally found at the end of the exposure period such as focal necrosis and slight atrophy of the olfactory epithelium. Sipernat induced a similar pattern of lesions, but to a distinctly lower degree, which also proved to be reversible [Degussa 1987; Reuzel et al. 1991].

Following long-term inhalation of 53 mg/m^3 (active dust exposure 8 h/d, passive exposure 16 h/d) up to 12 months (Dow silica, pyrogenic: 85 % from 1 – 10 µm), at significantly higher concentrations of SAS than used in above-mentioned studies, the majority of rats spontaneously died from pulmonary vascular obstruction and emphysema: 26/35 animals (75 %) and 11/25 animals (44 %) in two experiments [Schepers et al. 1957a]. Nodules formed progressively throughout the lung parenchyma showing manifestation of fibrosis in the nodules.

Excess inhaled SAS cleared to the lymphatic system was associated with formation of parenchymatous nodules consisting of chromophoric macrophages. The progress of lesions is associated with a high lung burden of SAS which apparently cannot be removed efficiently anymore due to overload. As a consequence, excess material not being cleared mechanically or by dissolution is apparently deposited to the pulmonary lymphatic system [Schepers et al. 1957a]. In guinea pigs, findings were qualitatively similar to those obtained in rats (and rabbits), but were in sharp contrast as to the kind of lesion and severity of effects: Chronic exposure to SAS was non-lethal to guinea pigs, but caused significant inflammatory reactions and pulmonary lesions, however, without apparent disability of the animals as seen with rats and rabbits, although the burden of silica in the guinea-pig lungs was significantly higher, 2.5 – 8 mg (12 and 24 months) vs. only 1.5 mg in rats [Schepers et al. 1957b].

Prolonged exposure of rats (3, 6, and 12 months), guinea pigs (12 months) and monkeys (13 months) to 15 mg/m^3 (total dust) of precipitated (Hi-Sil), pyrogenic (Cab-O-Sil type) (particles ≤4.7 µm: approx. 50 to 65 %), and gel silica (no data) produced effects including impairment of lung function, clear inflammatory reactions with signs of early nodular fibrosis. High deposition of SAS was noted in macrophages in lung and tracheal lymph nodes of the monkeys, not or barely found in rat and guinea pig. Macrophage and mononuclear cell aggregation was found to be significantly

more pronounced in monkeys (bronchioles, alveolar ducts venules, arterioles) than in rats and guinea pigs (Groth et al. 1981).

Oral

There are several well-performed studies on SAS (3 – 6 months), one not verifiable two-years study with a CS and a limited testing programme on a NAS over 21 – 24 days.

A *precipitated SAS*, Sipernat 22, administered at dietary levels of 0, 0.5, 2, and 6.7 % (analytical value) [mean estimated doses: 0, 300-330, 1200-1400, 4000-4500 mg/(kg bw∗d), 13 weeks] produced no adverse effects based on clinical, haematological, blood-chemical, urinary and (histo-)pathological examinations in groups of male and female Wistar rats (10 animals each) [Degussa 1981].

In another feeding study, male and female CD-1 rats received Syloid 244, an *amorphous silica* gel, at dietary levels of 3.2 and 10 % for 6 months, corresponding to average doses of 2170 – 2420 and 7950 – 8980 mg/(kg bw∗d). Likewise, no treatment-related findings were noted. Isolated pathological findings were unrelated to dosing and common in untreated rats. No histo-pathological changes were observed in the kidneys and reproductive organs [Grace 1975].

In two limited 14-d feeding studies, groups of Fischer rats and B6CF1 mice (5 per sex and dose) received an unspecified NAS at levels of 0.625, 1.25, 2.5, 5, and 10 % in the diet. There were no substance-related clinical and histopathological findings at any dose level. Only the body-weight gain of the high-dosed male rats was significantly reduced (-39 %). The NOAEL can be estimated to be approx. 2500 mg/(kg bw) (at 5-% dietary level). Despite the small group sizes, there were 30 animals in two species (2.5, 5, and 10 % level) that received a dose of more than 1000 mg/(kg bw∗d), which is a reasonable high number of high-dosed animals from which to draw firm conclusions on effects [Cannon 1979a,b].

In a non-verifiable two-years feeding study, four groups of male and female rats (unspecified albino) received 1.0, 5.0, 7.5, and 10 % of a CS (Silene EF) in the diet. The highest dose may be estimated to be about 5000 mg/(kg bw∗d). No deaths and no gross signs of toxicity were noted except growth depression and slight elevation of organ weights (no details available)No increases in any tumour type were observed [Columbia Southern Chemical Corp. 1957].

Conclusion

For *inhalation*, there are no experimental data on synthetic amorphous silicates. It is deemed reasonable to assume a similar effects profile for the synthetic amorphous silicates as for SAS for which abundant data exist, based on the assumption that the particle size and morphology rather than particle composition is the determinant of inflammatory response in the lung. Although NAS and CS are more alkaline than SAS, the apparent pH factor is assumed to be negligible, as physiological buffer capacities of the lung tissue are sufficiently high as to compensate minor pH shifts at exposure levels of the order of 1 mg/m^3.

The *inhalation* of respirable particles of SAS produces a time- and dose-related inflammation response of the lung tissue in animal studies. Progressive events following excess exposure are characterised as “interstitial fibrosis/early nodular fibrosis/incipient fibrosis”. However, a progression process of any lesion has not been observed like that seen after quartz exposure, i.e. all observations suggest reversibility, although rather slow at high and prolonged exposure. There are no signs of classical nodular silicosis or a lymphatic-type pneumoconiosis. On the other hand, crystalline silica produce persistent lung inflammation even at much lower exposure levels.

The incidence and severity of the tissue reaction after exposure to the different types of SAS are roughly similar, somewhat more marked for the pyrogenic type. It is influenced by animal species and is sex-specific (Rats were more sensitive than guinea pigs, and male rats more than females).

After 5 exposures (6 h/d) to 1 mg/m^3, no tissue reaction was observed (TNO 2003a, b, c). After 13 weeks at 1.3 mg/m^3, there was no morphological tissue effect that could be considered as a *pathological* manifestation (slight reversible collagen stimulation and no significant increase in lung weight) [Degussa 1987; Reuzel et al. 1991].

Based on the pathological relevance of effects, 1 mg/m^3 could be established as NOEL (short-term) and NOAEL(sub-chronic). This appears to be justified also in light of the fact that the sub-chronic study was conducted with a pyrogenic SAS which appears to induce more marked tissue responses than the precipitated SAS type.

The short-term LOAEL (5 d) was 5 mg/m^3 for the pyrogenic SAS, but this concentration was more of a NOAEL for the precipitated types [TNO 2003 a,b,c].

A subchronic LOAEL(13 weeks) of 15 mg/m^3 (about 7 to 9 mg/m^3 respirable particles ≤ 4.7 µm MMAD) was found in a study on rats, guinea, pigs and monkeys [Groth et al., 1981].

The inhalation studies gave no evidence of systemic adverse effects at high pulmonary and/or lymphoid deposition of SAS, although systemic bioavailability of SAS may be assumed, given the fact that this material appears to be partly eliminated by solubilisation [Vogelsberger, 1999, 2003].

After oral application, for *SAS and CS*, no adverse effects could be demonstrated after long-term administration to rats but at very high doses. An overall NOAEL (chronic, oral) of approx. 2500 mg/kg bw can be established.

Discussion on the practical relevance of experimental results (inhalation):

The experimental test design requires the application of high shear stress in order to produce homogeneous particle distribution and exposure to the highest possible fraction of fine particles able to migrate to the peripheral region of the lung. The particle-size distribution in the above-mentioned studies was in general such that about 60 - >80 % of the SAS mass applied had MMADs of 5 µm and below (see TNO 2003a,b,c; Schepers et al. 1957; Groth et al. 1981).

Under occupational exposure conditions, shear forces are not or no longer operative. Therefore, free settling SAS tend to form higher aggregates and agglomerates (>100 µm) which are not respirable or even not inhalable: In fact, in the commercial products, that fraction of particles in the whole-size range of air-borne particles according to EN/DIN481 that is potentially able to reach the thoracic and alveolar site is below 1 vol% (= wt%) (Stintz 2001, p. 30-32).

This means that in experimental studies, the toxicologically relevant particle fraction is assumed to be at least at a factor of 50 higher than under workplace conditions.

Studies in Humans

Inhalation

Company health records from 1941 to 1959 were reviewed for 78 workers (average age about 34 years; exposure time 1 – 16.6 years) who were employed in the manufacturing and processing of Hi-Sil (precipitated SAS) and Silene (CS). The dust concentration ranged from 0.35 to 204 mg/m^3. No evidence of silicosis or other pulmonary disease was found by evaluation of the chest X-rays [Plunkett and DeWitt 1962].

Medical records were reviewed for 165 workers employed at two plants and exposed for a mean of 8.6 years to precipitated SAS. 44 workers had been exposed 18 years (range 10-35 years) on the average. Dust levels varied between <1 – 10 mg/m^3 with some higher intermittent levels.

Linear regression analysis of yearly change of all pulmonary function variables showed no correlation with either the dose of precipitated SAS nor total years of exposure [Wilson et al. 1979, 1981].

Among the 44 workers with a mean exposure time of 18 years, yearly decline of pulmonary function variables were similar to the overall group of 165 workers.

Eleven workers had radiographic evidence of minimal pneumoconiosis, but this effect was biased by prior occupational exposure to limestone. Respiratory symptoms such as cough and dyspnoea correlated with mean pack-years of smoking but not with precipitated SAS exposure, while serial pulmonary function values and chest radiographs were not adversely affected by long-term exposure [Wilson et al. 1979, 1981].

An in-house evaluation was conducted on 143 workers who had been involved in the production of Aerosil, covering the time from 1959 through 1985. 54/143 workers (36 %) complained of some disorder or exhibited abnormalities in lung function or histology. Of those, 34/54 (63%) suffered from dry cough, expectoration or dyspnoea; 42/54 affected workers (78 %) had some characteristics that could confound any effect from Aerosil exposure (pre-existing disorder and/or previous confounding exposure: 32/54 = 59 %, smoking: 30/59 = 56 %), only 12/54 (22 %) had neither, which represents 8 % of the cohort. Radiological examination did not show any signs of fibrotic disease [Ferch et al. 1987] [Degussa 1988].

In a production plant of SAS, a total of 215 workers was examined during 1947 and 1959 and in total 720 chest X-rays were made. Past exposure is reported to have been between 2 to 7 mg/m^3. Levels were considerably higher at the filling nozzles when immediately measured (15 – 100 mg/m^3). 44/215 workers were classified as having long-term exposure experience with 9/44 employed more than 10 years. The only significant observation was the hairline accentuation of the interlobar fissures, suggesting slight interlobar pleuritis. There were no signs of pneumoconiosis or silicosis [Volk, 1960].

Conclusion

Occupational exposure to SAS gave no evidence of pneumoconiosis or silicosis. Other disorders of the respiratory tract could not be correlated to exposure to SAS alone. However, the available epidemiological data base on workers is too limited as to draw firm conclusions; furthermore, appropriate control populations were lacking in these studies.

3.1.6 Mutagenicity

Studies in Animals

Experimental data are available for SAS and for CS, both *in vitro* and *in vivo*.

In vitro Studies

Various types of SAS have not demonstrated mutagenic activity in bacterial Salmonella and E. coli reverse mutation assays in the presence and absence of an external metabolising system [Mortelmans et al. 1981; Cabot 1989a], in cytogenetic mammalian cell systems including chromosomal aberration in human embryonic lung cells (Wi-38) [Litton Bionetics 1974] and Chinese hamster ovary (CHO) cells [Cabot 1990b], furthermore in a gene mutation assay in

mammalian cells, HGPRT assay in CHO cells [Cabot 1990a] as well as in a DNA repair system, a UDS test, in primary rat hepatocytes [Cabot 1989b]. CS is reported to be void of mutagenic potential in a limited bacterial and an acceptable cytogenetic assay using human embryonic lung cells (Wi-38) [Litton Bionetics 1974].

In vivo Studies

A valid cytogenetic assay in rats failed to demonstrate an increase in chromosomal aberrations in bone-marrow cells from rats treated with single and fivefold oral synthetic amorphous silica or silicate doses as high as 5000 mg/kg bw per treatment [Litton Bionetics 1974]. Likewise, a well-performed dominant lethal assay conducted in rats did not produce significant adverse effects on reproductive performance parameters after exposure of male rats to both SAS and silicates, respectively, under above-mentioned exposure conditions [Litton Bionetics 1974].

Following sub-chronic inhalation exposure of rats to a mean dust concentration of 50 mg/m^3 (pyrogenic SAS Aerosil 200) for 13 weeks, the study also including crystalline silica (cristobalite), alveolar type-II cells were isolated from the bronchoalveolar lavage fluid (BAL) and subjected to the HPRT gene-mutation assay *in vitro*. The cells were cultured for 14 – 21 days in selective medium prior to fixation. There was no increase in 6TG-resistant mutants vs. control (7.6 +-3.4 mutants/10^6 cells in control), whereas after exposure to crystalline silica, the mutant frequency was significantly enhanced (approx. 30 mutants/10^6 cells) [Johnston et al. 2000].

Conclusion

There is no evidence for synthetic amorphous silica or silicates to induce mutations either *in vitro* or *in vivo* using standard methods. There was also no evidence for mutagenic activity to arise from long-term inhalation exposure to synthetic amorphous silica. However, in the same study, there was an association between the mutation rate at the HPRT locus induced by crystalline silica (quartz) in isolated alveolar epithelial cells and the development of chronic inflammation in rat lung [comp. also IARC 1997, p. 201-204]. This underlines the distinction of effects produced by synthetic amorphous silica/silicates and crystalline silica.

3.1.7 Carcinogenicity

In vivo Studies in Animals

Inhalation

There appears to be only one early study to show an increased incidence of lung tumours in mice following inhalation exposure to precipitated SAS (Campbell, 1940). One group of male and female mice (not specified) had been exposed to a cloud of dust for 10 min/h, 6 times/d for one year i.e. for a total of one hour per day (cited as 0.5g/day). After cessation of the exposure period, the animals were observed for their whole life-span. The increase noted in those treated animals still alive at 600 experimental days and above (equivalent to some 690 days of age and more) was 21.3 % (13/61) vs. 7.9 % (5/63) in controls. 8/13 tumours were carcinomas as compared with 3/5 in the control group. Non-neoplastic effects included fibrotic overgrowth and hyperplasia in lymph nodes and mediastenal connective tissue, but there was no evidence of lung fibrosis.

The incidence of pneumonia appeared to be somewhat increased in treated animals (21.3 % vs. 15.9 % the control) [Tab VII], this trend being more pronounced in comparison to the other control groups of other concurrent test series.

Oral

Long-term feeding studies are reported for SAS and CS: Three groups of Fischer rats and B6C3F_1 mice received a SAS (Syloid 244) at dietary levels of 1.25, 2.5, and 5 % for 102 and 93 weeks, respectively. The mean cumulative intake was 143.5, 179.6 and 581.2 g/rat in males and 107.3, 205.0 and 435.3 g/rat in females, respectively, and was 38.5, 79.8 and 160.0 g/mouse in males and 37.0, 72.5 and 157.6 g/mouse in females, respectively. The animals were in good condition throughout and showed high survival. The tumour responses in all organs of SAS-fed rats and mice were not statistically significantly different from the controls (Fisher´s exact test and Cochran-Armitage test for trend) [Takizawa et al. 1988] (see also: IARC 1997, p. 171).

In a non-verifiable two-years feeding study, four groups of male and female rats received 1.0, 5.0, 7.5, and 10 % of a CS (Silene EF) in the diet. No deaths and no gross signs of toxicity were noted. No increases in any tumour type were observed [Columbia Southern Chemical Corp. 1957].

Other Route: intra-pleural

Within the scope of a comprehensive test programme on the carcinogenesis of various minerals, several silicates (crystalline and amorphous) as well as quartz and TiO_2, along with fibrous minerals, UICC crocidolite (blue asbestos) and Oregon erionite (fibrous zeolite) which served as positive control substances were examined (Unilever Research 1995). The intra-pleural route was selected as special application mode in rats, as this test model was known to be responsive on fibrous materials (asbestos, silica), resulting in the induction of mesotheliomas after one single dose. Test materials (20 mg) were administered as suspensions in sterile saline by single intra-pleural injection under halothane anaesthesia. Male and female Wistar rats (30 – 50 per group and sex) were allowed to live their whole life-span or maximally 3 years. No pleural mesotheliomas appeared in the saline group. No pleural mesotheliomas were induced by the amorphous NAS and the other non-fibrous minerals including TiO_2 and quartz, apart from a single benign testicular mesothelioma. The application of asbestos material distinctly produced pleural mesotheliomas in 71 – 93 % of the animals. The treatment with the test minerals, irrespective of the fibrous or non-fibrous nature, did not influence the pattern of prevalence of isolated spontaneous tumours other than mesotheliomas (most of them thyroid follicular tumours).

Conclusion

Based on the negative results after long-term oral application of SAS and CS, there is no evidence of a carcinogenic potential arising from ingestion of these amorphous minerals. Due to technical deficiencies and failure of substance definition and description, the results of the long-term inhalation study are inconclusive and cannot be correctly evaluated. According to IARC (1997, p. 210/211), there is *inadequate* evidence in humans and animals for the carcinogenicity of synthetic amorphous silica. Amorphous silica is *not classifiable* as to its carcinogenicity in humans (Group 3).

The animal model after comparative intra-pleural treatment with various types of minerals underlines that the cancerogenic potential of amorphous silica/silicates can be considered as negligible.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

An early limited one-generation study on Wistar rats gave no evidence of any adverse effects arising from long-term feeding of Aerosil [500 mg/(kg bw∗d)] to both genders for a premating

period of 4.5 months and continued up to 6 months [Degussa 1963]. Five pregnant test females and four pregnant untreated control females delivering 45 and 37 pups, respectively, were included in this test. The study had shortcomings with respect to the low number of pregnant animals used and the mating ratio of 1(m):5(f) which was too low according to current standards.

Developmental Toxicity

Within the scope of a comprehensive and valid testing programme, SAS and silicates (NAS and CS) were examined for embryotoxic and developmental effects during the gestation phase in various animals species, rat, mouse, rabbit and hamster, at oral doses up to 1600 mg/(kg bw∗d). There were no significant signs of maternal or embryotoxic/developmental toxic effects in any species tested. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the frequencies occurring spontaneously in the sham-treated controls [FDA 1972, 1973a,b].

Conclusion

The experimental data on intra-uterine development produced in four animal species across all three types of synthetic amorphous silica and silicates suggest that there is no potential for adverse effects on embryonal/foetal development arising from exposure to these SAS/silicates.

Specific investigations on fertility to current standard are not available for hydrophilic SAS and synthetic amorphous silicates. The one-generation study conducted with a hydrophilic SAS type is not adequate to contribute reliable information for biostatistical reasons. However, numerous subchronic studies as well as a dominant lethal study with a CS failed to demonstrate any histopathological changes or deleterious effects in the reproductive organs of treated animals. Furthermore, given the inherent physico-chemical properties and ubiquitous nature of this class of compounds, there is no structural alert to indicate a potential for reproductive and developmental toxicity.

Therefore, based on the weight of evidence, prolonged exposure to synthetic amorphous silica, applied before and during pregnancy at high doses, is not expected to produce harmful effects on the reproductive performance or embryonic/foetal development in experimental animals.

3.1.9 Additional Relevant Information

In a comprehensive comparative mechanistic study, the impact of various particulate materials (quartz, amorphous silica, carbon black and coal dust) on the lung tissue of female Wistar was studied. After intratracheal instillation (20 instillations each with 2-wk intervals between the treatments), various indicative parameters for characterising and differentiating the inflammatory reaction of the tissue were examined (histopathology, cell differentiation in the bronchiolar lavage, characterization of the cellular immunogenic responsiveness of lavage cells to a LPS (E. coli antigen) or zymosan stimulus 9 months after first instillation. Furthermore, immunobiological endpoints, such as generation of reactive nitrogen and oxygen species and production of TNF-alpha (tumor necrosis factor) served as additional markers.

According to the authors, among the particles tested, only SAS failed to impair the natural cellular responsiveness to LPS stimulation, while all others more or less suppressed this function. The high number of neutrophils in the SAS group correlated with the reactivity of the cells to produce TNF-alpha upon stimulation (note: TNF-alpha plays a major role in recruitment of neutrophils into the lung.). Furthermore, the relatively high protein content in lungs after treatment with SAS may account for the enhanced production of reactive species. Although the implication of these findings for pulmonary cytotoxicity have not yet been completely clarified, the histopathological

observations clearly demonstrate that exposure to SAS was less damaging than exposure to quartz and other tested materials.

3.2 Initial Assessment for Human Health

The physico-chemical and toxicological properties of synthetic amorphous silica and silicates allow the category approach to be taken in order to bridge data gaps where specific experimental information is lacking.

For inhalation, it is reasonable to assume a similar effects profile for the synthetic amorphous silicates as for SAS for which abundant data exist, based on the assumption that the particle size and morphology rather than particle composition is the determinant of inflammatory response in the lung. Although NAS and CS are more alkaline than SAS, the apparent pH factor is assumed to be negligible, as physiological buffer capacities of the lung tissue are sufficiently high as to compensate minor pH shifts at exposure levels of the order of 1 mg/m^3.

Therefore, for all synthetic amorphous silica/silicate species it is proposed to adopt the NOAEL of SAS of 1mg/m^3 for prolonged exposure.

The material used in the animal studies to derive the NOAEL of 1 mg/m^3 contained of the order of 50 times the proportion of respirable material compared to SAS to which humans are exposed. It is important that account is taken of this when considering whether margins of exposure are of any concern with regard to human health.

All other endpoints, even though based on a limited data base in isolated cases (e.g. fertility), give no rise of substantial concern, due to the general low toxicity of the compounds.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Fish

Acute toxicity to *Brachydanio rerio* has been determined in 2 studies with SAS (Degussa 1992a,b). Test solutions were prepared by stirring an excess concentration (1000 or 10000 mg/l loading) for 20 hours and the resulting suspension was tested. No effects were observed at 10000 mg/l and the result is expressed as a loading rate: 96h-LL_0 = 10000 mg/l.

Acute toxicity to *Brachydanio rerio* has been determined in one study with NAS (Degussa 1998a). 10000 mg/l loading was stirred for 24 hours at 25 °C and then filtered and the pH adjusted to 7.0 before testing. No effects were observed and the result is expressed as a loading rate: 96h-LL_0 = 10000 mg/l.

It can be concluded that SAS and NAS are not acutely toxic to fish. Due to the similar structure and physico-chemical properties of CS, it is assumed that CS also shows no acute toxicity to fish.

Aquatic invertebrates

Data is only available for SAS. Two studies were conducted with *Daphnia magna*.

In the first study, test solutions were prepared by stirring an excess loading (1000 and 10000 mg/l) for 20 hours, and the resulting suspensions were tested (Degussa 1992c). The test media remained turbid throughout the test, and starchy particles were observed on the bottom of the test vessels. After 24 hours of exposure, 7.5% and 2.5% of the Daphnia were immobile at the loading rate of 1000 and 10000 mg/l, respectively. The observed effects were not dose-related, and the immobile animals had some particles on their appendages. Therefore, it is likely that the effects on mobility were caused by physical hampering of the animals.

In a second study, three different tests solutions were prepared (Degussa 1992d):

- suspensions of 1000 and 10000 mg/l were stirred for 20 hours;
- suspensions of 1000 and 10000 mg/l were stirred for 20 hours, then filtered on perlon wool;
- suspension of 1000 mg/l was stirred for 20 hours, then filtered through microfibre-glass filter with 1.7 µm and 1.2 µm successively.

With the first methodology, tests suspensions were homogeneously white turbid, and some undissolved material was present on the surface. 5% and 25% of the Daphnia were immobile with the suspensions of 1000 and 10000 mg/l, respectively.

With the second methodology, the solutions were still turbid after filtration, and undissolved material was found on the bottom of the vessels after 24 hours. 10% and 22.5 % of the Daphnia were immobile with the solutions of 1000 and 10000 mg/l, respectively.

With the third methodology where clear solutions were obtained, no significant immobilization was observed (4%). Therefore, it is suspected that the immobility observed, particularly with the 10000 mg/l suspensions, could be attributed to physical effects.

On the basis of these studies, an LL_0 of 1000 mg/l was derived for SAS, which indicates that SAS shows no acute toxicity to Daphnia.

Due to a similar structure and physico-chemical properties of NAS and CAS, it is assumed that also NAS and CAS show no acute toxicity to Daphnia.

Algae

A growth inhibition test with *Scenedesmus subspicatus* has been conducted for NAS (Degussa 1998b). The test was conducted with excess loadings of test substance (10000, 1000, and 100 mg/l) stirred for 24 hours followed by filtration. No significant effect of growth inhibition related to biomass production and growth rate was observed, and results based on loading rate are 72h-NOEL = 10000 mg/l. On the basis of the similarity of the structures and physico-chemical properties of SAS and CS, it is assumed that SAS and CS show no toxicity to algae, too.

Chronic Toxicity Test Results

There are no chronic aquatic toxicity data, but due to the known inherent physico-chemical properties, absence of acute toxic effects as well as the ubiquitous presence of silica/silicates in the environment, there is no evidence of harmful long-term effects arising from exposure to synthetic amorphous silica/silicates.

Toxicity to Microorganisms

No experimental data have been located for synthetic amorphous silica/silicates.

4.2 Terrestrial Effects

Tests have been conducted on the German cockroach and Grain weevil which demonstrate a lethal effect on these insects due to the sorption of the cuticular lipids, thus leaving the insect vulnerable to dehydration. However, the validity of these old studies could not be assigned. In these studies on insects, it is indicated that SAS was studied in relation to its use as a biocide carrier in some insecticide formulations (Gowers and Le Patourel, 1984; Le Patourel and Zhou, 1990).

4.3 Other Environmental Effects

No data

4.4 Initial Assessment for the Environment

SAS, NAS and CS are solids in powder form which have a low water solubility, based on the sum of soluble SiO_2 and cations (water-soluble fraction): ≤70 mg/l (SAS), approx. 70 – 80 mg/l (NAS), and approx. 260 mg/l (CS) at 20 °C. They are not volatile and have no lipophilic character. These compounds will be distributed mainly into soils/sediments and weakly into water and are expected to combine indistinguishably with the soil layer or sediment due to their chemical similarity with inorganic soil matter. The bioavailable forms of silica are dissolved silica [$Si(OH)_4$] almost all of which is of natural origin. The ocean contains a huge sink of silica and silicates where a variety of the marine habitat (diatoms, radiolarians, and sponges) is able to exploit this resource as a construction material to build up their skeletons. Based on the chemical nature of silica and silicates (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no photo- or chemical degradation is expected. Biodegradation is not applicable to these inorganic substances.

Studies on fish, Daphnia and algae using excess loadings of SAS or NAS showed no acute toxicity, although physical effects on Daphnia were observed in tests using unfiltered test medium. Test results, based on loading rates, are as follows: 96h-LL_0 *(Brachydanio rerio)* = 10000 mg/l for SAS and NAS; 24h-EL_{50} *(Daphnia magna)* >10000 mg/l for SAS; 72h-NOEL *(Scenedesmus subspicatus)* = 10000 mg/l for NAS. Since SAS, NAS and CS have similar chemical structures and physico-chemical properties, the conclusion of low acute aquatic toxicity applies to the whole category.

There are no chronic aquatic toxicity data, but due to the known inherent physico-chemical properties, absence of acute toxic effects as well as the ubiquitous presence of silica/silicates in the environment, there is no evidence of harmful long-term effects arising from exposure to synthetic amorphous silica/silicates.

Tests have been conducted on the German cockroach and Grain weevil which demonstrate a lethal effect on these animals, due to sorption of the lipid cuticle followed by dehydration. However, the validity of these tests is not assignable.

5 RECOMMENDATIONS

SAS, NAS and CS are of low priority for further work for the environment due to their low hazard potential.

The members of the category, SAS, NAS and CS, possess properties indicating a hazard for human health (repeated inhalation toxicity). Based on data presented by the Sponsor country, the exposure to humans to respirable dust is anticipated to be low, and therefore this chemical is currently of low

priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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- Calcium silicate - NIOSH Pocket Guide.html,
- Silica physchem BiblioLine.doc,
- Silica, amorphous - NIOSH Pocket Guide.html,
- SILICON DIOXIDE - HSDB - Hazardous Substances Data Bank.html,
- SODIUM ALUMINOSILICATE - HSDB - Hazardous Substances Data Bank.
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- TOXNET SODIUM ALUMINOSILICATE.doc
- Merck Index, 13th Edition, 2001

I U C L I D

Data Set

Existing Chemical	:	ID: 7631-86-9
CAS No.	:	7631-86-9
EINECS Name	:	silicon dioxide[1]
EC No.	:	231-545-4
TSCA Name	:	Silica
Molecular Formula	:	O2Si

Producer related part

Company	:	Association of Synthetic Amorphous Silica Producers (ASASP)
Creation date	:	29.06.2004

Substance related part

Company	:	Association of Synthetic Amorphous Silica Producers (ASASP)
Creation date	:	29.06.2004
Status	:	
Memo	:	Origin Degussa AG, 04 June1994, Rev. 6
Printing date	:	06.12.2004
Revision date	:	21.09.2004
Date of last update	:	06.12.2004
Number of pages	:	157
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

[1] Note: Silicon dioxide (CAS No. 7631-86-9) is the general CAS No. which includes all forms of silicas (e.g. also crystalline and natural forms) (see family tree SIAR). Only the silica sub-classes, the synthetic amorphous silicas, are subject of this evaluation.

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	other: Consortium
Name	:	ASASP (Association of Synthetic Amorphous Silica Producers) (CEFIC Sector Group)
Contact person	:	
Date	:	
Street	:	Avenue E. van Nieuwenhuyse, 4
Town	:	B-1160 Brussels
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Flag	:	Critical study for SIDS endpoint
Type	:	lead organisation
Name	:	Degussa AG, ZN Wolfgang
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Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Flag	:	Critical study for SIDS endpoint
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Flag	:	Critical study for SIDS endpoint
Type	:	cooperating company
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Flag : Critical study for SIDS endpoint

Type : cooperating company
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Telefax : +32 3 568 4311
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint

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Telex : 467724
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint

Type : cooperating company
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Contact person :
Date :

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Town : DK-2665 Vallensbaek Strand
Country : Denmark
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint

Type : cooperating company
Name : INEOS Silicas Ltd
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Town : Warrington, Cheshire, WA5 1AB
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Telex :
Cedex :
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Homepage :

Flag : Critical study for SIDS endpoint

Type : cooperating company
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Homepage :

Flag : Critical study for SIDS endpoint

Type : cooperating company
Name : RHODIA SILICA SYSTEMS
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Phone :
Telefax :
Telex :
Cedex :
Email : marie-christine.rosset@eu.rhodia.com
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Remark : contact point:
RHODIA SERVICES
Etoile Part-Dieu

		190, Avenue Thiers F-69006 LYON France Tel: +33 4 37 24 88 63 Fax: +33 4 37 24 88 81
Flag	:	Critical study for SIDS endpoint
Type	:	cooperating company
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Telefax	:	+49 83 - 5590; - 6814
Telex	:	
Cedex	:	
Email	:	axel.bosch@wacker.com; mario.heinemann@wacker.com
Homepage	:	
Flag	:	Critical study for SIDS endpoint

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Silicon dioxide, chemically prepared
Smiles Code	:	
Molecular formula	:	
Molecular weight	:	
Petrol class	:	

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	Inorganic
Physical status	:	Solid
Purity	:	ca. 98.5 % w/w
Colour	:	White
Odour	:	
Remark	:	Available in powder form, granules and in preparations Synthetic amorphous precipitated silica and silica gel after drying are typical >95 % SiO2 and are solid, amorphous forms of hydrous silicon dioxide distinguished by its microporosity and hydroxylated surface. Composition of typical Synthetic Amorphous Precipitated Silica:

Parameter	wt.%
SiO2	> 95
Na2O	0.2 - 2.4
Sulfates as SO3	0.2 - 3.0
Fe2O3	< 0.05
Trace oxides	< 0.07

The technical forms "wet process silica" (precipitated silica and silica gel) or "thermal" = "pyrogenic" = "fumed" silica" (silica by flame hydrolysis, are silica and plasma silica) are used for synthetic amorphous silica with high purity which are purposely produced under controlled conditions (see 1.7.2).

The term "fused silica" is used for various mixtures of crystalline/non crystalline silica and other compounds like heavy metals. Naturally occurring silica like diatomaceous earth can also contain some crystalline parts, depending on the thermal after treatment.

The data presented here are limited to synthetic amorphous silica species which are produced or imported by the industrial companies which prepared this data set. Therefore only data were considered, which were obtained with "non-crystalline" silica.

The CAS-Number 7631-86-9 listed in the EINECS is an old CAS-Number with the CAS-Name "Silica".

The new CAS-Numbers distinguish between the different types of synthetic amorphous silicas:
CAS-No. 112945-52-5, CAS-Name: Silica, amorphous, fumed, crystalline-free;
CAS-No. 112926-00-8, CAS-Name: Silica gel, precipitated, crystalline-free.

Flag : Critical study for SIDS endpoint

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Amorphous silica

Remark : Sipernat®, Ultrasil®, Sident®, Neosyl, Tixosil, Hi-Sil, Perkasil, Aerosil, CAB-O-SIL®, Syloid®

Colloidal silica

Dental type silica

Fumed silica

Gefaellte Kieselsaeuren

Highly dispersed silica

Kieselgel

Kieselsaeure

Precipitated silica

Pyrogene Kieselsaeuren

Silica

Silica gel

Silica hydrogel

Silicon dioxide

Synthetic amorphous silica

White carbon

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Remark : Heavy Metal Impurity Data:

Metal Impurity/ppm	Precipitated Silica
Antimony	< 5
Barium	< 50
Chromium	< 10
Arsenic	< 3
Lead	< 10
Mercury	< 1
Cadmium	< 1
Selenium	< 1

The given limits are typical data. The mentioned products are in line with the quality requirements of DIN EN 71/3 (toys), BGVV Recommendation LII (Fillers for Commodities Made of Plastic) and of quality requirements for

direct food additive E551, E552 and E554 (2000/63/EU and 2001/30/EU).

Purity : typical for marketed substance
CAS-No : 7757-82-6
EC-No : 231-820-9
EINECS-Name : sodium sulphate
Molecular formula :
Value : <= 3 % w/w

Remark : Only in precipitated silicas
Flag : Critical study for SIDS endpoint

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 392000 - tonnes produced in 2000

Remark : The production volume in Europe includes pyrogenic (72000 t/a), precipitated silica (285500 t/a), and silica gels (34600 t/a).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.09.2004 (18)

Quantity : ca. 411000 - tonnes produced in 2002

Remark : Production volume in Europe includes pyrogenic (73900 t/a), precipitated silica (337100 t/a). For silica gels and silicates no data were provided.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.09.2004 (18)

1.6.1 LABELLING

Labelling : no labelling required (no dangerous properties)
Specific limits : No

1.6.2 CLASSIFICATION

Classified : no classification required (no dangerous properties)
Class of danger :
R-Phrases :
Specific limits :

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : Type

Category : Use resulting in inclusion into or onto matrix

Remark : As in general the amorphous silicas/silicates become an integral part of a product matrix, the powder form no longer exists in most applications.
Flag : Critical study for SIDS endpoint
29.09.2004

Type of use : Type
Category : Wide dispersive use

Remark : The applications of silicates are versatile, but in general for consumers not freely available as powders, as the silicates are bound in the matrix of an article.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Agricultural industry

Remark : Amorphous silica types have successfully been employed against juvenile and adult store-product pests, predominantly exerting their lethal activity on juvenile and adult forms by sorption of the cuticular lipid layer, thus causing dehydration of the insects (Mewis and Ulrichs, 1999). Amorphous silica [CAS No. 112945-52-5] is also included in the list of notified biocides in Europe (EU Regulation 2003).
Flag : Critical study for SIDS endpoint
24.09.2004 (84) (152)

Type of use : Industrial
Category : Leather processing industry

Remark : No data on this application available
24.09.2004

Type of use : Industrial
Category : Paints, lacquers and varnishes industry

Remark : Paints: Synthetic amorphous silica and silicates are used as functional pigments in emulsion paints.
Lacquers: The most commonly used flatting agents in lacquers are synthetic amorphous silica.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Paper, pulp and board industry

Remark : Paper: Small amounts of synthetic amorphous silica and silicates added to paper improve printability and opacity. Synthetic amorphous silica is also used in specially coated paper grades for ink jet printing, copying etc.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Polymers industry

Remark : Plastics: Plastic films often tend to stick to each other but this can be prevented by the addition of an synthetic amorphous silica as an anti blocking agent. Synthetic amorphous silica is also used in polyester and epoxy resins for thixotropy control. For polyethylene battery separators,

precipitated SAS is used to generate the porosity of the separator to enable the sulphuric acid flow from electrode to electrode.

Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Textile processing industry

Remark : No data on this application available
24.09.2004

Type of use : Industrial
Category : other: Silicon rubber industry

Remark : Rubber and Silicones: Synthetic amorphous silica and silicates are used as reinforcing fillers for many non-staining and colored rubber and silicones products. A new application for synthetic amorphous silica is in energy conserving automobile tyres (green tyres).

Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Absorbents and adsorbents

Remark : No data on this application available
24.09.2004

Type of use : Use
Category : Anti-set-off and anti-adhesive agents

Remark : For example, silicas provide thickening in pastes and ointments to inhibit the separation of components.

Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Cosmetics

Remark : Due to their inert nature, synthetic amorphous silicas/silicates are used in cosmetics (especially tooth paste). They can also function as a carrier for fragrances or flavors.

Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Fillers

Remark : For example in Rubber and Silicones: Synthetic amorphous silica and silicates are used as reinforcing fillers for many non-staining and colored rubber and silicones products. A new application for synthetic amorphous silica is in energy conserving automobile tyres (green tyres).

Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Food/foodstuff additives

Remark : Animal Feed: Synthetic amorphous silica and silicates serve as carriers and anticaking agents in vitamins and mineral premixes.

Flag : Critical study for SIDS endpoint

24.09.2004

Type of use : Use
Category : Insulating materials

Remark : No details on application
24.09.2004

Type of use : Use
Category : other: Free flow agent

Remark : Silicas maintain flow properties in powder products.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : other: Thickening agent

Remark : SAS provide thickening in pastes and ointments to inhibit the separation of components.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use :
Category : Personal and domestic use

Remark : Consumer Use Products: Due to their inert nature synthetic amorphous silicas are used in cosmetics (especially tooth paste), pharmaceuticals and foods. Synthetic amorphous silica for pharmaceutical use meet the requirements of international pharmacopoeias, such as DAB 10, USP/NF XXIV/ 19, and the European Pharmacopoeia 1997 2002(Add. 2001). They provide thickening in pastes and ointments to inhibit the separation of components and maintain flow properties in powder products. They can also function as a carrier for fragrances or flavors. They are also used in beer and wine clarification.
Food additive grades of synthetic amorphous silica meet the requirements of the Joint Expert Committee on Food Additives of WHO/FAO and many other national requirements. Synthetic amorphous silica is registered in the European Union as Hydrated Silica E551 [Directive 95/2/EC and 96/77/EC].
Flag : Critical study for SIDS endpoint
24.09.2004

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Method : A. Synthetic Amorphous Pyrogenic (fumed) Silica: Thermal Process
Volatile chlorosilanes and/or methylchlorosilanes are fed into the reactor together with a mixture of hydrogen and air. Reaction takes place at temperatures between 1200 up to 1600°C. Hydrolysis of the silanes leads to SiO2 molecules.
Nucleation, condensation and coagulation leads from molecules to protoparticles of SiO2 which combine to primary particles of SiO2 (5-50

nm). Primary particles under the condition of the reaction zone stick together building stable SiO2 aggregates 100-500 nm which further combine to agglomerates of SiO2 (1-200 um).

note: Primary particles do not exist outside the reaction zone.
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 hydrochloric acid containing off-gas.

B. Synthetic Amorphous Precipitated Silica: Wet Process Raw materials for the production of precipitated silica and silica gels are aqueous alkali metal silicate solution (e.g. water glass) and acids, generally sulphuric acid.

The reaction conditions (e.g. acid:alkali ratio, temperature, concentration, stirring) determine the size of the silica polymer particle and the way they bind together to form higher structures like aggregates and agglomerates.

In contrast to silica gels, which are produced under acidic conditions (see C.), for synthetic amorphous silica, precipitation is carried out in neutral or alkaline media. To date, only batch precipitation processes in stirred vessels have attained economic importance, although continuous precipitation techniques have been reported. The suspension received from precipitation is filtered. For this purpose, usual filter presses, membrane filter presses or belt/drum filters are used. Equipment selection is dependent on the properties and structure of the silica produced. The solid content of the filter cake typically varies between 15 to 25 wt%, depending on the filter technique employed.

After filtration a washing step follows to remove salts (normally done in the filtration equipment). The level of salt retained in the product depends on the intended application of the final silica. For drying, contact dryers are mostly used (plate, belt, rotary drum) as well as spray dryers are used.

After conventional drying, the product has to be milled in jet mills or mechanical mills. During this process, the particle size distribution and sieve residue characteristics of the product are modified. The reaction conditions (e.g. acid:alkali ratio, temperature, concentration, stirring) determine the size of the silica polymer particle and the way they bind together to form higher structures like aggregates and agglomerates.

C. Synthetic Amorphous Silica Gels: Wet Process. As with precipitated silica, silica gels are produced by the neutralisation of aqueous alkali metal silicates with acids. The technical process comprises raw material dilution (optional), synthesis (sol formation/gelation), washing/ageing and drying, followed by sieving, milling, or surface modification depending on the final product. The first synthesis step comprises the formation of a HYDROSOL which is produced by the controlled mixing of water glass and diluted sulphuric acid. During the sol-forming step, an unstable intermediate, monomeric orthosilicic acid, is formed which then rapidly undergoes an acid-catalysed condensation reaction to form oligomers. When the molecular weight reaches approx. 6000, a sudden increase of both the viscosity and the modulus of elasticity is observed. This increase marks the transformation of the sol to a gel that will then further develop its internal structure. In the hydrogel state, larger agglomerates are generated which are cross-linked to form an open, branched-chain structure. Choice of the gelation conditions can define the particle size and form of the hydrogel; industrial processes normally form either lumps or spherical beads. During the subsequent washing process, excess salts are removed in order to purify the gel, which also causes structural changes within the framework of the gel. The HYDROGEL formed has a continuous structure giving a three-dimensional network of pores filled with water. The total volume of pores per mass-unit is called the Pore Volume and is a specific

characteristic of the gel type. While for a few applications silica as a HYDROGEL can be used, in most instances the GEL must be dried. During the drying process, the surface tension of the solvent in the pores can act to shrink the hydrogel volume. In slow drying, as water is evaporated from a silica hydrogel, the structure collapses gradually 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 the shrinkage and removal of water by solvent exchange followed by drying has the same effect. Materials that are dried with negligible loss of pore volume are known as AEROGEL.

Remark : Producers´ information
Flag : Critical study for SIDS endpoint

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : 4 mg/m3

Remark : "Gesamtstaub", measured as total dust

(72)

Type of limit : other: TWA
Limit value : 10 mg/m3

Remark : Precipitated silica and silica gel.
The value is for total dust containing no asbestos and < 1 % crystalline silica

(1)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: (provisionally) Degussa AG
Labelled by : other: (provisionally) Degussa AG
Class of danger :

Remark : WGK (Germany) = Water endangering/hazard class: nwg (generally not water polluting)

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : AICS

Additional information :

Type : DSL
Additional information :

Type : ECL
Additional information : KE-31032

Type : ENCS
Additional information : Section No.: 1
Section Structure No.: 810
Class Reference No.: 548

Type : CHINA
Additional information :

Type : PICCS
Additional information :

Type : TSCA
Additional information :

Type : EINECS
Additional information : EC-No. 231-545-4

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Occupational exposure: Past exposures were higher: The total dust concentrations were reduced from <= 100 mg/m3 in 1959 to <= 42 mg/m3 between 1974 and 1982. Between 1984 and 1986 the total dust concentrations were between 2.2 and 4.4 mg/m3.
Exposure data from morbidity study 2002 to be added.
Flag : Critical study for SIDS endpoint
(85) (138)

Source of exposure : Human: exposure by production
Exposure to the : Substance

Remark : The morbidity study part is still in progress (status 05 April 2004).
Result : In a comprehensive monitoring programme and morbidity study on workers in Germany (in progress), more than 1000 inhalable and respirable dust measurements were performed in synthetic amorphous silica plants

(involved companies: Degussa, Wacker, Cabot).
The measurements were carried out according to BIA-Kennzahl 7752 and 7490 (BIA-Arbeitsmappe Messung von Gefahrstoffen, Erich Schmidt, Bielefeld, 1989 / Loseblatt-Ausgabe).
Overall the mean dust concentrations were 1.2 mg/m³ (inhalable) and 0.3 mg/m³ (respirable). The highest mean values were observed for job categories involved with packaging and loading operations (up to 3 mg/m³ inhalable and up to 1 mg/m³ respirable dust).
All mean values of all job categories comply with the German MAK workplace threshold limit of 4 mg/m³ (inhalable dust).
The results can be summarized as follows:

	inhalable[mg/m3]		respirable[mg/m3]	
plant	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

The job categories that were defined are related to specific operations and locations at the workplace and are supposed to differ in the degree of exposure.
For example:
Production: Reaction / precipitation
Filling and loading station
Quality management
Technical service

Reliability : (1) valid without restriction
1c: Meets national standard methods
Flag : Critical study for SIDS endpoint
23.09.2004 (28)

1.11 ADDITIONAL REMARKS

Remark : In the USA silica (silicon dioxide; hydrated silica) has GRAS status (generally recognized as save). The following uses in foods are authorized :

use	FDA-reference
- adjuvant in microcapsules for flavoring	21 CFR 172.230
oils anticaking agent; brewing stabilizer;	21 CFR 172.480
special adsorbent antifoaming agent	21 CFR 182.1711
- substances migrating to food from paper and paperboard packaging materials defoaming agent	21 CFR 173.340
- pigments and colourants in resinous and coatings	21 CFR 175.300 polymeric
- defoaming agent in coatings	21 CFR 176.200
- defoaming agent in the manufacture of paper and paperboard	21 CFR 176.210
- in coatings on cellophane used for packaging foods	21 CFR 177.1200
- filler for rubber articles used repeatedly in connection with foods	21 CFR 177.2600

(89) (142)

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	ca. 1700 °C
Decomposition	:	no, at °C
Sublimation	:	No
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable Manufacturer data / data from handbook or collection of data.
Flag	:	Critical study for SIDS endpoint

(30) (31) (32)

Value	:	= 1710 °C
Decomposition	:	no, at °C
Sublimation	:	No
Method	:	
Year	:	
GLP	:	No
Test substance	:	
Test substance	:	Type not specified
Reliability	:	(4) not assignable Data from handbook or collection of data.
Flag	:	Critical study for SIDS endpoint

(157)

2.2 BOILING POINT

Decomposition	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	>>1700 °C: not relevant for normal and intended use
Reliability	:	(4) not assignable

2.3 DENSITY

Type	:	density
Value	:	ca. 2 g/cm³ at 20 °C
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Sipernat 22, Ultrasil VN 3 SP, Sident 3, Mattierungsmittel HK 125, Mattierungsmittel HK 400
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

(30) (34)

Type	:	density

Value : ca. 2.2 g/cm³ at 20 °C
Method : other: DIN ISO 787/X or JIS K 5101/17
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Density relates to that of the primary particles, not to the silica in aggregated/agglomerated form as it exists (compare also 2.14).
Test substance : Aerosil 200, Aerosil 300, Aerosil 380 (CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5), Aerosil TT 600, Mattierungsmittel TS 100, Mattierungsmittel TK 900
Aerosil 200: CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint
(2) (32) (34) (151) (192)

Type : density
Value : = 2.1 g/cm³ at °C
Method : other: DIN ISO 787/X or JIS K 5101/17
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test substance : Sipernat 22, Kieselsaeure FK 320, Kieselsaeure FK 700
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
(35)

Type : bulk density
Value : 50 - 130 at °C
Method : other: DIN ISO 787/11 or JIS K 5101/18
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : An accurate volume of a sample is measured in a glas cylinder in such a way that no empty space remains and the surface is horizontal. The glass cylinder containing this samples is being tapped (tamped) in a volumeter 1250 times. Then the resulting volume is read off. That means the sample is not pressed to a minimum under high pressure. Tapped/tamped density is the minimum bulk density.
Remark : Test substance (pyrogenic silicas) Tapped density (kg/m3)

Aerosil OX 50	approx. 130
Aerosil 90	approx. 80
Aerosil 130	approx. 50
Aerosil 150	approx. 50
Aerosil 200	approx. 50
Aerosil 300	approx. 50
Aerosil 380	approx. 50
Aerosil TT 600	= 60

Method: DIN ISO 787/XI or JIS K 5101/18 Year: no data
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint
(34) (35) (36)

Type : bulk density

Value : 50 - 320 at °C
Method : other: DIN ISO 787/11 or JIS K 5101/18
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : An accurate volume of a sample is measured in a glass cylinder in such a way that no empty space remains and the surface is horizontal.

The glass cylinder containing this sample is being tapped (tamped) in a volumeter 1250 times. Then the resulting volume is read off. That means the sample is not pressed to a minimum under high pressure. Tapped/tamped density is the minimum bulk density.

Remark : Test substance (wet process silicas) — Tapped density (kg/m3)

Durosil	= 210
FK 160	= 70
FK 300 DS	= 90
FK 310	= 130
FK 320	= 240
FK 320 DS	= 80
FK 383 DS	= 80
FK 500 LS	= 80
FK 700	= 320
Mattierungsmittel TS 100	= 50
Mattierungsmittel TK 900	= 110
Mattierungsmittel HK 125	= 130
Mattierungsmittel HK 400	= 110
Sident 9	= 350
Sident 12	= 230
Sident 12 DS	= 200
Sident 15	= 150
Sident 18	= 200
Sident 22 S	= 100
Sipernat 22	= 270
Sipernat 22 S	= 120
Sipernat 22 LS	= 80
Sipernat 50	= 200
Sipernat 50 S	= 100
Wessalon	= 270
Wessalon S	= 120

Method: DIN ISO 787/XI or JIS K 5101/18 Year: no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint

(29) (34) (35) (37)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 13.3 hPa at 1732 °C
Decomposition :
Method :
Year :

GLP	:	no
Test substance	:	no data
Remark	:	The stated value is specified as 10 mmHg. It was measured at the melting point. That means, at ambient temperature, the substance has practically no vapour pressure (approx. 0 Pa).
Test substance	:	Type not specified
Reliability	:	(4) not assignable Manufacturer data / data from handbook or collection of data. Value not useful for assessment, only technical information.

(157) (201)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	at °C
pH value	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	This parameter is not considered applicable to this compound due to its physico-chemical nature (inorganic compound, not lipophilic).
Flag	:	Critical study for SIDS endpoint

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 15 - 24 mg/l at 20 °C
pH value	:	= 5.6 - 6.6
concentration	:	10 g/l at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	slightly soluble (0.1-100 mg/L)
Stable	:	Yes
Deg. product	:	
Method	:	OECD Guide-line 105
Year	:	2003
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	TEST PROCEDURE Shake-flask method: 1 g shaken in 100 ml water (purissima) in a PE bottle for a defined period of time (see Results), followed by micro-filtration (0.45 µm). Two samples were tested. ANALYSIS: In filtrate, Si was determined based on the ICP-OES method (Inductive Coupled Plasma Optical Emission Spectroscopy: EN-ISO 11885).
Result	:	Aerosil OX50:

Incubation time	pH	SiO2[mg/l]
Sample 1		
24 h	5.6	14.3
48 h	5.7	18.9
72 h	5.8	19.2
96 h	5.9	24.0
Sample 2		
24 h	6.6	21.0
144 h	6.6	15.0
192 h	6.6	13.8
240 h	6.5	18.9

The equilibrium was reached after about 48 h. Therefore, given values (concentrations and pH) related to incubation times of >= 48 h.

Test substance : Aerosil OX 50: CAS Name, Silica, amorphous, fumed (pyrogenic), CAS No. 112945-52-5
Reliability : (2) valid with restrictions
Guideline study, no GLP
Flag : Critical study for SIDS endpoint

(46)

Solubility in : Water
Value : = 36 - 68 mg/l at 20 °C
pH value : = 5.5 - 5.8
concentration : 10 g/l at 20 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : slightly soluble (0.1-100 mg/L)
Stable : Yes
Deg. product :
Method : OECD Guide-line 105
Year : 2003
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : TEST PROCEDURE
Shake-flask method: 1 g shaken in 100 ml water (purissima) in a PE bottle for a defined period of time (see Results), followed by micro-filtration (0.45 µm).
Two samples were tested.
ANALYSIS:
In filtrate, Si was determined based on the ICP-OES method (Inductive Coupled Plasma Optical Emission Spectroscopy, EN-ISO 11885).
Result : Aerosil 200:

Incubation time	pH	SiO2[mg/l]
Sample 1		
24 h	4.4	29.0
48 h	5.5	53.6
72 h	5.4	62.0
96 h	5.5	68.4

Sample 2

24 h	6.7	51.0
144 h	5.7	36.0
192 h	5.7	39.0
240 h	5.8	45.0

==========

The equilibrium was reached after about 48 h. Therefore, given values (concentrations and pH) related to incubation times of >= 48 h.

Test substance : Aerosil 200: CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5

Reliability : (2) valid with restrictions
Guideline study, no GLP

Flag : Critical study for SIDS endpoint

(46)

Solubility in : Water
Value : ca. 110 - 160 mg/l at 37 °C
pH value : = 7.1 - 7.4
concentration : 1000 mg/l at 37 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1999
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : A. Solubility in buffer
Determination of dissolution kinetics of different SAS: rate constants (pH 7.3 t = 37°C) and the saturation concentrations were determined.

Test substance: Loading depending on surface area (40 m2/100 ml test solution)==> approx. 1000 - 3000 mg/l, shaking at 37 °C

Dissolution temperature: 37 °C
pH = approx. 7.35
Buffer system: TRIS (0.1 mol/l), meant to represent physiological osmolar and pH conditions
Osmotic concentration: 309 mosmol/l
Electrolyte NaCl 0.112 mol/l
Dissolution time: 97 h
Replicates: 4-fold each concentration in duplicate.

ANALYTICAL METHOD:
Determination of dissolved test substance: Separation of solids by centrifugation, molybdic-acid method (Malachit green forms a colored ion association complex with molybdosilicate which is stabilised by addition of polyvinyl alcohol.)

Solubility is expressed in mol/l, based on 60 g/mol(SiO2).
B. Solubility in buffer plus surfactant (surrogate of physiological media/external body fluid)

As surfactant L-alpha-dipalmoyl-phosphatidylcholine [DPPC] (25 mg/100 ml) was used.
C. Solubility in NaCl-solution (Vogelsberger 2003)
Test substance: HDK T40

Electrolyte NaCl 0.112 mol/l,
pH = 7.1 - 7.4
T = 37 °C
Other test conditions as mentioned under A.

Remark : The water solubility was measured at 37 °C and pH 7.1 - 7.4 (physiological conditions), which probably explains the higher solubility as compared with results found at 20 °C and pH <7(see previous entries).

Result : The saturation concentrations for all analysed silica are reached quickly within 5 to 10 h, in an exceptional case about 20 h.
The saturation concentration increases with increasing specific surface area of the corresponding silica, i.e. higher value with decreasing particle size (Kelvin effect).
The range of solubilities is 1.91 +-0.05 to 2.76 +-0.02 mmol/l
One substance showed a lower solubility: 1.27 +-0.08 mmol/l.
Influence of surfactant (Vogelsberger 2003):
DPPC had no significant effect on water solubility.
The maximal solubility of HDK T40 was approx. 2.5 mmol/l = approx. 150 mg/l (Vogelsberger 2003).
There was no substantial difference in water solubility between the tested media.

Test substance : pyrogenic (HDK H15 and other HDK types, CAB-O-SIL M5, Aerosil 300), precipitated (Sipernat and Zeosil types) and gel types (Syloblanc, Sylobloc, Syloid)

Reliability : (2) valid with restrictions
Comparable to guideline study, containing scientifically justified modifications (see: Method).

Flag : Critical study for SIDS endpoint

(194) (195)

Solubility in : Water
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: DIN ISO 787/IX, ASTM D 1208, JIS K 5101/24
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : pH-value of an aqueous suspension (4 % for pyrogenic sili-cas): 3.6 - 4.5
Test substance : Aerosil types: OX50, 90, 130, 150, 200, 300, 380, TT600
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint

(32) (34) (35) (36)

Solubility in : Water
Value : at °C
pH value :
concentration : At °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Deg. product :
Method : other: DIN ISO 787/IX, ASTM D 1208, JIS K 5101/24
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : pH-value of an aqueous suspension (5 % for wet process silicas)

Test substance (wet process silicas)	pH-value
Durosil	= 9
FK 160	= 5
FK 300 DS	= 6.5
FK 310	= 7
FK 320 (and FK 320 DS)	= 6.3
FK 383 DS	= 8.3
FK 500 LS	= 6.5
FK 700	= 7
Mattierungsmittel TS 100	6 - 7
Mattierungsmittel TK 900	3.5 - 4.5
Mattierungsmittel HK 125	5 - 7
Mattierungsmittel HK 400	5 - 7
Sident 9	= 7
Sident 12 (and Sident 12 DS)	= 6.5
Sident 15	= 6.5
Sident 18	= 6.5
Sident 22 S	= 6.3
Sipernat 22 (and Sipernat 22 S or LS)	= 6.3
Sipernat 50 (and Sipernat 50 S)	= 6.5
Ultrasil VN 3	= 6.3
Wessalon (and Wessalon S)	= 6.3

Reliability : (2) valid with restrictions
Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint

(29) (30) (31) (34) (35) (37)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Not combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(22)

2.8 AUTO FLAMMABILITY

Method :
Year :
GLP :

Test substance : as prescribed by 1.1 - 1.4

Remark : Not combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(21)

2.9 FLAMMABILITY

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Not combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(21)

2.10 EXPLOSIVE PROPERTIES

Result : not explosive
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Amorphous silica can be used as a fire-extinguishing agent.
Reliability : (4) not assignable
Manufacturer data / data from handbook or collection of data.

(29)

2.11 OXIDIZING PROPERTIES

Result : no oxidizing properties
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Not combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(22)

2.12 DISSOCIATION CONSTANT

Acid-base constant : no data
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Surface area and particle size

Remark : Test substance (pyrogenic silicas) | BET surface area (m2/g)

Test substance (pyrogenic silicas)	BET surface area (m2/g)
Aerosil OX 50	50 +- 15
Aerosil 90	90 +- 15
Aerosil 130	130 +- 25
Aerosil 150	150 +- 15
Aerosil 200	200 +- 25
Aerosil 300	300 +- 30
Aerosil 380	380 +- 30

Method (BET surface area): Brunauer, Emmet, Teller (BET);
J. Amer. Chem. Soc., 60, 309 (1938)
(DIN 66 131)
Current simplified method acc. to Haul and Duembgen = ISO 5794/1 (Annex D)

Remark: For comments on particle size and aggregation as well as recent measurements under technical handling and use conditions: compare also entry Chap. 6.1 (Stintz 2001). Aerosil aglomeration particle size not well measurable.
Primary particles are not referred to because they are not existent as individual unit (compare also IARC, 1997, Tab. 7, p. 57).

Reliability : (2) valid with restrictions
Meets national and international standard methods: but limited documentation

Flag : Critical study for SIDS endpoint
(2) (33) (34) (107) (181)

Memo : Surface area and particle size

Remark : Test substance (wet process silicas) | BET surface area (m2/g) | Particle size, average, aggregates (µm)

Test substance (wet process silicas)	BET surface area (m2/g)	Particle size, average, aggregates (µm)
Durosil	60	15
FK 160	160	7
FK 300 DS	300	4.5
FK 310	650	4
FK 320	170	15
FK 320 DS	170	4
FK 383 DS	170	5
FK 500 LS	450	3.5
FK 700	700	15
Mattierungsmittel TS 100	no data	4
Mattierungsmittel TK 900	no data	5
Mattierungsmittel HK 125	no data	4
Mattierungsmittel HK 400	no data	3
Sident 9	50	8
Sident 12	80	13
Sident 12 DS	80	6
Sident 15	140	6

Sident 18	100	6
Sident 22 S	190	9
Sipernat 22	190	100
Sipernat 22 S	190	7
Sipernat 22 LS	190	4.5
Sipernat 50	450	50
Sipernat 50 S	450	8
Wessalon	190	100
Wessalon S	190	7

Method (BET surface area): based on Brunauer, Emmet, Teller (BET);
J. Amer. Chem. Soc., 60, 309 (1938)
(DIN 66 131)
Current simplified method acc. to Haul and Duembgen = ISO 5794/1 (Annex D)

Method (particle size): multisizer, 100 µmm, according to ASTM C690-1992.

Remark: For comments on particle size and aggregation as well as recent measurements under technical handling and use conditions: compare also entry Chap. 6.1 (Stintz 2001). Primary particles are not existent as individual units (compare IARC, 1997, Tab. 7, p. 57). Therefore, primary particle size is generally not accounted because of the particles aggregate.

Reliability : (2) valid with restrictions
Meets national and international standard methods: but limited documentation

Flag : Critical study for SIDS endpoint

(29) (33) (34) (107) (181)

3.1.1 PHOTODEGRADATION

Type	:	other: air, water
Light source	:	
Light spectrum	:	Nm
Relative intensity	:	based on intensity of sunlight
Remark	:	Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no light-induced transformation expected.
Flag	:	Critical study for SIDS endpoint

3.1.2 STABILITY IN WATER

Type	:	Abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Remark	:	Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable towards acids and alkali), no chemical transformation under environmental conditions significant and relevant.
Flag	:	Critical study for SIDS endpoint

3.1.3 STABILITY IN SOIL

Remark	:	"SiO2" is a stable substance. In the environment, it occurs in different forms (as amorphous and crystalline silica, as silicates complexed with metals), and it is one of the most abundant materials on the earth's surface (see also Sec. 3.2). Whatever its origin, man-made or natural silica, and whatever its structure, crystalline or amorphous silica, once released and dissolved into the environment, no distinction can be made between the initial forms of silica. Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable towards acids and alkali), SAS is considered as an inert substance, and no chemical transformation under environmental conditions is expected to be significant and relevant.
Flag	:	Critical study for SIDS endpoint

3.2.1 MONITORING DATA

Type of measurement	:	other: natural occurrence
Media	:	other: soil and sediment
Concentration	:	
Method	:	
Remark	:	Monitoring data about synthetic amorphous silicas are not available. Silicon is the most abundant chemical after oxygen in the earth's crust mass (28,1%).

The natural occurring amorphous silica are diatomite, flint and opal. Diatomite contains up to 94 % SiO2 (amorphous) and - depending on the deposit - considerable amount of quartz.

Silica is also found in living organisms like diatoms, sponges and in plants like grasses, rice, sugar cane.

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3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	Volatility
Media	:	soil - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	

Remark : SiO2 is not volatile under environmental conditions due to its chemical nature and inherent physical properties:
Due to its low water solubility and extremely low vapour pressure, SiO2 is expected to be distributed mainly into soils/sediments, weakly into the water and probably not at all in the air.

Type	:	other: segregation/deposition
Media	:	other: air - water – soil
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	

Remark : SAS is expected to combine undistinguishably with the soil layer or sediment due to its chemical identity with inorganic soil matter and will be subjected to slow natural transformation processes of weathering.

Flag : Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

Memo : Stability

Remark : Amorphous silicas are not degraded in actual use.

3.5 BIODEGRADATION

Remark : Due to the chemical nature (inorganic structure) biodegradation is not applicable.
Flag : Critical study for SIDS endpoint

3.6 BOD5, COD OR BOD5/COD RATIO

Remark : not applicable (inorganic substance)

3.7 BIOACCUMULATION

Remark : Due to its inherent chemico-physical properties, such as absence of lipophilicity, as well as the capability of the organism to excrete absorbed SiO2 components, bioaccumulation can be disregarded.

But silica can be actively accumulated by terrestrial plants (e.g. grass) and some marine organisms (e.g. diatoms, radiolarians, and sponges), which are normal natural processes.
Flag : Critical study for SIDS endpoint

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	= 10000
Limit test	:	
Analytical monitoring	:	No
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1992
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	The nominal concentrations of 1000 and 10000 mg/l were tested, and result refers to the loading. Because of the poor water solubility of the test substance, the test solution was stirred for 20 h, then allowed to stand for 4 h before testing; the resulting suspensions at the beginning of the test were homogeneous and milky, at the end of the test in addition a layer of white, starchy flocks on the bottom of the vessels was observed. The range of the pH of the various test solutions was between 7.3 and 8.2 over time from 0 to 96 h. Concentrations can be described as loading rate. Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).
Test substance	:	Aerosil 200: >98 % (SiO2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(66)

Type	:	Static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	= 10000
Limit test	:	
Analytical monitoring	:	No
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1992
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	Concentrations of 1000 and 10000 mg/l were tested, and result refers to the loading. Because of the poor solubility of the test substance the test solution was stirred for 20 h; the suspensions remained turbid throughout the test and starchy particles were observed on the bottom of the vessels. The range of the pH of the various test solutions was between 7.3 and 8.3 over time from 0 to 96 h. Concentrations can be described as loading rate. Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).
Test substance	:	ULTRASIL VN 3 (>98 % SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(1) valid without restriction

1a: GLP guideline study
Flag : Critical study for SIDS endpoint

(68)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	= 1000
EC50	:	> 10000
Analytical monitoring	:	No
Method	:	OECD Guide-line 202
Year	:	1992
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Sample 1: 5% and 25% of the daphnias were immobile (for loadings of 1000 mg/l and 10000 mg/l respectively). Sample 2: 10% and 22.5% of the daphnias were immobile (for loadings of 1000 mg/l and 10000 mg/l respectively). Sample 3: One immobile animal (4%) (loading of 1000 mg/l). Conclusion: With the third methodology where clear solutions were obtained, no significant immobilization was observed (4%). Therefore, it is suspected that the immobility observed, particularly with the 10000 mg/l suspensions, could be attributed to physical effects.
Test condition	:	The concentrations of 1000 and 10000 mg/l were tested, and result refers to loading: The test solution had been stirred for 20 hours prior to test. 1. Suspensions of 1000 and10000 mg/l 2. Test solutions of 1000 and 10000 mg/l were filtered (through perlon wool), undissolved material was still present after filtration. 3. Test solution of 1000 mg/l (10000 mg was technical not possible) was filtered with a microfibre-glass filter (1.7 µm and a combination of 1.7 µm and 1.2 µm). A clear solution resulted. The range of the 24-h pH of the various test solutions was between 6.2 and 8.1. Concentrations can be described as loading rate. Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).
Test substance	:	Aerosil 200: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions: 24 h instead of 48 h applied.
Flag	:	Critical study for SIDS endpoint

(67)

Type	:	Static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	> 10000
Analytical monitoring	:	No
Method	:	OECD Guide-line 202
Year	:	1992
GLP	:	Yes

Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	After 24 h of exposure 7.5 % and 2.5 % of the daphniae were immobile at test concentrations of 1000 and 10000 mg/l, resp. The observed effects were not dose related, and the immobile animals had some particles on their appendages. Therefore, the effects can be attributed to physical hampering of the daphnias.
Test condition	:	Concentrations of 1000 and 10000 mg/l were tested, and results refer to loading. Because of the poor solubility of the test substance the test solution was stirred for 20 hours. The test media remained turbid throughout the test and starchy particles were observed on the bottom of the test vessels. The range of the 24-h pH of the various test solutions was between 5.5 and 7.9. One value of a replicate was at 4.2. Concentrations can be described as loading rate. Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).
Test substance	:	ULTRASIL VN 3 (>98 % SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions: 24 h instead of 48 h applied.
Flag	:	Critical study for SIDS endpoint

(69)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	other: biomass and growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 10000 measured/nominal
EC10	:	> 10000 measured/nominal
Limit test	:	
Analytical monitoring	:	No
Method	:	
Year	:	1998
GLP	:	Yes
Test substance	:	other TS
Result	:	Results are given in nominal concentrations (loadings). After 72 h, an increase in biomass (cell numbers) at a factor of >30 was achieved in all tests without significant difference of the highest concentration from the control run, while at the lower concentrations results may indicate slight stimulation of growth. [Note - this test was conducted on sodium aluminium silicate CAS No. 1344-00-9]
Test condition	:	PREPARATION of TEST SOLUTIONS: Water extracts from 6250, 630, and 60 mg/l silica were produced by stirring the suspensions for 24 h in 0.5 l ultrapure water, followed by filtration through paper filter. The final nominal concentrations in the test media were obtained by addition of the algal preculture and the mineral salt concentrate to the filtrated extract, corresponding to 10000, 1008, and 96 mg/l nominal. Empty controls ("blanks") without the algae suspension were prepared for each concentration with the suitable water-silica extract. 3 to 5 parallel tests were prepared for each concentration and respective controls. Further TEST CONDITIONS: Temperature was 24.9 +-0.3°C; Illumination: approx. 8000 lux (>= 120 uE/m2sec).

Initial pH: 8.00 (control); between 8.12 and 8.58 (tests).
Initial cell concentration: approx. 8.5 x10exp4 cells.
Extinction differences were determined at 24, 48, and 72 h at 578 nm.

Test substance : SIPERNAT 820A, sodium aluminium silicate (Degussa) [CAS No. 1344-00-9]

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(61)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : other: suspended in bouillon

Species : other bacteria: Aerobacter aerogenes, Pseudomonas putida, Proteus sp., Escherichia coli, Bacillus subtilis, Staphylococcus aureus other fungi: Candida albicans

Exposure period :

Unit :

Analytical monitoring : No

Method : other: see Test condition

Year : 1968

GLP : No

Test substance : other TS: Aerosil (Type not specified)

Remark : Results: EC100:

Pseudomonas putida	after 6 hours (22 °C)
	after 3 days (37 °C)
Escherichia coli	after 2 days (22, 37°C)
A. aerogenes	after 3 days (22 °C)
	after 2 days (37 °C)
Proteus sp.	after 2 days (22, 37°C)
S. aureus	after 18 days (22 °C)
	after 22 days (37 °C)
C. albicans	after 10 days (22 °C)
	after 3 days (37 °C)
B. subtilis	after 18 days (22 °C)
	after 2 days (37 °C)

Test condition : Exposure period: 1 - 28 days
Endpoint: mortality (growth inhibition)
Method:
0.15 ml of inocculated Bouillon were added to 0.2 g Aerosil (dilution 1:50000 for Aerobacter aerogenes, Proteus sp., Pseudomonas aeruginosa, Escherichia coli and Staphylococcus sp.; and 1:100000 for Candida albicans and Bacillus subti-lis, resp.).
Inocculation temperature: 22 and 37 °C, resp.
Inocculation time: 2 h - 28 d;
After inocculation 5 ml of sterilized Bouillon with sugar were added and mortality of microorganism were determined. As control instead of aerosil physiological sodium chloride solution were used.

Reliability : (3) invalid
Significant methodological deficiences.
Method not comparable to bacteria toxicity tests.

(27) (126)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species : other: Blattella germanica (German cockroach)
Endpoint : mortality
Exposure period : 24 hour(s)
Unit : other: µg/cm2 surface
LC50 : >= 23
Method : other: see Test condition
Year :
GLP : no data
Test substance : other TS: Sipernat 22, Gasil 23F, Gasil HP25, Gasil HP37, Gasil 114, Gasil AF, Gasil 200, Gasil GM2, HDK H20, HDK N20, EH5, H5, M-7D

Remark : Results:

type of silica	LC50 (g/m2 surface; 24 h)
precipitated amorphous silica	
Gasil 23 F	0.23
Gasil HP37	0.32
Gasil HP25	0.74
Gasil 114	0.92
Gasil AF	1.61
Sipernat 22	> 7.86
Gasil GM2	> 7.86
Gasil 200	> 7.86
pyrogenic amorphous silica	
HDK H20	0.53
EH5	0.56
H5	0.58
HDK N20	0.66
M-7D	2.41

The toxicity to B. germanica generally increased with increasing oil absorption capacity of the precipitated silicas but no such correlation was evident for the pyrogenic silicas. In an additional experiment it was shown that the lethality was significantly reduced by increasing rel. humidity.

Test condition : Male adult cockroaches were used. Dust samples were weighed into plastic petri dishes and distributed with a paint brush. The base was divided into ten equal segments using a card insert. Cockroaches were cooled to 0 °C and then placed singly in individual segments. The covered dishes were kept at 75 % rel. humidity and 30 °C. Mortality was assessed at 24 hours. There was no control mortality within this time.
Test substance : amorphous pyrogenic and precipited silica (see Remark)

Conclusion : There are some methodological deficiences (no control was used). Yet, toxicity values are in large agreement with those described by others (see next entry).
Reliability : (4) not assignable
4e: Documentation limited and insufficient for assessment, but useful in relation to findings of others.
Flag :

(140)

Species : other not soil dwelling arthropod: Sitophilus granarius (grain weevil; curculionidae/beetle)
Endpoint : Mortality
Exposure period : 96 hour(s)
Unit : other: µg/cm2 surface
LC50 : ca. 21 - 150
Method : other: see Test condition
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : Furthermore, ranking of toxicity is not consistent with current criteria: The lowest LC50 of 21 ug/cm2 cannot be considered as a high toxicity. The following criteria can be used for screening tests on insecticides: <0.5 ug/cm2 = very active, 0.5 - 2.5 ug/cm2 = active.
Result : Results (Wessalon):

Surface		Aqueous susp.	Dry powder
Glas	LC50 (96 h)	52 µg/cm2	21 µg/cm2
Tile	LC50 (96 h)	33 µg/cm2	37 µg/cm2
Concrete	LC50 (96 h)	126 µg/cm2	(20, 160) µg/cm2
Sacking	LC50 (96 h)	362 µg/cm2	149 µg/cm2
Wheat grain	LC50 (7 d)	> 1137 µg/g	451 µg/g

(note: In wheat grain the results are expressed as µg/g)

Test condition : In this study sorptive silica dust (Cab-O-Sil) was applied to a number of substrates, both as a dry powder and as an aqueous suspension and the toxicity of the deposits to the grain weevil S. granarius was determined. The amount of deposit picked up by the insect (30 animals/substrate) was measured on each substrate. Temp.: 25 - 27 °C, rel. humidity: 55 - 60 %. Mortality was determined after 96 hours except in the case of grain for which 7 days exposure were used.
Test substance : Wessalon S: amorphous precipitated silica, 98 % SiO2, BET surface 190 m2, mean aggregate size 7 µm
Conclusion : Toxicity values are in large agreement with those described by others (see previous entry).
Reliability : (4) not assignable
4e: Documentation limited and insufficient for assessment, but useful in relation to findings of others.
Flag :

(92)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Remark	:	Results cannot be used as such for the risk assessment of silica. Some explanations were proposed on the action of silica through deshydration. Type: Accumulation and insecticidal action Species: Sitophilus oryzae (L.) (rice weevil, curculioni-dae/beetle) Method: Radiolabelled ((35)Na) silica was mixed with wheat to provide silica concentrations of 150 mg/kg. The insects were introduced in batches of 50 insects into the jars and incubated for 48 hours in the dark at 25 °C. After incubation 10 insects were randomly selected and the adsorbed silica content was determined by radioactivity. Result: No animals died. The insects moving through wheat treated with silica picked up a considerable portion of the total dust accumulated within the first 5 min of moving through the dusted wheat (mean after 48 hours: 3.83 µg/insect). In an additional experiment with dust concentrations of 1 mg/kg wheat it was shown that the beetles were covered with a thin layer of dust with deposits accumulated between the legs, on the terminal segments and around the rectum. This aggregates appeared translucent rather than opaque, which was interpreted by the authors as beeing due to saturation with lipid from the cuticle.
Test substance	:	SIPERNAT 22S >98 % (SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8 Surface area (Ströhlein): 160 - 195 m2/g Primary particle size: see Test Condition
Reliability	:	(3) invalid 3a: Documentation insufficient for assessment

(141)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males : 10
Females : 10
Doses
Males : see Test conditions
Females : see Test conditions
Vehicle :
Route of administration : inhalation
Exposure time : 90 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure : see Chapter 5.4, entry No. 4
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: acc. to OECD Guide-line 413
Year : 1987
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Remark : More details are provided under 5.4, entry 4.
Result : SILICA DEPOSITION
Silica could be detected in lungs only in relatively small amounts at the end of the exposure period, on the average 0.2 mg in all animals of the 30-mg groups. Only one male exposed to 30 mg/m3 showed a small amount of silica in the regional lymph node. During the post-exposure observation period, no silica could be recovered from any animal.
Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.
Examinations primarily focussed upon changes in the lung, respiratory tract, and regional (hilus and mediastial) lymph nodes, including collagen and silica determinations in the lung.
Post-exposure recovery period up to one year was enclosed: 10 m / 10 f animals per group sacrificed after 13 wks, 50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks).

TEST CONCENTRATIONS and FREQUENCY
1.3, 5.9 or 31 mg/m3 (mean analytical values) 6 h/d; 5 d/wk
Test substance : Aerosil 200: >99.8 % (SiO_2): CAS-Name: Silica, amorphous,fumed (precipitated), cryst.-free; CAS-No.: 112945-52-5
Surface area (BET): 150 - 200 m2/g Particle size: see Test Condition
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
24.09.2004 (65)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males :

Females :
Doses
Males :
Females :
Vehicle :
Route of administration : Inhalation
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method :
Year : 1969
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : A.
Species: rat
Strain: Sprague-Dawley
Sex: female
Route of admin.: inhalation
Exposure period: 12 months
Freq. of treatment: 5 hours/day, 2 - 3 days/week (at the beginning 5 days/week, not specified)
Post. obs. period: 5 months
Doses: 0.050 - 0.055 mg/l
Control group: yes
Method: Interim kill after 6 and 18 weeks.
After the occurence of bronchitis, putrid, lung inflammation and pronounced cell reactions the incidence of exposure was reduced to 2 - 3 times per week.
GLP: no
Results: After 6 weeks, 0.5 mg SiO2 was found in the lungs and 0.02 mg SiO2 in the mediastinal lymph node.
After 18 weeks lungs, 1.2 mg SiO2 and lymph node 0.11 mg SiO2.
After 12 months lungs 1.37 mg SiO2 and lymph node 0.13 mg SiO2.
Corresponding to the respiration volume, 1 % of the inhaled SiO2 was retained in the lungs. After a post-observation of 5 months, 0.160 mg SiO2 in lungs and 0.047 mg SiO2 were found in the mediastinal lymph node.
B. SUMMARY:
Exposure to 50 - 55 mg/m3 (total dust) amorphous silica, HDK V15, (approx. 30 mg/m3 respirable) for 12 months of rats (5 h/d; 5 d/wk): After 3 days, about 0.25 mg and after 6 weeks 0.5 mg SiO2 was found in the lungs. After 12-months exposure, about 1 % of administered total respirable dust was estimated to be still retained in the lung. The increase in lung deposition was rapid at the initial exposure, then low from 18 weeks to 12 months of exposure (6 weeks: 0.5 mg, 18 weeks: 1.2 mg, 12 months: 1.37 mg SiO2). (note, however, that the frequency of exposure had been reduced from 5 to 3 exposure sessions per week after a not stated time.). Mediastinal lymph nodes contained about 0.02 mg SiO2 after 6 weeks and 0.13 mg SiO2 after 12 months. After 5 months post-exposure, mean levels of SiO2 were 0.16 mg/lung and 0.047 mg/lymph node, i.e. a reduction at some 88 % in the lung and more than 50 % in the lymph nodes.
Test substance : HDK V15: >99,8 % SiO2, 150 m2/g (BET), CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented,

acceptable for assessment

Flag : Critical study for SIDS endpoint
24.09.2004 (132) (150)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : Inhalation
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1963
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Comprehensive study programme to quantify retention and elimination of various siliceous dusts from rat lung after prolonged inhalation exposure.
Three types of silica were examined: Quartz, corundum, AEROSIL 150 (amorphous).
Rats (unspecified inbred albino rat, female) were exposed to AEROSIL 150 4 h/d on 5 days/week:
Exposure concentration:
0 - 40 days lower than from 41 - 120 days (no details given)
41 - 120 days: 40 - 50 mg/m3 (p. 427; p. 431).

Result : The average one-day retention value was 28 ug/lung at the lower concentration (not specified).
During the first 10 days, a steep linear increase was seen with about 28 ug/day as theoretically expected; thereafter, increments became significantly smaller, suggesting that elimination increased and that an equilibrium between retention and elimination was established (p. 427).
After 40 exposures, the average one-day retention value was 59 ug/lung at the high concentration (40-50 mg/m3, see p. 431).
After 120 exposures, the total deposit (lung and medistinal lymph nodes) was found to be only at 435 ug/lung, equivalent to 7.4 % of the theoretically deposited material (5840 ug/lung, based on the measured one-day retentions), ie. more than 92 % of the deposited SiO2 in the alveoles was eliminated during the exposure period.
At that time, the mean retention of the lungs was only 300 ug/lung (= approx. 69 % of the total).
The deposition rate in the mediastinal lymph nodes was negligible during the first 40 days, but was increasing gradually.
After 120 exposures, the retention there was substantial amounting to some 135 ug (about 31 % of the total deposit).
A test for the determination of free alveolar cells showed a decrease immediately after a single exposure and 24 hours later an increase of 100 % was seen.

Test substance : Aerosil 150 : CAS-Name: Silica, amorphous, fumed (pyrogenic), CAS No.:

112945-52-5

Conclusion : After prolonged exposure of rats to high concentrations of amorphous silica (40-50 mg/m3), overall elimination was high without accumulation in the lung: only 5-6 % of respirable (theoretically deposited) material was found after 120 exposure days. On the other hand, transfer to mediastinal lymph nodes was substantial after prolonged exposure under these conditions with about 31 % of total deposit = 1.5- 2 % of the respirable (theoretically deposited) material. The involvement of lymphatic elimination appears to be not relevant after short exposure periods (here up to 40 times), at least at lower body burden of amorphous silica. [note: In other studies, higher retentions after 3 months were found: 1.5 mg SiO2/lung for DOW CORNING silica (p. 431) (see Schepers et al., 1957)].

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

Flag : Critical study for SIDS endpoint

24.09.2004 (133)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males :
Females :
Doses
Males : 53 mg/m3: 6 and 12 months (rats); 12 and 24 months (guinea pigs); 8 h/d, 5 d/wk
Females : 53 mg/m3: 6 and 12 months (rats); 12 and 24 months (guinea pigs); 8 h/d, 5 d/wk
Vehicle :
Route of administration : Inhalation
Exposure time : 365 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure : see other entries in Chapter 5.4
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other: single-dose inhalation study
Year : 1957
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Part of a comprehensive testing programme (see other entries in Chapter 5.4):
Whole-body exposure: active dust exposure for 8 h/d (dust-disseminating apparatus: mechanical agitation and compressed air-jet through Venturi tube into inhalation chamber), and passive exposure (dust settling) for the remainder 16 h/d.
Dust analysis and sampling: millipore filter method: average air concentration was 1.5 mg/cubic foot = 53 mg/m3, with most measurements between 0.7 and 2.4 mg/cubic foot (= 25 and 85 mg/m3, respectively).
Size distribution of the particles (an electrostatic precipitator used): 1- to 10-µm particles accounted for some 85 % of the dust mass in the chamber.
RATS:
a) 35 animals were used in a first set (exposure <=12 months)
b) 25 animals were used in a 2nd set (exposure 6 months, followed by recovery period up to 12 months).
Control group: 42 animals in normal environment, autopsied at 6-months

intervals.
GUINEA PIGS:
Several test protocols were used:
a) 40 animals exposed for up to 24 months and interim sacrifices every 2 months (Tab. 3);
b) 15 animals exposed for 12 months with variable recovery (Group II, Tab. 2), and 18 animals exposed for 24 months with variable recovery up to 1 year (Tab. 3);
c) 17 animals exposed for 12 months, with recovery for one month, followed by another exposure of 8 to 24 hours (Group III, Tab. 2). 80 guinea pigs of both sexes were kept in normal environment as controls and were sampled at intervals ranging from 1 month to 36 months.

Remark : SILICA BURDEN of the lung (Rat) [Schepers 1957a]:
During exposure of rats to 53 mg/m3 (DOW silica, pyrogenic: 85 % from 1 - 10 µm, active dust exposure for 8 h/d and passive exposure for 16 h/d), for up to 12 months, the development of pulmonary lesions was accompanied by a rapid increase in SAS in the lung, not seen in studies at lower exposure concentrations.
Average lung content reached 1.5 mg SiO2 (= approx. 10 % of lung ash) after exposure of 3 months, thereafter residing on a steady-state level. After 2 post-exposure months, levels subsided to about 0.3 mg SiO2 per lung. In guinea pigs, under identical conditions as mentioned above, average lung content reached 2.5 mg SiO2 per lung after 12 months, about 4 % of lung-ash weight,
SILICA BURDEN of the lung (Guinea pig) [Schepers 1957b]:
The development of pulmonary lesions was accompanied by a progressive and rapid increase in silica in the lung. Average lung content reached 2.5 mg SiO2 per lung after 12 months, about 4 % of lung-ash weight, clearly relatively lower than found in the rat, but increased disproportionately the following 12 months to about 8 mg per lung (= approx. 12 % of lung ash) (Fig. 1).
There was hardly any deposition of SAS in the lymphatic system, which was characteristic of the rat under identical test conditions. After cessation of exposure, silica content rapidly decreased to about 0.6 mg per lung along with a significant decrease in lung ash.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessment

Flag : Risk Assessment

24.09.2004 (176) (177)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males :
Females :
Doses
Males :
Females : 1500 mg/(kg*d) (aqueous suspension: not specified)
Vehicle :
Route of administration : Gavage
Exposure time : 30 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method : other: no data

Year : 1968
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Result : Body weight gain, food consumption and behaviour were notinfluenced. The SiO2-content in liver was 1.5 ug, in kidney6.4 ug and in spleen 5.3 ug. The corresponding control va-lues were 1.8, 7.2 and 7.8 ug SiO2, resp..
Test condition : 1500 mg/(kg*d) (aqueous suspension: not specified)
Test substance : FK 700, 86.65 % SiO2, 7.3 % hydration water (SiO2): Silica,precipitated, crystalline-free, CAS No.: 112926-00-8:Specific surface area (BET) = 700 m2/g
Reliability : (4) not assignable
Abstract/Summary
Flag : Critical study for SIDS endpoint
24.09.2004 (50)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : other: gavage and s.c.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method :
Year : 1969
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Species: rat
Strain: Sprague-Dawley
Sex: female
Route of admin.: a) inhalation
b) s.c.
c) oral (gavage, aqueous suspension)
Exposure period: a) 3 days
b) single administration
c) 1 month
Freq. of treatment: a) 5 hours/day
b) -
c) 20 administrations
Post. obs. period: a) up to 3 months
b) up to 2 months
c) no
Doses: a) 0.050 mg/l/5h
b) 10 mg/animal
c) 100 mg/animal (approx. 500 mg/kg)
Control group: yes
Method: no further data Year: no data

GLP: no
Results:
a) 20 hours after the last exposure 0.25 mg SiO2 were found in the lungs. After 3 months the SiO2 content was 0.018 mg SiO2. In the lymph node 0.018 mg SiO2 was found after 1 month and 0.008 mg SiO2 after 3 months.
b) After 24 hours 6.89 mg SiO2 were found in the tissue at the application site. After 1 month the amount was decreased to 0.646 mg SiO2 and after 2 months 0.298 mg SiO2 was found.
c) No clinical signs were observed. The SiO2 content in the liver was 4.2 ug (control value 1.8 ug), in the spleen 5.5 ug (7.2 ug) and in the kidneys 14.2 ug (7.8 ug).
SUMMARY (oral)
In 20 rats receiving 20 daily oral doses of 100 mg HDK V15 per animal (about 500 mg/kg bw) each, tissue values apparently were very slightly increased in liver and kidney: in liver 4.2 µg (control value 1.8 µg), in the spleen 5.5 µg (7.2 µg) and in the kidneys 14.2 µg (7.8 µg).
SUMMARY (s.c.)
Amorphous silica (HDK V15), 10 mg subcutaneously injected in 0.3 ml water, was rapidly removed from the site of injection: mean recovery 24 h post-treatment 6.90 mg, after one month 0.65 mg (approx. 10 % left) and after two months 0.30 mg (less than 5 % left) [Klosterkoetter 1969]. Similar results were obtained in rats after subcutaneous application of 30, 40, and 50 mg AEROSIL 150 as suspension in water or in 0.5-% Tween or as dry powder (operative, subcutaneous): after 6 weeks 95 - 97 % of the substance was eliminated [Degussa 1964].

Test substance : HDK V15: >99,8 % SiO2, 150 m2/g (BET), CAS-Name: Silica, amorphous, fumed (precipitated), cryst.-free; CAS-No.: 112945-52-5

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

Flag : Critical study for SIDS endpoint

24.09.2004 (26) (132)

In Vitro/in vivo : In vivo
Type : Excretion
Species : Human
Number of animals
Males : 10
Females : 2
Doses
Males : 2x 1250 mg (morning and midday)
Females : 2x 1250 mg (morning and midday)
Vehicle : other: apple juice
Route of administration : other: oral in juice
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1966
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : TEST
To 5 m / 1 f persons (age 22 - 28), Aerosil 175 was administered in two

portions of 1.25 g (suspended in 250 ml apple juice each time) at day 4 of an experimental period of 7 days.

Six other volunteers (also 5 m /1 f) received the same amount FK 700 suspended in 250 ml apple juice each time, at day 4 of an experimental period of 7 days.

The total urine was collected daily and analysed for the mononomer SiO2-content. Individual changes of the SiO2 excretion were determined (comparison SiO2 before and after silica application).

ANALYSIS
SiO2 according to Baumann (determination after alkaline hydrolysis with molybdate).

Result : During the four days post-treatment, significant changes of the renal SiO2 secretion were not seen. Daily SiO2 increments in urine after ingestion ranged between 7 and 23 mg.
Aerosil:
The individual baseline values of the pre-test phase were very variable and individually different, mean excretion rates ranging from 25 to 87 mg/day. In the post-treatment phase, individual mean excretion rates ranged from 32 to 61 mg/day.
FK 700:
The individual baseline values of the pre-test phase were very variable and individually different, mean excretion rates ranging from 16 to 71 mg/day. In the post-treatment phase, individual mean excretion rates ranged from 20 to 81 mg/day.
Overall, increases in excretion were not unequivocally detectable. The small apparent increases were in marked contrast to the high dose of 2500 mg SiO2 applied.

Test substance : Aerosil 175, CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5
FK 700, Silica, precipitated, crystalline-free, CAS No. 112926-00-8

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

Flag : Critical study for SIDS endpoint

24.09.2004 (71) (139)

In Vitro/in vivo : In vivo
Type : Distribution
Species : Rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1968
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Rats were exposed 5 hours to 55 mg/m3 precipitated silica (FK 700). The mean retention value (20 hours later) was 0.138 mg SiO2/lung. For Aerosil OX 50 the value was 0.130 mg SiO2/lung.

Result : RETENTION of silica:
For, FK700, the one-day mean retention value was 0.138 mg/lung (derived from intermittent single exposures with control animals). For Aerosil OX 50, the value was 0.130 mg SiO2/lung.

For FK700: Average SiO2-content of the lungs after 4 months: 1.022 mg, after 12 months: 3.443 mg.
The corresponding values for the mediastinal lymphatic nodes were after 4 months: 0.033 mg and after 12 months: 0.069 mg.
Five months after exposure, the average value for the lungs was only 0.457 mg (elimination rate 87 %), the corresponding value for the mediastinal lymphatic nodes was 0.052 mg 5 months after end of exposure.

Test substance : Aerosil OX 50: CAS Name, Silica, amorphous, fumed (pyrogenic), CAS No. 112945-52-5
FK 700, 86.65 % SiO2, 7.3 % hydration water (SiO2), specific surface area (BET) = 700 m2/g: Silica, precipitated, crystalline-free, CAS No. 112926-00-8

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

(49)

In Vitro/in vivo : In vivo
Type : Distribution
Species : guinea pig
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Remark : Experiments with (31)SiO2 indicated, that orally administered silica was rapidly absorbed and excreted. Time dependent levels were determined in liver, kidney, muscle, brain, blood and urine. The max. excretion rate was 10.3 mg in 48 hours. The half life was 2.82 hours. An influence of the pH to the absorption/excretion rate was observed. After intraperitoneal administration the excretion rate was higher than after oral administration. The tissue levels of SiO2 in organs of guinea pigs are relatively low. In muscle liver and kidney the range was between 2.89 and 7.03 mg SiO2/100 g dry matter. Greater values were found in hair and lungs (27.06 or 12.63 mg SiO2/100 g dry matter, resp.).
The tissue levels in a cow were similar to those of guinea pigs. Diets containing different SiO2 concentrations (0.75 or 46.5 mg SiO2/g dry feed) did not influence the organ levels.

(170)

In Vitro/in vivo : In vivo
Type : Distribution
Species :
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Remark : The SiO2 content of organs and tissues of rabbits are between 18 and 128 ug/g wet tissue. The lowest value was found in the liver and the highest in the lung. SiO2 levels in serum, plasma and blood are comparable. SiO2 levels are also found in the urine. The elimination rate was in the range of 9.6 mg/day in rabbits. A correlation between blood and urine levels was observed. Comparable levels were observed in humans and other mammalians (guinea pig, calves, cow, cat, sheep, goose, pig and dog).

Test substance : Colloidal silica

(3)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 3300 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	Water
Doses	:	2000 and 3300 mg/kg bw.
Method	:	other
Year	:	1977
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No clinical symptoms or other pathological findings following autopsy.
Test condition	:	Ten male and 10 female animals were used per single dose. The dose was applied by gavage as aqueous suspension/gel containing 1 % methyl-hydroxyethyl cellulose. A maximal attainable concentration was tested. Post-observation period was 4 weeks.
Test substance	:	Aerosil 200: >98 % (SiO_2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study

(54)

Type	:	LD50
Value	:	> 5110 mg/kg bw
Species	:	Rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	Water
Doses	:	limit test: 5110 mg/kg
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1987
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Results: no clinical symptoms or other findings
Test condition	:	Five male and 5 female animals were used. The dose was applied by gavage as aqueous suspension (21.5 ml/kg bw = 237 mg silica/ml suspension) containing 1 % CMC.
Test substance	:	Sident 9, >98% (SiO_2), Na_2O <1%, Al_2O_3 <0.2%, SO_3 <0.8%, Fe_2O_3 <0.03%: CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(58)

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20

Vehicle	:	Water
Doses	:	2000 and 5000 mg/kg bw
Method	:	other
Year	:	1977
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No clinical symptoms or other pathological findings following autopsy.
Test condition	:	Ten male and 10 female animals were used per single dose. The dose was applied by gavage as aqueous suspension/gel containing 1 % methyl-hydroxyethyl cellulose. A maximal attainable concentration was tested. Post-observation period was 4 weeks.
Test substance	:	Sipernat 22, 97-98 % (SiO_2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(2) valid with restrictions 2c: Comparable to guideline study with acceptable restrictions

(55)

Type	:	LD50
Value	:	= 470 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	other TS: FDA compound
Remark	:	Method: Male rats. Dose range 10 to 5000 mg/kg, suspended in 0.85 % saline. Observation period 10 days. Result: At doses above 100 mg/kg distended stomach with bloody patches at the pyloric end. At 5000 mg/kg additionally a vascular stomach and reddened inte-stinal lining were found. Remark: The result of this test is questionable, because in other acute and subacute toxicology studies (in vivo genetic toxicity test, see chapter 5.6) 5000 mg/kg did not cause lethality.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(3) invalid 3c: Inconsistent results

(143)

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: see Remark
Year	:	
GLP	:	No
Test substance	:	other TS: FDA-Compound 71-48 (Syloid 244)
Remark	:	Method: Male rats. The substance was suspended (12.1 % (w/v) in 0.85 % saline. Observation period 10 days. Result: No clinical symptoms or other findings.

Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8

(143)

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: dispersion of 10 % gum arabicum in water
Doses	:	1000, 2500, and 5000 mg/kg (pre-study); 5000 mg/kg (main study)
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1985
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	5 animals were used per sex. In the pre-study 2 animals per sex and group were used.
Result	:	No clinical changes and or other findings observed.
Test substance	:	Tixosil 53, precipitated, CAS No. 112926-00-8, no further data
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(167)

Type	:	LD50
Value	:	> 10000 mg/kg bw
Species	:	Rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: diet
Doses	:	approx. 10 g/kg bw. over 24 hours
Method	:	other
Year	:	1979
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The product was mixed with the stock diet at a ratio of 1:4 (w/w) and fed to trained animals during a 24-h period.
Result	:	Most animals consumed the supplemented diet quantitatively. No clinical symptoms or other pathological findings following autopsy. No diarrhea, stool changed colour to grey, but showed normal consistency with faecal pellets considerably bigger than normal.
Test substance	:	About 30 silica types included, amorphous, fumed and precipitated, not further specified, such as Aerosil 130, 150, 200, 300, OX 50, Ultrasil VN 2 and 3, silica FK types, Sident 3, Sipernat AS 7, 22, 30 and 42.
Reliability	:	(2) valid with restrictions 2b: Comparable to guideline study with acceptable restrictions (only summary report)
Flag	:	Critical study for SIDS endpoint

(47)

Type	:	LD0
Value	:	> 5620 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Number of animals	:	30
Vehicle	:	Water

Doses : 5620 mg/kg (max. attainable dose)
Method : other
Year : 1974
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Observation period 14 days. Administration by single gavage.
Result : No clinical symptoms; the stools were white coloured (reversible after 2 days).
Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

(100)

Type : LD0
Value : > 20000 mg/kg bw
Species : Rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle : Water
Doses : 10000, 12600, 15800, and 20000 mg/kg
Method : other
Year : 1978
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Five animals per sex and group were used. Substances were suspended in water (ZEOSYL 200: 15 % w/w; ZEOFREE: 20 % w/w; ZEOSYL 113 and ZEO 49: 33 % w/w); administration by gavage. Observation period 14 days.
Remark : Method: suspended in water (33 % w/w); administration by gavage. Observation period 14 days.
Results: no clinical symptoms; after 1 day the stools were white coloured (reversible after 2 days)
Result : No clinical symptoms; after 1 day, the stools were white coloured (reversible after 2 days).
Test substance : ZEO 49, ZEOSYL 113, ZEOSYL 200, and ZEOFREE 153 (not further specified): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint

(113) (114) (115) (116)

Type : LD0
Value : = 10000 mg/kg bw
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method :
Year :
GLP : No
Test substance : other TS: Ludox (aqueous colloidal: 30% SiO2), neutralized with HCl

(74)

Type : LD0

Value	:	= 40000 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	
GLP	:	No
Test substance	:	other TS: Positive Sol 130M (26 % SiO_2, 4 % Al_2O_3, 1.5% Cl, 0.22 % MgO and 0.25 % Na_2O in H_2O) (pH = 4.5)

(80)

Type	:	LD50
Value	:	> 3160 mg/kg bw
Species	:	Mouse
Strain	:	Swiss
Sex	:	Male
Number of animals	:	10
Vehicle	:	other: corn oil
Doses	:	178, 316, 562, 1000, 1780 and 3160 mg/kg
Method	:	other
Year	:	1964
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The test substance was given by gavage at variable volumes, at maximum 10 ml/kg.
Result	:	No adverse signs of toxicity in any animal during the study, no macroscopic lesions upon necropsy after 14-d observation.
Test substance	:	Cab-O-Sil M-5 and F-2 (unspecified): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(2) valid with restrictions 2d: Test procedure in accordance with national standard methods with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

(15)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC0
Value	:	> .139 mg/l
Species	:	Rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	maximum attainable concentration: 139 mg/m3 (see Test condition)
Exposure time	:	4 hour(s)
Method	:	OECD Guide-line 403 "Acute Inhalation Toxicity"
Year	:	1982
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No clinical symptoms and no findings at autopsy after 14 d post-treatment.
Test condition	:	Nose-only exposure system. Five animals each per sex were used. Analysed chamber concentrations ranged from 110 to 190 mg/m3 (note:

		Technically, the maximally achievable aerosol concentration due to substance-inherent properties resulting in sedimentation and adsorption to the equipment.). About 47.3 % of the aerosol comprised particles with an aerodynamic diameter of <5 um (respirable fraction).
Test substance	:	Aerosil 200: >98 % (SiO2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study
Flag	:	Critical study for SIDS endpoint

(44)

Type	:	LC0
Value	:	> .691 mg/l
Species	:	Rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	maximum attainable concentration: 691 mg/m3 (see Test condition)
Exposure time	:	4 hour(s)
Method	:	other: see Remark
Year	:	1982
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No clinical symptoms except some restlessness and eye closing. Body weight gain was not affected in males, but females hardly gained weight during two days after exposure, however, subsequently, showed normal development. No findings at autopsy after 14 d post-treatment.
Test condition	:	Nose-only exposure system. Five animals each per sex were used. Analysed chamber concentrations ranged from 650 to 725 mg/m3 (note: Technically, the maximally achievable aerosol concentration due to substance-inherent properties resulting in sedimentation and adsorption to the equipment.). About 45 % of the aerosol comprised particles with an aerodynamic diameter of <5 um (respirable fraction).
Test substance	:	SIPERNAT 22S >98 % (SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8 Surface area (Ströhlein): 160 - 195 m2/g Primary particle size: see Test Condition.
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study
Flag	:	Critical study for SIDS endpoint

(45)

Type	:	LC0
Value	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	other: see Remark
Year	:	
GLP	:	No
Test substance	:	other TS: Ludox (30% SiO2)
Remark	:	Method: 10.4 mg/l/6 h or 11.1 mg/l/2.5 h; The test substance was diluted to 5 % SiO2 and sprayed as a mist. The actual concentrations of silica were

0.52 mg/l/6 h and 0.56 mg/l/2.5 h.

Reliability : (3) invalid
3a: Significant methodological and documentary deficiences
(74)

Type : LC0
Value : = 3.1 mg/l
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time : 7 hour(s)
Method : other: see Remark
Year :
GLP : No
Test substance : no data

Remark : Method: 2 male rats, exposure to dust, the concentration was determined by weighing (actually nominal conc.)
Reliability : (3) invalid
3a: Significant methodological and documentary deficiences
(73)

Type : LC0
Value :
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
Method : other: see Remark
Year :
GLP : no data
Test substance : other TS: colloidal silica

Remark : Method: animals were exposed to mist of 5, 20 and 30 %
Results: 0.76 mg/l/3.25 h (5 % solution; pH 7.05)
2.24 mg/l/4 h (20 % solution; unneutralized)
2.5 mg/l/2 h (20 % solution; unneutralized)
3.3 mg/l/1.5 h (30 % solution; pH 9.4)
Reliability : (3) invalid
3a: Significant methodological and documentary deficiences
(73)

Type : LC50
Value : > 2.2 mg/l
Species : Rat
Strain : Sprague-Dawley
Sex :
Number of animals : 10
Vehicle :
Doses :
Exposure time : 1 hour(s)
Method : other: see Remark
Year : 1977
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark	:	Method: only 1-h exposure; actual conc. 2.2 mg/l, nominal conc. 27 mg/l. Observation period 14 days. Results: Death in 1/10 animals; during the exposure signs of irritation and dyspnea were apparent in most animals.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(3) invalid 3a: Significant methodological deficiences: only 1-h exposure (101)

Type	:	LC50
Value	:	> 2.08 mg/l
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	2.08 mg/l
Exposure time	:	4 hour(s)
Method	:	
Year	:	1981
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Whole-body exposure: A control group of ten rats exposed to clean air was run in parallel. Post-exposure observation 14 d. Air concentration was analysed by sampling dust on glas fiber filters and determining the sampled amount by gravimetry. Particle size distribution was measured using a Delron Cascade impactor (MMAD = 0.76 um +-3.11). Approx. 84% of the particles had a diameter of <=3 um, approx. 98 % <=10 um. All animals were subjected to gross necropsy.
Result	:	No animals died. Nasal discharge during exposure, crusty eyes, crusty nose and alopecia at days post-exposure. No macroscopic organ lesions, but in one animal discoloration of the lung.
Test substance	:	CAB-O-SIL M5: CAS-Name: Silica, amorphous, fumed (pyrogenic), crystalline-free; CAS-No.: 112945-52-5, purity ca. 100 %
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study, well documented.
Flag	:	Critical study for SIDS endpoint

23.09.2004 (10)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	Other: see Remark
Year	:	1976
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Remark	:	Method: Application to the intact and abraded skin. Post observation

period 48 hours.
Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions
(99)

Type : LD50
Value : > 5000 mg/kg bw
Species : Rabbit
Strain : New Zealand white
Sex : no data
Number of animals : 16
Vehicle : Water
Doses : 2000, 3000, 4000, and 5000 mg/kg
Method : other
Year : 1978
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Four animals per group used, two each treated on the intact and abraded skin: The substance was mixed with distilled water to form an aqueous paste. Application to the intact and abraded skin under occlusive bandage. Observation period 14 d.
Result : Local effect: very slight erythema (score 1 of 4), reversible after 2 days (ZEO 49), after 4 d (ZEOSYL) or 5 d (ZEOFREE) in one or a few animals. No systemic signs of toxicity or organ toxicity.
Test substance : ZEO 49, ZEOSYL 113, ZEOSYL 200, and ZEOFREE 153 (not further specified): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint
(109) (110) (111) (112)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : other: LD
Value :
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : i.p.
Exposure time :
Method :
Year :
GLP : No
Test substance : other TS: precipitated silica (FK 700)

Remark : Results: Doses of 50 mg and higher caused deaths.
(49)

Type : other: LD
Value :
Species : Rat
Strain :
Sex :

Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	
GLP	:	No
Test substance	:	other TS: Mattierungsmittel TK 800

Remark : Results: Doses of 50 mg and higher caused deaths.
(38)

Type	:	LD50
Value	:	= 15 mg/kg bw
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	other: see Remark
Year	:	
GLP	:	No
Test substance	:	other TS: Aerosil

Remark : Method: Suspension of amorphous fumed silica with and without heparin, vene of the tail. Remark: In presence of heparin the LD50 was reduced.
(4)

Type	:	other: LD
Value	:	
Species	:	Mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	
Year	:	
GLP	:	No
Test substance	:	other TS: various amorphous silica

Remark : Results: The lethal doses were between 0.2 and 0.5 mg/30 g bw (6.7 and 16.7 mg/kg). It appears that the toxicity fell off with an increasing size of the particles (The toxicity of amorphous silica was considerably less than that of the crystalline type of the same particle size).
(182)

Type	:	LCLo
Value	:	= 1.8 other: mg/cm3
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	

Route of admin.	:	other: intratracheal
Exposure time	:	
Method	:	
Year	:	
GLP	:	No
Test substance	:	other TS: molecular-soluted siliceous acid
Remark	:	Results: Changes in the tissue consisted of serous reactions of the end-arteries with diapedesis of the plasma, erythrocytes, and leucocytes. Desquamative catarrhs were also found.

(129)

5.2.1 SKIN IRRITATION

Species	:	Rabbit
Concentration	:	.5 g
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	12
Vehicle	:	Water
PDII	:	0
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Patch-Test; Hazardous Substances, Part 191, Section 11, FDA, Washington, 1965
Year	:	1978
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	There were no signs of irritation.
Test condition	:	The substance (0.5 g) was applied as 12-% suspension/gel in 1-% methyl-hydroxyethyl cellulose to an intact (6 animals) and scarified (6 animals) skin area of approx. 6.25 cm2.
Test substance	:	Aerosil 200 (not further specified): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study
Flag	:	Critical study for SIDS endpoint

22.09.2004 (52)

Species	:	Rabbit
Concentration	:	.5 g
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	12
Vehicle	:	Water
PDII	:	0
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Patch-Test; Hazardous Substances, Part 191, Section 11, Federal Register, FDA, Washington, 1965
Year	:	1977
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	There were no signs of irritation.
Test condition	:	The substance (0.5 g) was applied as 23-% suspension/gel in 1-% methyl-hydroxyethyl cellulose to an intact (6 animals) and scarified (6 animals) skin area of approx. 6.25 cm2.

Test substance	:	SIPERNAT 22S >98 % (SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8 Surface area (Ströhlein): 160 - 195 m2/g Primary particle size: see Test Condition
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study

22.09.2004 (53)

Species	:	Rabbit
Concentration	:	.5 g
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	3
Vehicle	:	Water
PDII	:	0
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1990
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	There were not any irritating effects.
Test condition	:	The substance (0.5 g) was moistened with 0.5 ml water and place on a skin area of approx 6.25 cm2.
Test substance	:	Sident 9, >98% (SiO2), Na20 <1%, Al2O3 <0.2%, SO3 <0.8%, Fe2O3 <0.03%: CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(57)

Species	:	Rabbit
Concentration	:	.5 g
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	12
Vehicle	:	other: none
PDII	:	0
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Patch-Test; Hazardous Substances, Part 191, Section 11, FDA, Washington, 1965
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Test substance	:	ULTRASIL VN 3 (not further specified): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8

(40)

Species	:	Rabbit
Concentration	:	20 mg
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	8
Vehicle	:	other: none
PDII	:	
Result	:	not irritating
Classification	:	not irritating

Method	:	other: Gemeinschaftsarbeiten der DGF: 54. Mitteilung. Empfehlungen fuer Hautvertraeglichkeitspruefungen. Fette, Seifen, Anstrichmittel, 73, 467-469 (1971)
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No irritating effects, but very slight erythema on the scarified skin of 1/8 animals.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study, well documented.

(102)

Species	:	Rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Patch-Test; Federal Hazardous Substances Act, Sect. 101.11
Year	:	
GLP	:	No
Test substance	:	other TS: Zeofree 80

(108)

Species	:	Rabbit
Concentration	:	190 mg
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	Water
PDII	:	.29
Result	:	not irritating
Classification	:	not irritating
Method	:	other:
Year	:	1992
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The substance was applied as aqueous suspension (17 % w/w = approx. 0.38 g/ml), 0.5 ml = 190 mg onto the intact and scarified skin.
Result	:	Slight erythemas were seen in 4/6 animals 0.5 h after 24-h exposure. No signs of irritation after 72 h.
Test substance	:	Tixosil 63 (approx. 100 % SiO2), CAS name: Silica, precipitated, CAS No. 112926-00-8
Reliability	:	(1) valid without restriction 1c: Meets national standard methods
Flag	:	Critical study for SIDS endpoint

(166)

Species	:	Rabbit
Concentration	:	33 mg
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6

Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: see Remark
Year	:	
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Method: 6 animals treated on intact and abraded skin Results: Slightly erythema (24 hours)
Test substance	:	Tixosil 375: CAS name: Silica, precipitated, CAS No. 112926-00-8
Reliability	:	(1) valid without restriction 1c: Meets national standard methods

(165)

5.2.2 EYE IRRITATION

Species	:	Rabbit
Concentration	:	100 mg
Dose	:	
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	3
Vehicle	:	None
Result	:	not irritating
Classification	:	not irritating
Method	:	Other: Draize-Test; Hazardous Substances, Part 191, Section 12, Federal Register, Vol. 37, No. 83, FDA, Washington
Year	:	1978
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No irritating response at any time after exposure (24 – 96 h).
Test substance	:	Aerosil 200 (not further specified): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study

(56)

Species	:	Rabbit
Concentration	:	100 mg
Dose	:	
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	3
Vehicle	:	None
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1990
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	There were weakly irritating effects on the conjunctivae only: redness score 2 (of 4) in all animals after 1 h, 2 and 1 after 24 h and reversible by 72 h. Chemosis and discharge was very slight only 1 h after application (score 1).
Test substance	:	Sident 9, >98% (SiO_2), Na20 <1%, Al_2O_3 <0.2%, SO_3 <0.8%, Fe_2O_3

<0.03%: CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(59)

Species : Rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : not irritating
Classification : not irritating
Method : other: Draize-Test; Hazardous Substances, Part 191, Section 12, Federal Register, Vol. 37, No. 83, FDA, Washington
Year : 1972
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Test substance : SIPERNAT 22S >98 % (SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Surface area (Ströhlein): 160 - 195 m2/g
Primary particle size: see Test Condition.

Reliability : (1) valid without restriction
1b: Comparable to guideline study

(41)

Species : Rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : not irritating
Classification : not irritating
Method : other: Draize-Test; According to Draize, J. H.: Appraisal of the safety chemicals in foods, drugs and cosmetics. The association of food and drug officials of the United States, 1959
Year : 1974
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Method: The substance was suspended in distilled water.
With or without eye irrigation after 2 and 4 sec., resp. (Grace 1974) and as powder or suspension (Grace 1976)

Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8

Reliability : (1) valid without restriction
1b: Comparable to guideline study

(93) (95)

Species : Rabbit
Concentration : 100 mg
Dose :
Exposure time :
Comment : not rinsed
Number of animals : 6

Vehicle	:	None
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Federal Hazardous Substance Act (1973)
Year	:	1978
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	All four product types produce no but -in isolated cases-very slight and transient irritating effects on the conjunctivae only: redness score 1 (of 4).
Test substance	:	ZEO 49, ZEOSYL 113, ZEOSYL 200, and ZEOFREE 153 (not further specified): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(2) valid with restrictions 1b: Comparable to guideline study
Flag	:	Critical study for SIDS endpoint
		(117) (118) (119) (120)
Species	:	Rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other: Federal Hazardous Substances Act, Sect. 191.12
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Method: the substance was applicated as an aqueous slurry (50 % w/v)
Test substance	:	ZEOFREE 80: CAS-Name: Silica, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study
		(108)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	Rat
Sex	:	Male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	5 days
Frequency of treatm.	:	6 h/d
Post exposure period	:	1 or 3 months
Doses	:	1, 5, 25 mg/m3
Control group	:	yes, concurrent no treatment
NOAEL	:	= 5 mg/m³
LOAEL	:	= 25 mg/m³
NOEL	:	= 1 mg/m³
Method	:	other: in accordance with OECD Guide-line 412, 12 May 1981 and directive 92/69/EEC, 29 Dec. 1992

Year : 2003
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Remark : Comparative study including three synthetic amorphous silica: Zeosil 45 (precipitated), Syloid 74 (silica gel), and CAB-O-SIL M5 (pyrogenic)(see 5.4 other entries).

Result : CLINICAL SIGNS of TOXICITY:
None particular, except transient decreased breathing frequency. Body weight normal; no mortality.

LUNG WEIGHT and LYMPH NODES:
Slight increases in lung weights of the high-dose group, statistically significant absolute weights in males and relative weights in females, increase in relative weights of tracheobronchial lymph nodes in females of the high-dose group.

CELL DIFFERENTIATION in lavage:
After 5 d, the absolute and relative number of neutrophils increased significantly in both genders, the relative (not the absolute) number of macrophages decreased concomittantly (p. 23, Tab. 5 + 6). Slight, but statistically significant shifts were also seen at the low-exposure level (Tab. 6.1: relative changes). After recovery, the cell stimulating effect passed away again, but a slight significant positive trend was noted in the high-dose group of males (concomittantly a slight decrease in macrophages as compared with the control). Slight trends were also seen in the mid-dose group, but only reflected in the relative neutrophil increases, and just at the margin of statistical significance for the male group (5 mg/m3) (Tab. 6.1). In the reference group (crystalline silica), time-related, inverse shifts were observed in neutrophils and macrophages, more pronounced in males. No treatment-related changes were seen in the low-dose group.

BIOCHEMICAL PARAMETERS:
Significant increases in enzymes and protein levels were found only at the high-dose exposure, which completely reversed after recovery (Tab. 7). TNF-alpha showed no difference from the control in any group. The OH-proline content revealed no treatment-related changes.

MACROSCOPIC EXAMINATION:
no particular findings

HISTOPATHOLOGICAL EXAMINATION:
Histologically manifested changes were hypertrophy and hyperplasia of the brochiolar epithelium in 1/5 males and 2/5 females (high dose). No case occurred in the recovery groups. Because of the very rare occurrence in rats, this lesion was considered treatment-related.
very slight to slight polymorphonuclear leukocyte infiltration (inflammation response) at all dose levels, but not in the control (Tab. 10.1).
The incidence and severity was not clearly dose-related, 1/5 very slight case at the low dose level in the male and female group, respectively.
This effect was occasionally observed in the recovery groups, but also in the control groups to the same extent (Tab. 10.2).

The authors considered this lesion to be unrelated to exposure. In recovery high-dose groups, tendency of accumulation of alveolar macrophages and hyperemic capillaries, unusual type-II hyperplasia 1/5 males (Tab. 10.3).

SILICON CONTENT:
One day after exposure, 30 - 40 µg Si were analysed in lungs of high-dose animals, which was below detection limit after 1 month recovery (<25 µg). On the contrary, in the crystalline silica group, Si accumulation was 4-5x

higher (150 - 160 µg) and still persisted on a high level after recovery of 1 month (80 µg in females, 140 µg in males). [note: no determinations carried out in the low and mid-dose groups] No increased Si levels were observed in the lymph nodes in any group tested.

Test condition : ANIMAL GROUPS: Three groups with 10 male and 10 female animals were used, exposed to the test article. 10 animals per sex served as untreated control groups. One extra group was exposed to 25 mg/m3 crystalline silica as a positive control group.
Satellite groups of 10 animals per sex were exposed correspondingly and kept for a recovery period of one and three months.

TEST PARAMETERS:
In addition to the comprehensive standard inspection, lung lavage was examined as well as the OH-proline and Si content of the lung and tracheobronchial lymph nodes were determined. At necropsy, 5 animals per group and sex were lavaged acc. to standard procedure. The lavage was used for white blood cell count, viability and cell differentiation (eosinophils, neutrophils, lymphocytes, monocytes/ macrophages, viable cells). The supernatant of the lavage was used for determination of biochemical parameters (total protein, albumin, ALP, LDH, N-acetyl glucosaminidase (NAG), SOD, GSH, and TNF-alpha).

TEST SYSTEM:
Nose-only exposure

AEROSOL GENERATION:
Miniature screw conveyor, a dust feeder, (Institute´s design) connected to a low-velocity eductor in which the test material was aerolised. The eductors were operated with compressed humidified air.

EXPOSURE LEVELS and PARTICLE SIZE:
Mean actual concentrations: 1.16 (+-0.36), 5.39 (+-0.58), 25.2 (+-1.5), and for the reference group 24.4 (+-2.9) mg/m3. Mass median aerodynamic diameter of particle size distribution (MMAD) = 2.83, 3.23, 3.27, and for the reference group 2.08 µm. [Note: This particle size distribution is artificial and experimentally produced, but the commercial product has a mean particle size of about 100 µm due to agglomeration of primary particles.] The test material was aerosolised and diluted with a defined amount of humidified air at the entrance of each exposure unit.

STATISTICS:
Various procedures acc. to the parameters under test (p. 19/20)

Test substance : ZEOSIL 45: CAS name, Silica, precipitated, crystalline-free; CAS No. 112926-00-8, impurities: Na (1.9 %), S (0.8 %), Al (0.045 %), Fe (0.02 %), Ca 0.06 %

Conclusion : The high exposure concentration (25 mg/m3) induced substance-related effects which reflect an inflammatory response of the lung tissue associated with morphological tissue reaction. These tend to disappear during recovery, but apparently not completely, but show clear signs of reversibility.
Effects in the mid exposure concentration (5 mg/m3) were confined to a very slight increase in the relative neutrophil count with concomitant decrease in the relative macrophage count at the day after exposure, but only statistically significant in males. There were no morphological tissue changes.
No effects were noted at the low-concentration level (1 mg/m3).
It is concluded that the NOEL(sub-acute) is at 1 mg/m3. The NOAEL could be defined as 5 mg/m3.

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(188)

Type	:	Sub-acute
Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	5 days
Frequency of treatm.	:	6 h/d
Post exposure period	:	1 or 3 months
Doses	:	1, 5, and 25 mg/m3
Control group	:	yes, concurrent no treatment
NOAEL	:	= 5 mg/m³
LOAEL	:	= 25 mg/m³
NOEL	:	= 1 mg/m³
Method	:	other: in accordance with OECD Guide-line 412, 12 May 1981 and directive 92/69/EEC, 29 Dec. 1992
Year	:	2003
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Comparative study including three synthetic amorphous silica: Zeosil 45 (precipitated), Syloid 74 (silica gel), and CAB-O-SIL M5 (pyrogenic)(see 5.4 other entries).
Result	:	CLINICAL SIGNS of TOXICITY: None particular. Body weight normal; no mortality.

LUNG WEIGHT and LYMPH NODES:
Significant mean increase in lung weight of the high-dose group (Tab. 11.1). Apparent increases in weights of tracheobronchial lymph nodes showed no dose-response relationship.

CELL DIFFERENTIATION in lavage:
After 5 d, the absolute and relative number of neutrophils increased significantly, the relative (not the absolute) number of macrophages decreased concomittantly (p. 22, Tab. 5 + 6). Slight, but statistically significant shifts were also seen at the mid-exposure level (Tab. 6.1: relative changes).
After recovery, the cell stimulating effect passed away again, but a slight significant positive trend for the macrophage count was noted in the mid-dose group after 1 month, but not after 3 months.
No treatment-related changes were seen in the low-dose group.

BIOCHEMICAL PARAMETERS:
Significant increases in enzymes and protein levels were found only at the high-dose exposure, which completely reversed after recovery (Tab. 7).
TNF-alpha showed no significant difference from the control in any group.
The OH-proline content revealed no treatment-related changes, but 3 months after recovery an increase was measured in the high-dose group.

MACROSCOPIC EXAMINATION:
no particular findings

HISTOPATHOLOGICAL EXAMINATION:
Histologically manifested changes were very slight hypertrophy of the brochiolar epithelium in 3/5 males (high dose). No case occurred in the recovery group.
- accumulation of alveolar macrophages accompanied by a few granulocytes/neutrophils in 3/5 animals (high dose) and 1/5 (mid-dose).
n recovery groups: no particular findings

SILICON CONTENT:

One day after exposure, 76 µg Si (average) were analysed in lungs of high-dose animals, which was below detection limit after 1 month recovery (<15 µg).[note: no determinations carried out in the low and mid-dose groups] No increased Si levels were observed in the lymph nodes.

Test condition : ANIMAL GROUPS:
Three groups with 10 male animals were used, exposed to the test article. 6 animals served as untreated control group. Selection of males only, because males tended to be more sensitive than females (as shown in the study with ZEOSIL 45). Satellite groups of 10 male animals were exposed correspondingly and kept for a recovery period of one and three months.

TEST PARAMETERS:
In addition to the comprehensive standard inspection, lung lavage was examined as well as the OH-proline and Si content of the lung and tracheobronchial lymph nodes were determined. At necropsy, 3 animals of the control group and 5 animals per treated group were lavaged acc. to standard procedure. The lavage was used for white blood cell count, viability and cell differentiation (eosinophils, neutrophils, lymphocytes, monocytes/ macrophages, viable cells). The supernatant of the lavage was used for determination of biochemical parameters (total protein, albumin, ALP, LDH, N-acetyl glucosaminidase (NAG), SOD, GSH, and TNF-alpha).

TEST SYSTEM:
Nose-only exposure

AEROSOL GENERATION:
Miniature screw conveyor, a dust feeder, (Institute´s design) connected to a low-velocity eductor in which the test material was aerolised. The eductors were operated with compressed humidified air.

EXPOSURE LEVELS and PARTICLE SIZE:
Mean actual concentrations: 0.94 (+-0.13), 5.13 (+-0.21), and 25.1 (+-0.5) mg/m3.
Mass median aerodynamic diameter of particle size dstribution (MMAD) = 1.71, 1.60, and 1.57 µm. [Note: This particle size distribution is artificial and experimentally produced, but the commercial product has a mean particle size of about 100 µm due to agglomeration of primary particles.]
The test material was aerosolised and diluted with a defined amount of humidified air at the entrance of each exposure unit.

STATISTICS: Various procedures acc. to the parameters under test (p. 19/20)

Test substance : Syloid 74, CAS-Name: Silica gel, precipitated, crystalline-free; CAS No. 112926-00-8, purity ca. 100 %

Conclusion : The high exposure concentration (25 mg/m3) induced substance-related effects which reflect an inflammatory response of the lung tissue, associated with a morphological tissue response (hypertrophy). These tend to disappear during recovery, but apparently not completely, but show clear signs of reversibility.
Effects at the mid-exposure concentration (5 mg/m3) were confined to a very slight, but significant increase in the relative neutrophil count with concomittant decrease in the relative macrophage count at the day after exposure. There were no morphological tissue changes.
No effects were noted at the low-concentration level (1 mg/m3).
It is concluded that the NOEL(sub-acute) is at 1 mg/m3. The NOAEL could be defined as 5 mg/m3.

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(189)

Type : Sub-acute

Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	5 days
Frequency of treatm.	:	6 h/d
Post exposure period	:	1 or 3 months
Doses	:	1, 5, 25 mg/m3
Control group	:	yes, concurrent no treatment
LOAEL	:	= 5 mg/m³
NOEL	:	= 1 mg/m³
Method	:	other: in accordance with OECD Guide-line 412, 12 May 1981 and directive 92/69/EEC, 29 Dec. 1992
Year	:	2003
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Comparative study including three synthetic amorphous silica: Zeosil 45 (precipitated), Syloid 74 (silica gel), and CAB-O-SIL M5 (pyrogenic)(see 5.4 other entries).
Result	:	CLINICAL SIGNS of TOXICITY: None particular. Slight significant body-weight loss during the exposure period of 5 days; no mortality. LUNG WEIGHT and LYMPH NODES: Significant mean increases in relative and absolute lung weights of the mid- and high-dose groups (Tab. 11.1). No increases in weights of the tracheobronchial lymph nodes. CELL DIFFERENTIATION in lavage: After 5 d, the absolute and relative number of neutrophils increased significantly in both the mid- and high-dose group, the relative (not the absolute) number of macrophages decreased concomittantly (p. 21/22, Tab. 5 + 6). After 1-month recovery, the cell stimulating effect passed away, but in the mid- and high-dose groups, there were still slight, but significant increases in the percentages of the neutrophil counts with concomittant decreases in relative macrophage counts, but no longer after 3 months (Tab. 6). No changes were observed in the total cell numbers. No treatment-related changes were seen in the low-dose group. BIOCHEMICAL PARAMETERS: Significant increases in enzymes, protein, and the TNF-alpha levels were found at the mid- and high-dose exposure, which completely reversed after recovery (Tab. 7). The OH-proline content revealed no treatment-related changes. MACROSCOPIC EXAMINATION: no particular findings HISTOPATHOLOGICAL EXAMINATION: Histologically manifested changes were - very slight hypertrophy of the brochiolar epithelium in 3/5 animals (mid dose) and slight hypertrophy in 4/5 (high dose). No case occurred in the recovery group. - accumulation of alveolar macrophages accompanied by a few granulocytes/neutrophils in 3/5 animals (mid-dose) and 5/5 (high dose). In 3/5 high-dose animals, alveolar accumulation of macrophages was accompanied by infiltration of polymorphonuclear leukocytes (Tab. 10.1). Following recovery of 1 month, very slight macrophage accumulation was

still present in the lungs 3/5 high-dose animals, but without epithelial changes and leukocyte infiltration.
At that time lymph nodes also contained aggregates of macrophages [1/5 mid-dose, 5/5 high-dose] (Tab. 10.2).
Following recovery of 3 months, focal accumulation of macrophages was still present in the lungs of 2/5 high-dose animals. The lymph nodes of 1/5 mid-dose and 5/5 high-dose animal still contained macrophage aggregates.

SILICON CONTENT:
One day after exposure, 43 µg Si (average) were analysed in lungs of high-dose animals, which was below detection limit after 1 month recovery (<15 µg). [note: no determinations carried out in the low and mid-dose groups]

No increased Si levels were observed in the lymph nodes (below detection limit (<15 µg).

Test condition : ANIMAL GROUPS:
Three groups with 10 male animals were used, exposed to the test article. 6 animals served as untreated control group. Selection of males only, because males tended to be more sensitive than females (as shown in the study with ZEOSIL 45). Satellite groups of 10 male animals were exposed correspondingly and kept for a recovery period of one and three months.

TEST PARAMETERS:
In addition to the comprehensive standard inspection, lung lavage was examined as well as the OH-proline and Si content of the lung and tracheobronchial lymph nodes were determined.
At necropsy, 3 animals of the control group and 5 animals per treated group were lavaged acc. to standard procedure. The lavage was used for white blood cell count, viability and cell differentiation (eosinophils, neutrophils, lymphocytes, monocytes/ macrophages, viable cells). The supernatant of the lavage was used for determination of biochemical parameters (total protein, albumin, ALP, LDH, N-acetyl glucosaminidase (NAG), SOD, GSH, and TNF-alpha).

TEST SYSTEM:
Nose-only exposure

AEROSOL GENERATION:
Miniature screw conveyor, a dust feeder, (Institute´s design) connected to a low-velocity eductor in which the test material was aerolised. The eductors were operated with compressed humidified air.

EXPOSURE LEVELS and PARTICLE SIZE:
Mean actual concentrations: 1.39 (+-0.15), 5.41 (+-0.34), and 25.3 (+-0.9) mg/m3.

Mass median aerodynamic diameter of particle size dstribution (MMAD) = 1.2 - 1.3 µm or 2.2 - 3.5 µm (depending on the technical device used: see p. 20). [Note: This particle size distribution is artificial and experimentally produced, but the commercial product has a mean particle size of about 100 µm due to agglomeration of primary particles.]

The test material was aerosolised and diluted with a defined amount of humidified air at the entrance of each exposure unit.

STATISTICS:
Various procedures acc. to the parameters under test (p. 19/20)

Test substance : CAB-O-SIL M5: CAS-Name: Silica, amorphous, fumed (pyrogenic), crystalline-free; CAS-No.: 112945-52-5, purity ca. 100 %

Conclusion : The pyrogenic silica seems to induce a more marked inflammatory reaction than the other tested precipitated amorphous silica compounds:
The mid and high exposure concentration (5 and 25 mg/m3) induced

substance and dose-related effects which reflect an inflammatory response of the lung tissue. These tend to disappear during recovery, but slowly and not completely during the observation time. After 3 months recovery, macrophage accumulation was still present without tissue lesions. The lymph nodes were also affected.

No effects were noted at the low-concentration level (1 mg/m3), except a transient body-weight loss noted throughout all treated groups.

It is concluded that the NOEL(sub-acute) is at 1 mg/m3.
Based on a hypertrophic effect already observed at the mid-dose level, the LOAEL is defined as 5 mg/m3.

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(190)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	13 weeks
Frequency of treatm.	:	6 hours/day, 5 days/week
Post exposure period	:	up to 52 weeks
Doses	:	1.3, 5.9 or 31 mg/m3 (mean analytical values)
Control group	:	Yes
NOAEL	:	= 1.3 mg/m³
LOAEL	:	= 5.9 mg/m³
NOEL	:	< 1.3 mg/m³
Method	:	other: acc. to OECD Guide-line 413, see Method
Year	:	1985
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Comparative study including Aerosil R974 (fumed, hydrophobic), Sipernat 22S (precipitated, hydrophil) as well as quartz (crystalline).

Special modifications as compared with standard study:

Examinations primarily focused upon changes in the lung, respiratory tract, and regional (hilus and mediastial) lymph nodes, including collagen and silica determinations in the lung.

Post-exposure recovery period up to one year was enclosed: 10 m / 10 f animals per group sacrificed after 13 wks, 50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks).

Haematology and urinalysis were conducted 5x periodically up to week 65 (including recovery). Blood chemistry was carried out group-wise on autopsy after defined intervals up to week 66 (including recovery).

Result : CLINICAL OBSERVATION
The respiration rate showed a concentration-related increase when compared to the controls (only qualitatively evaluated); the body-weight gain was slightly depressed. (Degussa 1987, p. 27)

HAEMATOLOGY / BLOOD CHEMISTRY
Red blood cell count and hemoglobin were statistically higher in males exposed to 30 mg/m3, but not in females.
White blood cell count due to increases in the numbers of neutrophilic leukocytes were elevated in both males and females of the 6- and 30-mg

groups, but concentration-response relationship was poor. After 3 months recovery, these blood parameters normalized.

Blood chemistry and urine analysis were without significant findings.

PATHOLOGY
At autopsy after exposure, swollen and spotted lungs and enlarged mediastinal lymph nodes were observed, the degree of severity being treatment-related.

At 6 and 30 mg/m3, the lung weights and the collagen content in the lungs were clearly increased, most pronounced in males showing this effect also at the 1-mg/m3 level.

The above-mentioned effects gradually subsided after the exposure period, but in males exposed to 6 and 30 mg/m3 the collagen content was still above control values at the end of the study.

SILICA DEPOSITION
Silica could be detected in lungs only in relatively small amounts at the end of the exposure period, on the average 0.2 mg in all animals of the 30-mg groups. Only one male exposed to 30 mg/m3 showed a small amount of silica in the regional lymph node. During the post-exposure observation period, no silica could be recovered from any animal.

HISTOLOGY
The microscopic examination at the end of exposure period showed accumulation of alveolar macrophages and granular material, cellular debris, polymorphonuclear leucocytes, increased septal cellularity, alveolar bronchialisation, focal interstitial fibrosis, cholesterol clefts and granuloma-like lesions in the lung.
The granuloma-like lesions did not show fibroblastic activity and hyalinization and regressed during recovery.
Accumulation of macrophages was seen in the mediastinal lymph node (disappeared after wk 39 post-exposure). Treatment-related, microscopic changes in the nasal region were occasionally found at the end of exposure period such as focal necrosis slight atrophy of the olfactory epithelium.
All types of pulmonary lesions were more marked in males than in females.
A level of 1.3 mg/m3 induced only slight changes, which generally recovered quickly, therefore the NOEL is lower than 1.3 mg/m3.
During the post-exposure observation period the changes in lungs and lymph nodes recovered totally or partly (see conclusions).
Interstitial fibrosis was not noted directly after the exposure period, but appeared with a delay, for the first time observed after 13 wks post-exposure: increasing incidence especially in 30-mg rats, and a few in the 6-mg group (p. 44), but decreased in severity and frequency until the end of the study (p. 51).

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.
Particle size distribution:
No MMAD range given because of analytical limitations (see below):
The very small primary particles (<6 - approx. 45 nm, calculated as the arithmetic mean of transmission electron micrograph magnification) [comp. Degussa AG 1987, part I, p. 62] form agglomerates and aggregates.
Because of the weakness of bonds and the electrostatatic charge of particles, it was impossible to determine the aerodynamic agglomerate/aggreagate size distribution in the test atmosphere.
The range of the geometric agglomerate/aggregate size distribution was 1 to about 120 µm for the amorphous silicas with a maximum at approx. 10

µm (Degussa 1987, p. 13)

Test substance : Aerosil 200: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5
Surface area (BET): 150 - 200 m2/g Particle size: see Test Condition

Conclusion : The NOEL is <1.3 mg/m3 based on the pulmonary response (collagen stimulation and increase in lung weight: not statistically significant).

At the 1 mg-level, the effects were mild, completely cured after 13 wks recovery. There were no histologically manifested tissue changes. Therefore, depending on the pathological relevance placed on observed effects, this exposure concentration may also be defined as NOAEL.

Inhaled amorphous silica provokes an inflammatory response in the respiratory tract of rats, in particular the lung, at low concentration.

A progression process of any lesion was not observed like that seen after quartz exposure, i.e. all observations suggest reversibility, although rather slow.

All synthetic amorphous silica was completely cleared from the lung, but clearance is different for various silica (see also other entries): for Aerosil very quickly.

The granuloma-like lesions were not progressive, i.e. no silicogenic nodules formed (no silicosis).

Mortality was not affected in any of the groups. The only clinical sign noted with Aerosil 200 was increased respiration rate.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint

24.09.2004 (65) (164)

Type : Sub-chronic
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : Inhalation
Exposure period : 13 weeks
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : up to 52 weeks
Doses : 35 mg/m3 (mean analytical values)
Control group : Yes
Method : other: see Method
Year : 1985
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study including Aerosil R 974 (fumed, hydrophobic), Sipernat 22S (precipitated, hydrophil) as well as quartz (crystalline).

Special modifications as compared with standard study:

One high-dosed group only within a combined study (see above).

Examinations primarily focussed upon changes in the lung, respiratory tract, and regional (hilus and mediastial) lymph nodes, including collagen and silica determinations in the lung.

Post-exposure recovery period up to one year was enclosed: 10 m / 10 f

animals per group sacrificed after 13 wks, 50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks).

Haematology and urinalysis were conducted 5x periodically up to week 65 (including recovery). Blood chemistry was carried out group-wise on autopsy after defined intervals up to week 66 (including recovery).

Result : Slightly decreased body weight; the organ weights of lung and thymus were increased. At autopsy swollen and spotted lungs and enlarged mediastinal lymph nodes were observed. Microscopic changes in lungs were accumulation of alveolar macrophages, intra-alveolar leucocytes and increased septal cellularity. Accumulation of macrophages was seen in the lymph nodes. The collagen content in lungs was slightly increased. Greater amounts of silica could be detected in lungs and lymph nodes. During the recovery period the changes disappeared mostly within 26 weeks. Only in the mediastinal lymph nodes slight accumulation of macrophages and the presence of silica could be found during the total observation period.

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.

Particle size distribution:
No MMAD range given because of analytical limitations (see below): The very small primary particles (5 - approx. 30 nm, calculated as the arithmetic mean of transmission electron micrograph magnification) [comp. Degussa AG 1987, part I, p. 65] form agglomerates and aggregates. Because of the weakness of bonds and the electrostatic charge of particles, it was impossible to determine the aerodynamic agglomerate/aggregate size distribution in the test atmosphere.
The range of the geometric agglomerate/aggregate size distribution was 1 to about 120 µm for the amorphous silicas with maxima at approx. 10 and 100 µm (Reuzel et al. 1991, p. 342).

Test substance : SIPERNAT 22S >98 % (SiO_2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Surface area (Ströhlein): 160 - 195 m2/g
Primary particle size: see Test Condition

Conclusion : SIPERNAT 22S (35 mg/m3) induced changes that were similar to those of Aerosil 200 (see previous entry). The changes quickly recovered, although silica was still detectable in the lungs after 26 weeks of recovery, and in the lymph nodes even at the end of the observation period.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint

(65) (164)

Type : Chronic
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : Inhalation
Exposure period : a) up to 1 year b) 1/2 year
Frequency of treatm. : 8 hours/day, 5 days/week
Post exposure period : a) without recovery b) up to 12 months
Doses : 53 mg/m3
Control group : Yes
LOAEL : = 53 mg/m^3
Method : other: single-dose inhalation study
Year : 1957
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Part of a comprehensive testing programme (see other entries): Whole-body exposure: active dust exposure for 8 h/d (dust-disseminating apparatus: mechanical agitation and compressed air-jet through Venturi tube into inhalation chamber), and passive exposure (dust settling) for the remainder 16 h/d.

Dust analysis and sampling: millipore filter method: average air concentration was 1.5 mg/cubic foot = 53 mg/m3, with most measurements between 0.7 and 2.4 mg/cubic foot (= 25 and 85 mg/m3, respectively).

Size distribution of the particles (an electrostatic precipitator used): 1- to 10-µm particles accounted for some 85 % of the dust mass in the chamber.

a) 35 animals were used in a first set (exposure <=12 months)
b) 25 animals were used in a 2nd set (exposure 6 months, followed by recovery period up to 12 months).

Control group: 42 animals in normal environment, autopsied at 6-months intervals.

Remark : Very detailed descriptive and visual documentation of macroscopic and histological lung pathology over time of exposure and post-exposure, quantitative evaluation limited by the low number of animals and absence of the documentation of the control group (For the experimental group only those pathological conditions which were not present in the control animals are reported, p. 131).

Result : MORTALITY:
Death rate was high, in most cases apparently caused by treatment-related pulmonary changes. 26/35 (75 %) died in Experiment a), 11/25 (44 %) in Experiment b), most of them during exposure to dust. Death rate decreased significantly during recovery.

AUTOPSY FINDINGS:
- Focal pigmentation: conspicuous after exposure of >= 3 months, profusely scattered small, dark-pink discrete but irregular subpleural foci of reaction, Congestion of the lungs: dominant after 3 months,
- Lymph node enlargement: visible after 3 months,
- Lung emphysema: incipient tendency after 4 months of exposure, macroscopically visible: lungs distended, superficial aveoli dilated,
- Atelectasis: tendency in some rats after 4 to 5 months.

After 6 months of exposure:
- aggravation of focal pigmentation visible as reddish-tan foci of dust reaction,
- moderately, well-established generalized emphysema,
- lymph nodes greatly enlarged and their firm consistency markedly increased.

The majority of the rats spontaneously died from pulmonary vascular obstruction and emphysema, commencing with the 4th month and continuing until the 9th month.

No changes were noted in other organs of the body.

HISTOLOGICAL CHANGES:
- Invasion of the lymphatic system of the lung by mononuclear macrophages forming clusters, of plasma cells, and lymphocytes;
- Production of large vacuolated cells within the alveolar spaces, with the cytoplasm having foamy appearance, macrophages apparently fused to giant cells;
- progressive nodule formation in the lung parenchyma with peri- and paravascular, in some cases para-brochiolar distribution and accumulation, consisting of central macrophages and surrounding plasma cells, the

nodules enveloped by an epithelial layer of cells.
- Some necrosis was noted in the central zone of the nodules, but not in the peripheral zone (p. 135).
- There was a progressive tendency to fibrosis in the nodules.
- There was evidence of progressive emphysematous processes around the nodules.

SILICA BURDEN of the lung: The development of pulmonary lesions was accompanied by a progressive and rapid increase in silica in the lung. Average lung content reached 1.5 mg SiO2 (= approx. 10 % of lung ash) after 3 months, thereafter residing on a steady-state level. Post-exposure levels subsided to about 0.3 mg SiO2 per lung.

RECOVERY PHASE:
On removal from dust environment after six months of exposure, progressive anatomical recovery continued, the lung weights decreased constantly: After 6 to 12 months in normal air, rat lungs showed very little emphysema and very little in the nature of dust foci with lymph nodes only slightly enlarged. After 12 months, most of the pathological changes were reversed to almost normal: The cellular nodules, perivascular infiltrations and emphysema were almost completely resolved.

Test substance : Dow Corning Silica obtained from Degussa: approx. 98 % (SiO2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5 [Note: Based on the flame process, Dow silica reported to be equivalent to Cabot material, Cab-O-Sil, but different from the Degussa product Aerosil as to polymorphous structure (demonstration by electron photomicrograph)].

Conclusion : High subchronic/chronic exposure to amorphous silica produces severe progressive pulmonary inflammation associated with increased mortality of the animals, primarily through partial obstruction of the pulmonary vasculature combined with pulmonary insufficiency due to emphysema. Acc. to authors, the emphysema noted seem to be characterized mainly by a distention of alveolar ducts without any associated bronchitis or bronchiolitis, presumably resembling that found in coal miners ("focal emphysema") (p. 145).

Although there are signs of early nodular fibrosis, no classical nodular silicosis occurs. The progress of lesions is associated with a high lung burden of silica which apparently cannot be removed efficiently anymore due to overload. As a consequence, excess silica not being cleared mechanically or by dissolution is apparently deposited to the pulmonary lymphatic system.

Pathological changes that occurred after 6 months of exposure were almost completely reversible after several months on cessation of exposure after rapid elimination of deposited silica.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessement.

Flag : Critical study for SIDS endpoint

24.09.2004 (178)

Type : Chronic
Species : guinea pig
Sex : male/female
Strain : other: Albino, inbred
Route of admin. : Inhalation
Exposure period : 12 and 24 months
Frequency of treatm. : 8 hours/day
Post exposure period : up to 13 months
Doses : 53 mg/m3
Control group : Yes
LOAEL : = 53 mg/m³

Method : other: single-dose inhalation study
Year : 1957
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Part of a comprehensive testing programe (see other entries):

Whole-body exposure: active dust exposure for 8 h/d (dust-disseminating apparatus: mechanical agitation and compressed air-jet through Venturi tube into inhalation chamber), and passive exposure (dust settling) for the remainder 16 h/d.

Dust analysis and sampling: millipore filter method: average air concentration was 1.5 mg/cubic foot = 53 mg/m3, with most measurements between 0.7 and 2.4 mg/cubic foot (= 25 and 85 mg/m3, respectively).

Size-frequency distribution of the particles (an electrostatic precipitator used): 1- to 10-um particles accounted for some 85 % of the dust mass in the chamber.
Several test protocols were used:
a) 40 animals exposed for up to 24 months and interim sacrifices every 2 months (Tab. 3);
b) 15 animals exposed for 12 months with variable recovery (Group II, Tab. 2), and 18 animals exposed for 24 months with variable recovery up to 1 year (Tab. 3);
c) 17 animals exposed for 12 months, with recovery for one month, followed by another exposure of 8 to 24 hours (Group III, Tab. 2).
80 guinea pigs of both sexes were kept in normal environment as controls and were sampled at intervals ranging from 1 month to 36 months.

Only those pathological states which were observed in exposed animals and did not occur in control animals were recorded.

Remark : Very detailed descriptive and visual documentation of macroscopic and histological lung pathology over time of exposure and post-exposure.

Result : MORTALITY:
Only two animals died, both deaths unrelated to dust exposure (contrary to rat experiments, see other entry).

AUTOPSY FINDINGS / HISTOLOGICAL CHANGES:
The fundamental pattern of a chronic reaction of the lung tissue was firmly established by the end of 4 months:
- Focal pigmentation: mild reaction after exposure of 1 months,
- Lymph node enlargement: marked after 1 months without increasing tendency over time, including hepatic ones.
- Lung emphysema: incipient tendency after 4 to 8 months of exposure
- Atelectasis: macroscopically not conspicuous, but histologically.
- No development of nodules.

HISTOLOGICAL CHANGES:
The dominant response consisted of periductal and peribronchiolar intra-alveolar accumulations of giant cells.
At about 8 to 12 months incipient atrophy of infiltrated alveoli apparently led to compensatory expansion of adjacent alveoli. There was a combined effect of atelectasis and consolidation around brochioli, but at the expense of brochioli distortion. Incipient fibrosis around bronchioli and shrunken alveoli was noted at this stage. By the end of the second year, there was a marked tendency toward cuboidal epithelization of atelectatic alveoli.

The lymphoid tissue was affected only to a low extent, although medullary hyperplasia with the formation of slight amounts of reticulum was prominent during the second year of exposure. No periadenitis and sinus catarrh as

well as fibrosis were noted in the lymph nodes.

SILICA BURDEN of the lung:
The development of pulmonary lesions was accompanied by a progressive and rapid increase in silica in the lung. Average lung content reached 2.5 mg SiO2 per lung after 12 months, about 4 % of lung-ash weight, and increased disproportionately the following 12 months to about 8 mg per lung (= approx. 12 % of lung ash) (Fig. 1).
After cessation of exposure, silica content rapidly decreased to about 0.6 mg per lung along with a significant decrease in lung ash.

RECOVERY PHASE:
On removal from dust environment after 12 months of exposure, progressive anatomical recovery occurred almost promptly, with no macroscopically visible anomalies after one year of recovery. Residual sequalae of the tissue reactions were emphysema, mural fibrosis, and bronchiolar and ductile stenosis.

Test substance : Dow Corning Silica obtained from Degussa: approx. 98 % (SiO2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5 [Note: Based on the flame process, Dow silica reported to be equivalent to Cabot material, Cab-O-Sil, but different from the Degussa product Aerosil as to polymorphous structure (see other entry on rat).

Conclusion : Chronic exposure to synthetic amorphous silica was non-lethal to guinea pigs, but caused significant inflammatory reactions and pulmonary lesions, however, without apparent disability of the animals. This is in sharp contrast to rats and rabbits.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessement.

Flag : Critical study for SIDS endpoint

24.09.2004 (179)

Type : Chronic
Species : Rat
Sex : Male
Strain : Sprague-Dawley
Route of admin. : Inhalation
Exposure period : 3, 6 and 12 months
Frequency of treatm. : 5.5 - 6 hours/day, 5 days/week
Post exposure period : No
Doses : 15 mg/m3 (total dust); 6 - 9 mg/m3 (respirable <=4.7 um)
Control group : Yes
LOAEL : ca. 6 - 9 mg/m³
Method : other: see Method
Year : 1981
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study with three silica types on three animal species (rat, guinea pig and monkey); whole-body exposure system: 80 rats were used per group. Clinical chemistry, hematology, autopsy and histopathology conducted.

Chamber atmosphere was analyzed gravimetrically at least 3x/d for dust concentration. Particle size distribution was determined dynamically on mass basis by means of an 8-stage Andersen cascade impactor. Additionally, electron microscopy was applied:

Precipitated silica: approx. 46 % <4.7 µm; fumed (precipitated) silica: approx. 65 % <4.7 µm. The respirable dust fraction (4.7 µm as upper limit, based on Andersen cascade impactor analysis) was estimated to be 9

mg/m3 for fumed (precipitated) silica and about 6 - 7 mg/m3 for the precipitated silica.

Result : In the lungs of rats exposed 12 months, a few macrophage aggregates were found in the lungs. Interstitial fibrosis associated with dense collections of most cells appeared in some of the rats of the control and treatment groups, although there was a trend of a more frequent incidence in those exposed to fumed silica, but obscured by the presence in some control animals.

The LOAEL refers to respirable fraction (<= 4.7 um MMAD).

Test substance : Three silica types:
a) pyrogenic (fumed) silica, Cab-O-Sil type [CAS-No.: 112945-52-5], commercial quality (note: in text stated "fume" silica which signifies a non-synthetic material.
Likely to be erroneous);
b) precipitated silica, Hi-Sil, [CAS-No.: 112926-00-8], commercial quality;
c) silica gel, commercial quality

Conclusion : The macrophage aggregating was less pronounced in rats under test conditions than in monkeys and comparable to that in guinea pigs (see other entry). Fibrosis was of minor importance as there was no significant difference from the incidence in the control groups.

Reliability : (4) not assignable
4e: Documentation limited and insufficient for assessment, only one concentration tested

Flag : Critical study for SIDS endpoint

23.09.2004 (103)

Type : Chronic
Species : Monkey
Sex : Male
Strain : Macaca Fascicularis
Route of admin. : Inhalation
Exposure period : 13 and 18 months
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : No
Doses : 15 mg/m3 (total dust); 6 - 9 mg/m3 (respirable <= 4.7 um)
Control group : Yes
LOAEL : ca. 6 - 9 mg/m³
Method : other: see Remark
Year : 1981
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study with three silica types on three animal species (rat, guinea pig and monkey); whole-body exposure system: 10 monkeys were used per group. Exposure period: 13 months (fumed silica and silica gel); 18 months (precipitated silica). Pulmonary function tests, clinical chemistry, hematology, autopsy and histopathology conducted.

Chamber atmosphere was analyzed gravimetrically at least 3x/d for dust concentration. Particle size distribution was determined dynamically on mass basis by means of an 8-stage Andersen cascade impactor. Additionally, electron microscopy was applied:

Precipitated silica: approx. 46 % <4.7 um; fumed (precipitated) silica: approx. 65 % <4.7 um.

The respirable dust fraction (4.7 um as upper limit, based on Andersen cascade impactor analysis) was estimated to be 9 mg/m3 for fumed (precipitated) silica and about 6 - 7 mg/m3 for the precipitated silica.

Remark : Comment:

The test results are suspect because of the probability that the lung damage was completely or partly due to a preexposure with other materials (eventually to asbestos, mica, etc.). The authors have found particles of different shape in macrophage aggregates in the lungs. A part of these particles were identified as mica (KAlSiO3) and kaolin (AlSiO3) (p. 127/136). The presence of quartz or asbestos fibres could not be ruled out by the authors and indicate to an unknown exposure. The monkeys used in this test were shipped to the laboratory (NIOSH) in large bags, which had previously been used to transport asbestos (personal communication). The tests had been also critized because the animals were sacrificed at the end of the exposure period and, therefore, a progression of the described lung effects could not be shown. The results are additionally contradictory to the parallel performed tests with the same test substance with rats and guinea pigs.

Result : LUNG FUNCTION studies indicated changes in lung respiratory volume and ventilatory mechanics in monkeys, more marked after exposure to pyrogenic silica. Following exposure to fume silica, LC (dynamic pulmonary compliance), FVC (Forced vital capacity), IC (inspiratory capacity), TLC (Total lung capacity), FEF (forced expiratory flow) were decreased, while average flow resistance (RL) and closing volume (CV) were increased. Lower lung volumes were also seen in the precipitated silica groups. No changes in lung volume parameters, but in ventilatory performance and mechanical parameters, dynamic lung compliance (CL) and forced expiratory flow (FEF) were observed in monkeys exposed to silica gel.

HISTOPATHOLOGY:
In macrophages in the lungs and tracheal lymph nodes, cytoplasmatic changes, ie. increase in number of vacuoles (indication of presence of silica) were observed, and microprobe studies confirmed the presence of silicon. In the lungs, large numbers of macrophages and mononuclear cell aggregates (bronchioles, alveolar ducts venules, arterioles) were found. In frequency and size the cell aggregates varied with the type of silica (precipitated silica > fumed silica > silica gel).
Reticulin fibres were present in the aggregates in all three groups. In 6/9 monkeys exposed to pyrogenic silica, collagen in varying amount was found in 5 - 50 % of the aggregates, with signs of early nodular fibrosis. In 3/9 animals no or only little collagen was present.
No collagen fibers were seen in aggregates in the lung of monkeys exposed to silica gel, and only very few after exposure to precipitated silica.

Test substance : Three silica types:
a) pyrogenic (fumed) silica, Cab-O-Sil type [CAS-No.:112945-52-5], commercial quality (note: in text stated "fume" silica which signifies a non-synthetic material. Likely to be erroneous);
b) precipitated silica, Hi-Sil, [CAS-No.: 112926-00-8], commercial quality;
c) silica gel, commercial quality.

Conclusion : Acc. to the authors, signs of early nodular fibrosis indicate that fumed silica is more detrimental than precipitated silica or silica gel. The smaller particle size of fumed silica may have been a contributing factor.

High deposition of amorphous silica in macrophages in lung and tracheal lymph nodes was most striking, less pronounced in rat and guinea pig (p. 125; 128). (But see also Remark: Deficiency possibly from confounding exposure to other materials: However, not considered serious by the authors (p.136): reportedly the greatest amount of collagen was seen in the lung of the monkey (silica, fumed) that did not contain the birefrigent crystals. The concentrations of these crystals that contained mica (KAlSiO3) and kaolin (AlSiO3) in most of the lungs was relatively insignificant).

Reliability : (4) not assignable
Meets generally accepted scientific standards, sufficiently documented, however, shortcomings in test conditions (see Remark)

Flag : Critical study for SIDS endpoint

23.09.2004 (103)

Type	:	Chronic
Species	:	guinea pig
Sex	:	Male
Strain	:	Hartley
Route of admin.	:	Inhalation
Exposure period	:	12 months
Frequency of treatm.	:	5.5 - 6 hours/day, 5 days/week
Post exposure period	:	No
Doses	:	15 mg/m3 (total dust); 6 - 9 mg/m3 (respirable <= 4.7 um)
Control group	:	Yes
Method	:	other
Year	:	1981
GLP	:	No
Test substance	:	other TS: several type
Method	:	Comparative study with three silica types on three animal species (rat, guinea pig and monkey); whole-body exposure system: 20 guinea pigs were used per group. Clinical chemistry, hematology, autopsy and histopathology conducted. Chamber atmosphere was analyzed gravimetrically at least 3x/d for dust concentration. Particle size distribution was determined dynamically on mass basis by means of an 8-stage Andersen cascade impactor. Additionally, electron microscopy was applied: Precipitated silica: approx. 46 % <4.7 um; fumed (precipitated) silica: approx. 65 % <4.7 um. The respirable dust fraction (4.7 um as upper limit, based on Andersen cascade impactor analysis) was estimated to be 9 mg/m3 for fumed (precipitated) silica and about 6 - 7 mg/m3 for the precipitated silica.
Result	:	A few macrophages containing particles of amorphous silica were observed in the lungs and lymph nodes of the animals, similar to rats.
Test substance	:	Three silica types: a) pyrogenic (fumed) silica, Cab-O-Sil type [CAS-No.:112945-52-5], commercial quality (note: in text stated "fume" silica which signifies a non-synthetic material. Likely to be erroneous); b) precipitated silica, Hi-Sil, [CAS-No.: 112926-00-8], commercial quality; c) silica gel, commercial quality
Reliability	:	(4) not assignable 4e: Documentation limited and insufficient for assessment, but useful in relation to findings of others.
Flag	:	Critical study for SIDS endpoint

(103)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	13 weeks
Frequency of treatm.	:	daily, continuous
Post exposure period	:	No
Doses	:	approx. 0.5, 2 and 6.7 % (based on analytical values) [mean estimated doses: 300-330, 1200-1400, 4000-4500 mg/(kg*d)]
Control group	:	Yes
NOAEL	:	= 6.7 %
Method	:	other: see Remark
Year	:	1981
GLP	:	No

Test substance	:	as prescribed by 1.1 - 1.4
Method	:	10 m / 10 f test animals per group, 5 per sex and cage; examined parameters comparable to OECD-Guidelines. Analysis of homogeneity of test substance has been performed.
Result	:	No clinical symptoms or other findings including haematological, blood-chemical and urinary parameters. Mean food intake was slightly increased in the female top-dose group (some +5 % after 4 wks) with no corresponding body-weight gain, but barely seen in males (Tab. 5, p. 23). The reduced food efficiency may be due to the rather high amount of inert Sipernat. Water consumption was normal throughout. Gross and microscopical examinations did not reveal any (histo-) pathological changes that could be attributed to the feeding of SIPERNAT 22.
Test condition	:	Treated feed: 6-kg batches mixed with the test material for 2 min, freshly prepared 5x/13 weeks and stored at 15 °C until use. Mean effective (analytical) silica levels in the diet were about 0.4-0.7, 1.7-1.9, 6.5-7.0 % (Tab. 1, p. 17). These dietary levels result in indicated doses of Sipernat, based on specified mean food intake and body weights.
Test substance	:	SIPERNAT 22, 97-98 % (SiO_2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study, well documented.
Flag	:	Critical study for SIDS endpoint

(64)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	oral feed
Exposure period	:	6 months
Frequency of treatm.	:	Daily
Post exposure period	:	No
Doses	:	approx. 2.3 and 8.47 g/(kg bw*day) (see Method)
Control group	:	Yes
NOAEL	:	= 8980 mg/kg bw
Method	:	other: see Method
Year	:	1975
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Examined parameters comparable to OECD-Guideline No. 408 and comprehensive: including haematology (after week 6, 13 and 26 using each 4 animals per sex and group), clinical-chemical blood parameters, urinalysis, macroscopic and histological examination (full spectrum of organs and tissues). Bone marrow was inspected at autopsy (26 weeks). calculated doses: low dose(m): 2170 mg/(kg*d) low dose(f): 2420 mg/(kg*d) high dose(m): 7950 mg/(kg*d) high dose(f): 8980 mg/(kg*d). The doses were selected, based on a 14-d range-finding study (dosing up to 20 % in the diet). 12 male and 12 female rats per group were used. The test compound was a powder and mixed with the diet at concentrations of 3.2 and 10 %, respectively. The mixture was prepared weekly.
Result	:	There were no treatment-related findings: General constitution and behaviour normal, body weights not affected. Isolated pathological findings

were unrelated to dosing and common in untreated rats. No histopathological changes in kidneys.

Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8

Reliability : (1) valid without restriction
1b: Comparable to guideline study, well documented

Flag : Critical study for SIDS endpoint

(98)

Type : Sub-chronic
Species : Rat
Sex : male/female
Strain : other: Charles River
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatm. : Continuous
Post exposure period : None
Doses : 1, 3, and 5 % in the diet [mean estimated dose: 700, 2100, and 3500 mg/(kg*d)]
Control group : Yes
NOAEL : ca. 3500 mg/kg bw
Method : other
Year : 1958
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : 15 female and 15 male rats were used per group; the control group received cosmetic talc (3 % in the diet). Interim sacrifices of 3 m and 3 f animals after 45 weeks. Macroscopic and microscopic examinations were performed.

Result : No clinical signs of toxicity, normal body-weight, food consumption and survival. No gross pathological and histopathological changes that could be attributable to the treatment.
Following ingestion of high-level diet, SiO2 content of liver, kidney, spleen, blood, and urine for the period of 45 and 90 d revealed no appreciable deposition of SiO2 as compared to the controls.

Test substance : Cab-O-Sil(fluffy) (>99 % SiO2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Reliability : (2) valid with restrictions
2d: Test procedure in accordance with national standard methods with acceptable restrictions: no complete documentation available.

(13)

Type : Sub-acute
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : Inhalation
Exposure period : 14 days
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : No
Doses : 17, 44 or 164 mg/m3 (mean analytical values)
Control group : Yes
NOAEL : < 17 mg/m^3
Method : other: see Method
Year : 1984
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study including synthetic amorphous and crystalline silica: Range-finding study (see main study: other entry): 40 m / 40 f test animals,

6 m / 6 f control animals were used.

Result : Respiratory distress (in all dose groups); 1 female animal died (high-dose group); reduced body weight and food consumption in males (mid and high dose group: food minus 10 and 20 %, respectively).

No haematological findings.

Increased lung weights (m/f): concentration-related mean increases of rel. weights ranged from about 47, 65, to 86 %, resp. (m/f) vs. control groups. Lower abs. and rel. liver weights in males, but not in females.

Dose-dependent changes in the lungs (pale, spotted and/or spongy, occasionally irregular surface, alveolar interstitial pneumonia, early granulomata); mediastinal lymph node enlarged.

A NOAEL cannot be established due to inflammatory responses of the lung and increase in lung weight at the lowest concentration of 17 mg/m3.

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.

Test substance : Aerosil 200: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessment

(62) (164)

Type : Sub-acute
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : Inhalation
Exposure period : 14 days
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : No
Doses : 46, 180 or 668 mg/m3 (mean analytical values)
Control group : Yes
NOAEL : < 46 mg/m^3
Method : other: see Remark
Year : 1984
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Remark : Method: 30 m / 30 f test animals; 10 m / 10 f control animals
Result : Respiratory distress (in all dose groups); 1 male animal died (high dose groups); reduced body weight and food consumption (mid and high dose groups): food about minus 13/14 % and 24/25 %, respectively (m); about minus 5-10 and 10-20 %, respectively (f) (Tab. 3, p. 19).

Increased lung weights (m/f): concentration-related mean increases of rel. weights ranged from about 25, 39, to 68 %, resp. (m), and from 34, 50, to 86 %, resp. (f) vs. control groups.

Decreased liver weights (all dose groups (m), high dose group (f)). Changes in the lungs (spotted, swollen, irregular surface, (high dose groups); alveolar interstitial pneumonia, early granulomata in the lungs (high dose groups) and mediastinal lymph nodes (mid and high dose groups) and one animal in the low dose group. Accumulation of alveolar macrophages and particulate material in lungs of males of the mid and high dose group.

A NOAEL cannot be established due to inflammatory responses of the lung and increase in lung weight at the lowest concentration of 44 mg/m3.

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.

Test substance : SIPERNAT 22S >98 % (SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Surface area (Ströhlein): 160 - 195 m2/g
Primary particle size: see Test Condition

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessment

(63) (164)

Type : Sub-chronic
Species : Monkey
Sex : Female
Strain : other: Macacus mulatta
Route of admin. : Inhalation
Exposure period : up to 12 months
Frequency of treatm. : 8 hours/day, 5 days/week
Post exposure period : No
Doses : 15 mg/m3
Control group : yes, concurrent no treatment
Method :
Year : 1962
GLP : No
Test substance : other TS

Method : Five animals were used in the test group, 15 in the untreated control group. 1/5 animals was killed after 3 months, 1/5 after 6 months, and 3/5 after 12 months.
Additional groups were exposed to crystalline silica [243 mg/m3] and fiberglass [162 mg/m3]. (note: The selection of the different exposure concentrations of the three siliceous materials was based upon the equivalence of their surfaces.)

Remark : Only limited number of animals. Appearance of the lungs of control animals not discussed: emphysema occurred independent of exposure, test substance poorly defined.

Result : The body weight gain was decreased during an initial period and the physical activity was decreased (lethargic). With prolonged exposure (after 12 months), the lesions present were marked pulmonary emphysema, alveolar wall sclerosis, vascular occlusions and cor pulmonale (marked right ventricular enlargement/hypertrophy after 12 months). Cor pulmonale was attributable to the emphysema and alveolar wall destruction. Emphysema was detectable within 3 months. At that time, considerable cellular infiltration of the alveoli and alveolar septae was demonstrable, associated with distention of alveoli or accumulation of exsudate and macrophages (p. 294).

With continued exposure, the cellular reaction decreased and became replaced by degenerative processes (loss of septae with confluence of alveoli), followed by destructive emphysema. Through extensive rupture of alveolar septae circulatory continuity was extensively impaired (p. 295). Collagen appeared in the alveolar septa.

Tracheobrochial lymph nodes were slightly enlarged, but did not appear fibrotic. There were some hepato-and splenomegaly, but not to a significant degree.
The silica content remained insignificant and actually decreased with the

passage of time.

Test substance : Synthetic amorphous silica, not further specified, prepared by dehydration of sodium silicate with alcohol, mean particle size 0.2 µm, secondary aggregation to 1 µm.

Conclusion : After exposure to synthetic amorphous silica, no indication of a focal pneumoconiotic response was detected radiographically (p. 284). But decisive emphysema was demonstrable. Primary inflammatory cellular reaction was replaced by degenerative processes (loss of septae with confluence of alveoli), followed by destructive emphysema after prolonged exposure p. 295). The recovery from degenerative lesions after cessation of exposure was not demonstrated in this study.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well documented, acceptable for assessment, but shortcoming due to low number of animals and limited characterisation of test substance

(174)

Type : Sub-chronic
Species : Rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : Inhalation
Exposure period : 12 months
Frequency of treatm. : 8 hours/day
Post exposure period : 6 and 12 months
Doses : 53 mg/m3
Control group : Yes
Method : other
Year : 1957
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Part of a comprehensive testing programme (see other entries):

Whole-body exposure: active dust exposure for 8 h/d (dust-disseminating apparatus: mechanical agitation and compressed air-jet through Venturi tube into inhalation chamber), and passive exposure (dust settling) for the remainder 16 h/d.

Dust analysis and sampling: millipore filter method: average air concentration was 1.5 mg/cubic foot = 53 mg/m3, with most measurements between 0.7 and 2.4 mg/cubic foot (= 25 and 85 mg/m3, respectively).

Size-frequency distribution of the particles (an electrostatic precipitator used): 1- to 10-um particles accounted for some 85 % of the dust mass in the chamber.

10 animals were used.

Result : Progressive functional incapacitation and elevation of hematocrit levels, possibly due to the combined effect of pulmonary vascular obstruction and emphysema, were observed in the majority of the animals. Blood pressure changes were also observed in the majority of the rabbits. These changes were partly reversed when the exposure was discontinued. The essential pulmonary changes included peribronchiolar cellular catarrh, mural cellular infiltration along with deposition of reticulum and some collagen, the formation of peri-vascular cellular nodules, ductal stenosis and emphysema.
When the rabbits were returned to normal air, the cellular reactions and emphysema regressed, but minor focal alveolar mural collagen persisted.

Test substance : Dow Corning Silica obtained from Degussa: approx. 98 % (SiO_2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5 [Note:

Based on the flame process, Dow silica reported to be equivalent to Cabot material, Cab-O-Sil, but different from the Degussa product Aerosil as to polymorphous structure (see other entry on rat).

Reliability : (4) not assignable
4e: Test design insufficient for assessment: low number of animals, although well documented.

(175)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	Male
Strain	:	Fischer 344
Route of admin.	:	Inhalation
Exposure period	:	13 weeks
Frequency of treatm.	:	6h/d, 5d/wk
Post exposure period	:	3 and 8 months
Doses	:	50 mg/m3
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	2000
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Comparative study including synthetic amorphous and crystalline silica: Whole-body exposure. The testing programme included cellular and biochemical Bronchoalveolar Lavage Fluid Analysis (BAL) on inflammatory markers, histopathology, inflammatory cytokine gene expression (MIP-2), immunohistochemistry for DNA damage (terminal transferase dUTP nick-end-labeling = TUNEL staining), and mutagenesis in alveolar epithelial cells.

Particle size of dust in exposure chamber: mass median diameter = 0.81 um Chamber concentration: 50.4 +-19 mg/m3 (note: Crystalline silica was administered only at 3 mg/m3, based on the expected lung burden and pulmonary reaction.)

Silica burden was measured after 6.5 and 13 weeks of exposure and 3 and 8 months of recovery.

For mutagenic assay: see other entry 5.6.

Result : SILICA BURDEN:
Amorphous silica increased quickly during the first 6.5 weeks of exposure (some 0.76 mg SiO2/lung), but only slowly after the second half of the exposure period (plateau phase, steady state at about 0.88 mg SiO2/lung), while the level of crystalline silica increased steadily from about 0.34 mg SiO2/lung (after 6.5 weeks) and even disproportionately to approx. 0.82 mg/lung (after 13 weeks).
During recovery, amorphous silica lung burden disappeared rapidly from lung tissue down to about 15 % (after 12 weeks post-exposure) and to about 6 % of the final level after exposure (at 32 weeks post-exposure). On the other hand, crystalline silica persisted in the lung with no substantial decrease post-exposure.

BAL ANALYSIS:
Mean cell number in the lavage increased at a factor of about 5 to 15 vs. control, comprising of more than 50 % PMN and some 2 % lymphocytes while the control lavages only contained less than 1 % of either cell type. Protein content and enzyme activities (LDH and glucuronidase) were markedly higher than under control conditions.

All BAL markers approached normal levels after 13 weeks post-exposure,

but a few ones still showing minimal increases.

HISTOPATHOLOGY:
Invasion of neutrophils and macrophages into alveoli was evident after both amorphous and crystalline silica exposure, more pronounced with the amorphous type after 6.5 weeks (which appears to correlate with the higher lung silica burden after that interval), but tended to decrease during the post-exposure period (p. 408), while the crystalline-exposed groups demonstrated continued elevation and cell proliferation after cessation od exposure.

Fibrosis was present in the alveolar septae (based on Gormor´s trichrome staining). Fibrosis subsided during recovery in the case of synthetic amorphous silica, but persisted for crystalline silica.

IMMUNOHISTOPATHOLOGY:
After 13-wk exposure to synthetic amorphous silica, intensely stained TUNEL-positive cells were detected throughout the terminal bronchiolar epithelium and throughout the parenchyma of rat lungs. Only little staining was seen after exposure to crystalline silica (p. 408). During recovery, TUNEL-staining was indistinguishable between the amorphous-treated and control group. In contrast, lungs exposed to crystalline silica showed intense staining localized to cell debris and macrophages in hypertrophic areas of the parenchyma cells (p. 409).

Test substance : Aerosil 200: CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5 (note: specified as "precipitated" in the report, apparently erroneous).

Conclusion : Synthetic amorphous silica produce a transient pulmonary inflammatory response and most biochemical markers return to control levels once exposure has stopped. On the other hand, crystalline silica procuce persistent lung inflammation even at much lower exposure levels.
The biological relevance of the different phases of TUNEL-stainining effects seen in rat lungs exposed to synthetic amorphous silica on one hand and to crystalline silica on the other hand is speculative: However, according to authors, the early effect seen with the first may indicate early cell death through apoptosis or necrosis.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

(123)

Type : Chronic
Species : Rat
Sex : Female
Strain : other: white, inbred
Route of admin. : Inhalation
Exposure period : 3, 6, 12 months
Frequency of treatm. : 5 hours/day, 5 days a week
Post exposure period : 5 months
Doses : 55 mg/m3 (effective respirable dust concentration)
Control group : No
Method : other: see Remark
Year : 1968
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Method: 110 f test animals were exposed to FK 700 for maximal 1 year in a dusting chamber according to Polley.

Result : PATHOLOGY:
At autopsy, some white-grey foci were observed subpleurally. The microscopic examination after 4 months showed desquamation of alveolar cells with fine granula. After 12 months peribronchial and particularly intra-

alveolar small dust cell foci with few reticulin fibres were found. In some alveolar septae, small changes (increased cell numbers and fibres (after formalin) were seen. The mediastinal lymph nodes were enlarged and contained dust cells with fine granules.

Neither a diffuse nor a nodula fibrosis was seen in lungs or lymph nodes.
Recovery phase:
Above mentioned effects regressed: lung weights normal, only few foci left, no significant desquamation. Lymph nodes slightly enlarged eventually with some dust cells.

RETENTION of silica:
The one-day mean retention value was 0.138 mg/lung (intermittently obtained 20 h after single exposure with control animals).

Average SiO2-content of the lungs after 4 months: 1.022 mg, after 12 months: 3.443 mg.
The corresponding values for the mediastinal lymphatic nodes were after 4 months: 0.033 mg and after 12 months: 0.069 mg.
Five months after exposure, the average value for the lungs was only 0.457 mg (elimination rate 87 %), the corresponding value for the mediastinal lymphatic nodes was 0.052 mg 5 months after end of exposure.

Test substance : FK 700, 86.65 % SiO2, 7.3 % hydration water (SiO2), specific surface area (BET) = 700 m2/g: Silica, precipitated, crystalline-free, CAS No. 112926-00-8

Conclusion : Neither a diffuse nor a nodula fibrosis was seen in lungs or lymph nodes. Acc. to the author, the lymphatic system appears to play a minor role in the elimination of the synthetic amorphous silica dust from the lung. Therefore, there is no evidence for a silicosis or a lymphatic-type pneumoconiosis to develop from exposure to synthetic amorphous silica.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

(49)

Type : Chronic
Species : Rat
Sex : Female
Strain : Sprague-Dawley
Route of admin. : Inhalation
Exposure period : 12 months
Frequency of treatm. : 5 h/d, 5x/wk, after unspecified time: 2 - 3x/wk (see Method)
Post exposure period : 5 months for part of the aninmals
Doses : 50 - 55 mg/m3 (total dust) = approx. 30 mg/m3 (respirable)
Control group : no data specified
Method :
Year : 1969
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : 150 animals were used.
Dust measurements were carried with a Gravimetric Dust Sampler (Cassella). Weekly exposure frequency was reduced because of fatal cases caused by massive substance-related purulent bronchitis, focal pneumonitis, and massive cellular reactions. Interim sacrifices at 6 and 18 weeks for examination of pulmonary dust levels.

Remark : Wacker: Full report available??

Result : RETENTION of silica:
After 12-months exposure, about 1 % of administered total respirable dust was estimated to be still retained in the lung. The increase in lung deposition was low from 18 weeks to 12 months of exposure (18 wk: 1.2

mg SiO2, 12 months: 1.37 mg SiO2). Mediastinal lymph nodes contained about 0.13 mg SiO2 after 12 months.

After 5 months post-exposure, mean levels of SiO2 were 0.16 mg/lung and 0.047 mg/lymph node, i.e. a reduction at some 88 % in the lung and more than 50 % in the lymph nodes.
PATHOLOGY:
Microscopically visible small dust foci could be observed under the pulmonary pleura, mediastinal lymph nodes were moderately enlarged. In the interior of alveoles, numerous macrophages accumulated, partially normal, partially destroyed, associated with deposition of cell debris ("desquamation catarrh"). Perivascular and peribronchiolar small dust foci of macrophages, associated with mild and moderate formation of connective tissue (ranked as grade I to II, based on a ranking system acc. to Belt&King).

In the alveolar septa the collagen formation was increased. In the mediastinal lymph nodes, foci and clusters of phagocytes, partially normal, partially showing decay, and in some cases collagenic fibrosis was observed.

Test substance : HDK V15: >99,8 % SiO2, 150 m2/g (BET), CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Conclusion : In some cases, the product - at sites with high concentrated depositions - caused a marked collagenic fibrosis, but without signs of typical silicosis. Acc. to the author, inhalation of quartz under similar conditions would have resulted in a marked silicosis of grade IV to V (after Belt&King).

Reliability : (4) not assignable
4e: Test design and documentation insufficient for assessment, but results in line with findings of others.

(132)

Type : Chronic
Species : Rat
Sex : Female
Strain : other: albino
Route of admin. : Inhalation
Exposure period : up to 1 year
Frequency of treatm. : 4 hours/day
Post exposure period : 3 to 8 months
Doses : approx. 45 mg/m3
Control group : Yes
Method : other: see Remark
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Method: 120 f test animals were exposed to Aerosil for maximal 1 year in a dusting chamber according Joetten. Interim kill.

Result : 41/120 animals died spontaneously. Autopsy: small white foci under the pleura; enlarged and discoloured lymph nodes with formation of collagen and local necrosis; perivascular and peribronchiolar dust cell granuloma with reticulin and collagen fibres; necrotic cells; desquamative catarrh; alveolar septs thickened. After the recovery period (3 and 8 months) the dust cell granuloma were reduced in number and size with only a few dust cells and fibres. The changes of the alveolar septs had also not completely disappeared. After 3 months post observation period the lymph nodes were much more enlarged, after 8 months the size and also the necrosis and fibres were reduced. The SiO2 content in the lungs was in the mean 0.32 mg/lung or lymph node, maximal 0.6 mg was detected. At the end of exposure 0.132 mg SiO2 were found in the mediastinal lymph node.

Test substance : Aerosil 150 (not further specified): CAS-Name: Silica, amorphous, fumed,

cryst.-free; CAS-No.: 112945-52-5

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, limited documented
(51) (131)

Type :
Species : Rat
Sex : no data
Strain : no data
Route of admin. : Inhalation
Exposure period : up to 300 days
Frequency of treatm. : up to 2 - 3 hours/day
Post exposure period : No
Doses : no data
Control group : No
Method :
Year :
GLP : No
Test substance : other TS: Molecular solution of siliceous acid (2 mg/ml)

Result : In 3/6 animals connective tissue were found perivascular of venules. In one animal subpleural small aerosol atelectasis was seen.
Reliability : (3) invalid
3a: Significant methodological deficiences (no complete study, screening)
(130)

Type : Sub-acute
Species : Rat
Sex : Male
Strain : Fischer 344
Route of admin. : Inhalation
Exposure period : 8 days
Frequency of treatm. : 6 hours/day
Post exposure period : up to 112 days
Doses : 30 mg/m3
Control group : Yes
LOAEL : = 30 mg/m³
Method : other: see Remark
Year : 1986
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study including exposure to alpha-quartz, synthetic amorphous and crystalline silica. 45 animals were used. Exposure to aerosols of synthetic amorphous silica. Histopathology of the lungs, bronchoalveolar lavage, lung tissue biochemistry.
Result : Under test conditions, exposure to synthetic amorphous silica caused an early and transient influx of cells into the lung tissue, returning to normal by day 12 post-exposure.
By 5 days post-exposure, total numbers and differential counts of alveolar lavage-derived cells were quite similar to cells of control animals.

Furthermore, the biochemical analysis of the lung tissue revealed increased BAL protein, lipid phosphorus, and saturated dipalmitoyl phosphatidyl -choline levels immediately after exposure, but were also normal by 5 d post-exposure (Low et al., 1985).

No significant differences from control lungs as to weight (small increase), DNA-, protein- (small increase) or hydroxyproline-content were noted (Hemenway et al., 1986).

With respect to above parameters, alpha-quartz induced no significant adverse inflammatory effect, whereas cristobalite produced a distinctly more severe inflammatory response than synthetic amorphous silica type.

Test substance : CAS-Name: Silica, amorphous, precipitated, cryst.-free; CAS-No.: 112945-52-5, not further specified (from J.M. Huber Corp.)

Conclusion : Synthetic amorphous silica elicit an early, transient alveolar inflammatory response, without producing fibrosis. From histological evidence only a mild inflammatory response with no evidence of connective tissue response.
Another polymorph silica, alpha-quartz, also tested fails to show significant adverse effects, much less than produced by precipitated amorphous silica, whereas crystalline silica (alpha-cristobalite) results in a sustained inflammatory reaction which persists as long as 120 d post-treatment and may eventually lead to lung fibrosis.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

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Type :
Species : Rat
Sex : Female
Strain : Wistar
Route of admin. : Inhalation
Exposure period : 6 weeks
Frequency of treatm. : 1 hour/day, 5 days/week
Post exposure period : up to 3 months
Doses : 8 and 40 mg/m3
Control group : Yes
Method : other: see Remark
Year : 1984
GLP : No
Test substance : other TS: HDK N 20

Remark : Method: interim kill 48, 7 d and 3 weeks after termination of inhalation

Result : No macroscopic changes. Histopathology: occurrence of dust cells in the lungs, which were decreasing during the post observation period; no fibrosis, also not of the reticulo-cellular type; normal parenchyma of the lungs; no emphysema.
A decrease of the SiO2 content in the lungs was seen 48 or 7 days, resp., after termination of the inhalation exposure.
After 3 month SiO2 was nearly disappeared.

Reliability : (4) not assignable
4e: Documentation limited and insufficient for assessment

(9)

Type : Sub-acute
Species : Rat
Sex : Male
Strain : other: CD BR
Route of admin. : Inhalation
Exposure period : 4 weeks
Frequency of treatm. : 6 hours/day, 5 days/week
Post exposure period : 10 and 94 days
Doses : 10.1, 50.5 and 154 mg/m3
Control group : Yes
NOAEL : = 10.1 mg/m³
Method : other: according to OECD, see also Remark
Year :
GLP : Yes
Test substance : other TS: Ludox (colloidal silica, grade CL-X)

Remark	:	Method: Prior to the exposures, the test material was diluted 4 : 1 (w/w) with deionized, distilled water. Lung tissue samples were analyzed for silica content.
Result	:	Exposure related lesions were seen only in lungs and associated drainage lymph nodes. Dose-related increased mean lung weights and lung-to-body weight ratios were observed after 4 weeks exposure in the 0.0505 and 0.154 mg/l groups. The mean lung-to-body ratio was still increased in the 0.154 mg/l group 10 days after exposure but was not different from the controls after the 3-months recovery period. Dust loaden alveolar macrophages, neutrophilic infiltration and Type-II pneumocyte hyperplasia were seen in the alveolar duct region of the lungs. The pulmonary lesions were progressively decreased in rats examined after the 10 day and 3 months recovery periods. At 3 months post-exposure, most dust-laden alveolar macrophages had cleared from the lungs but small numbers of minute silicotic nodule-like lesions were present in the alveolar ducts and perivascular regions where dust-laden alveolar macrophages had aggregated. There was minimal collagen deposition seen in the silicotic nodule-like lesions and the lesions did not increase in number or size with time. The lung clearance half-life, measured in the 0.0505 and 0.154 mg/l groups, was approx. 50 days. An increase in mean neutrophil count and globulin concentration and a decrease in mean lymphocyte count were observed at the end of the 4-week exposure period in the 0.154 mg/l group. The increase in mean neutrophil count and decrease in mean lymphocyte count were still present following the 3 month recovery period. The tracheal and mediastinal lymph nodes were enlarged with nodular aggregates of dust-laden alveolar macrophages and hyperplastic R-E cells.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

24.09.2004 (81) (198) (199)

Type	:	
Species	:	Rat
Sex	:	Female
Strain	:	other: Albino
Route of admin.	:	Inhalation
Exposure period	:	1 year
Frequency of treatm.	:	5 hours/day, 5 days/week
Post exposure period	:	4 months
Doses	:	0.112 mg/l
Control group	:	Yes
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	After 4 months 1.578 mg SiO_2 were found in the lungs and 0.151 mg in the lymph nodes. After 12 months the corresponding values are 1.820 and 0.430 mg SiO_2. At autopsy white foci under the plasma were seen, the mediastinal lymph node was enlarged. The histological examination showed desquamative catarrh, sporadic dust nodules and foci with minimal to moderate fibrosis, increased collagen and sporadic diffuse fibrosis of the alveolar septes and perifocal emphysema. Typical silicatic nodules were not seen.

In lymph nodes an increase of dust cells which occurred partly accumulated, and slight to moderate fibrosis, sporadic collagen fibrosis.

After the recovery time the SiO2 contents in lungs were 0.92 mg (decrease) and in lymph nodes 0.814 mg SiO2 (increase). At autopsy subpleural dust foci and enlarged lymph nodes were observed. The lung weight was increased. Microscopically cell desquamation had disappeared, whereas the other changes did not show pronounced differences to the findings at the end of the exposure period.

Test substance : Aerosil OX 50: CAS Name, Silica, amorphous, fumed (pyrogenic), CAS No. 112945-52-5

Reliability : (4) not assignable
4e: Test design and documentation insufficient for assessment, but results in line with findings of others.

(48)

Type : Sub-acute
Species : Rat
Sex : Male
Strain : other: Albino
Route of admin. : Inhalation
Exposure period : 3 days
Frequency of treatm. : no data
Post exposure period : 11 - 12 days
Doses : 0.5 - 2.4 mg SiO2/l/2.5-7 h
Control group : no data specified
Method : other
Year : 1952
GLP : No
Test substance : other TS: colloidal silica diluted to 5 % neutralized and unneutralized

Result : The symptoms and pathology of the animals exposed to both the neutralized and unneutralized solutions were generally the same: slight irritation to the eyes and nose, rapid, irregular respiration and congested areas in the lungs. No evidence of foreign material was seen.

Reliability : (3) invalid
3a: Documentation insufficient for assessment

(73)

Type : Sub-acute
Species : Rat
Sex : Male
Strain : other: CD
Route of admin. : Inhalation
Exposure period : 3 days
Frequency of treatm. : 1x/d, 6 h /d
Post exposure period : 1, 8, 30, and 90 d
Doses : 10 and 100 mg/m3
Control group : yes, concurrent no treatment
LOAEL : = 10 mg/m³
Method :
Year : 1995
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study including exposure to amorphous, colloidal, and crystalline silica. 24 animals per group were used. Inhalation system: nose-only. MMAD 2.4 - 3.4 um.
After termination of exposure, groups of animals were sequentially killed and their lungs washed.
Responses of the lung were evaluated on various markers for inflammation

and cytotoxicity in the broncho-alveolar lavage (BAL).

Result : Exposure to 10 mg/m3 amorphous silica produced a transient inflammatory response which was present 24 h post-exposure, but subsided within 8 d, reflected in an increase and subsequent decrease in the number of granulocytes, extracellular LDH activity, protein levels, and NAG (N-acetyl-glucosaminidase) in the BAL. Also after exposure to 100 mg/m3, the biochemical parameters returned to normal in a similar way as after exposure to 10 mg/m3.

In contrast, crystalline silica produced sustained or even aggravating inflammatory effects.

Test substance : ZEOFREE 80: CAS-Name: Silica, precipitated, cryst.-free; CAS-No. 112926-00-8

Conclusion : Low concentration of synthetic amorphous silica induces a transient inflammatory tissue reaction and, therefore, is less potent in producing pulmonary toxicity than the crystalline silica types.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

24.09.2004 (200)

Type : Sub-chronic
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 6 months
Frequency of treatm. : Daily
Post exposure period : No
Doses : 495 - 497 mg/kg
Control group : Yes
NOAEL : = 497 mg/kg
Method : other: see Remark
Year : 1963
GLP : No
Test substance : other TS: Aerosil (Type not specified)

Remark : Method: 20 m / 20 f test animals; 20 m / 20 f control animals
Result : no clinical symptoms or other findings
Reliability : (4) not assignable
4e: Test design and documentation insufficient for assessment, but results in line with findings of others.

(51)

Type : Sub-acute
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. : Daily
Post exposure period : No
Doses : group a: 16.5 g/kg/day (10 % w/w in feed); group b: 5.8 g/kg/day for day 1 - 10 (5 % w/w in feed) and 24.2 g/kg/day for day 11 - 14 (20 % w/w in feed)
Control group : Yes
NOAEL : >= 24200 mg/kg bw
Method : other: pre-study
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method	:	Range-finding study: 5 animals per sex and group were used. No pathology examinations performed.
Result	:	No clinical symptoms or other findings (food or water consumption, body weight gain, behaviour)
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(3) invalid 3a: Significant methodological deficiences (no complete study, screening) (97)

Type	:	Sub-acute
Species	:	Rat
Sex	:	male/female
Strain	:	other: Charles River CD
Route of admin.	:	oral feed
Exposure period	:	4 weeks
Frequency of treatm.	:	Daily
Post exposure period	:	Yes
Doses	:	800 mg/kg
Control group	:	Yes
Method	:	other: see Remark
Year	:	1970
GLP	:	No
Test substance	:	other TS

Remark	:	Method: clinical signs, hematology, clincal chemistry, urine analysis, autopsy, histopathology of the kidneys
Result	:	In comparison with the control group no treatment related changes were observed with the silicon-dioxide product
Test substance	:	Sodium silicate, magnesium trisilicate, Aluminium silicate and silicon dioxide were tested (not further specified)
Reliability	:	(3) invalid 3a: Significant methodological deficiences (test substance unclear, probably not as described) (156)

Type	:	Sub-acute
Species	:	Rat
Sex	:	Male
Strain	:	other: Albino
Route of admin.	:	oral feed
Exposure period	:	2 weeks
Frequency of treatm.	:	10 times
Post exposure period	:	11 days
Doses	:	7500 mg/kg
Control group	:	No
Method	:	
Year	:	
GLP	:	No
Test substance	:	other TS: Ludox (aqueous colloidal, 30 % SiO2), neutralized with HCl

Result	:	Results: All 6 animals lost weight during treatment but gained over the weekend and during post observation period. No significant pathology was obsreved.
Reliability	:	(3) invalid 3a: Significant methodological deficiences (no complete study, screening) (74)

Type	:	Sub-acute
Species	:	Rat
Sex	:	Female

Strain	:	other: inbred
Route of admin.	:	Gavage
Exposure period	:	1 month
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	1500 mg/(kg*d) (aqueous suspension: not specified)
Control group	:	Yes
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Body weight gain, food consumption and behaviour were not influenced. The SiO2-content in liver was 1.5 ug, in kidney 6.4 ug and in spleen 5.3 ug. The corresponding control values were 1.8, 7.2 and 7.8 ug SiO2, resp..
Test substance	:	FK 700, 86.65 % SiO2, 7.3 % hydration water (SiO2): Silica, precipitated, crystalline-free, CAS No.: 112926-00-8: Specific surface area (BET) = 700 m2/g
Reliability	:	(4) not assignable Only abstract/Summary

(49)

Type	:	Chronic
Species	:	Rabbit
Sex	:	no data
Strain	:	no data
Route of admin.	:	Inhalation
Exposure period	:	approx. 3 years
Frequency of treatm.	:	4 - 5 hours/day, 5 days/week
Post exposure period	:	30 - 150 days
Doses	:	no data
Control group	:	No
Method	:	
Year	:	
GLP	:	No
Test substance	:	other TS: Aerosil (Type not specified, = 99.7 % SiO2)
Result	:	No clinical signs during inhalation, cases of deaths (the correlation to treatment is not clear). Macroscopically: emphysema of the lungs; microscopically: bronchial and alveoar dequamative catarrh; lymphocytes and leucocytes increased in the alveoles, oedema, accumulation of macrophages in the lymph nodes and in the interstitium (perivascular, peribronchial, alveolar septes) granuloma of macrophages, dust cells, in some cases thickening of the alveolar septes. Formation of connective tissue was minimal.
Reliability	:	(3) invalid 3a: Significant methodological deficiences. Findings in agreement with results in other studies.

(25) (90)

Type	:	Chronic
Species	:	Rabbit
Sex	:	no data
Strain	:	New Zealand white
Route of admin.	:	Inhalation
Exposure period	:	up to 27 months
Frequency of treatm.	:	8 hours/day, 5 days/week
Post exposure period	:	No
Doses	:	0, 28.2, 134 and 360 mg/m3
Control group	:	Yes
LOAEL	:	= 28 mg/m³

Method	:	other: see Remark
Year	:	1959
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Method: duration of test for mid and high dose approx. 9 months; low dose and control group 27 months
Result	:	No NOAEL could be established. When exposed to the dust in high concentrations, the rabbits soon became distressed; this continued as long as they inhaled the silica. Symptoms, were fewer, commenced later, and receded more promptly at the lower concentrations. A compound-related effect on the body weight gain was seen. When exposure ceased, this trend was reversed. Also observed was a compound-related dyspnea. Cyanosis accompanied the shortness of breath, particularly in the highest dose group Pathological examination revealed emphysema which decreased when the rabbits were turned to normal air. Pulmonary emphysema, vascular stenosis, alveolar cell infiltration, sclerosis and epithelization, granulomatosis, macrophage catarrh were some of the remarkable findings. Lesions were also seen in the liver, spleen and kidney. Elevation of the right and left ventricular pressures was concentration and time related. After 6 months of exposure to the lowest concentration of 28 mg/m3, cardiac pressure increased and continued steadily so that at the end of 24-months period, an elevation of 64 % over the pre-exposure pressure was established. The elevations were partly reversible on cessation of dust exposure (after 12 months post-exposure. still 34 % above starting level). Findings: Concomitant radiographic changes, electrocardiagraphic deviations, modifications of lung functions, hematolytic changes; anatomical cor pulmonale, congestive cardiac failure, emphysema and chemical pneumonitis.
Test substance	:	Hi-Sil types: CAS-Name: Silica, precipitated, crystalline-free, CAS-No.: 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

(173)

Type	:	
Species	:	Dog
Sex	:	male/female
Strain	:	Beagle
Route of admin.	:	oral feed
Exposure period	:	4 weeks
Frequency of treatm.	:	Daily
Post exposure period	:	Yes
Doses	:	800 mg/(kg*d)
Control group	:	Yes
Method	:	other: see Remark
Year	:	1970
GLP	:	No
Test substance	:	no data
Remark	:	Method: clinical signs, hematology, clinical chemistry, urine analysis, autopsy, histopathology of the kidneys.
Result	:	In comparison with the control group no treatment related changes were observed for SiO2.
Test substance	:	Sodium silicate, magnesium trisilicate, Aluminium silicate and silicon dioxide were tested (not further specified)

Reliability	:	(3) invalid 3a: Significant methodological deficiences (test substance unclear, probably not as described) (155)
Type	:	Chronic
Species	:	other: rabbits, rats, guinea pigs
Sex	:	no data
Strain	:	
Route of admin.	:	Inhalation
Exposure period	:	12 months (rabbits), 15 months (rats) and 24 months (guinea pigs)
Frequency of treatm.	:	8 h/d, 5 d/wk
Post exposure period	:	yes, up to 12 months
Doses	:	average 126 mg/m3 [3.57 mg/ft3]
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	1981
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The value of the study was limited because of a pneumonic disease (viral infection) as well as by lack of reporting (particle concentrations during the actual dust generation, particle size, techniques to assess particle effects and tissue sampling). There are several shortcomings which limit evaluation: Only one high concentration used, ranking system for pathogenicity of various silica unclear, infection in rats, documentation complex.
Result	:	PATHOGENICITY: There were no significant, treatment-related differences in mortality between treated and non-treated groups: Rats 23/84 (27.3 %) vs. 19/50 (37.3 %) (control); guinea pigs 8/82 (9.7 %) vs. 8/100 (8 %) (control); rabbits 18/50 (36 %) vs. 4/19 (20 %) (control), discounting artificial deaths that occurred from cardiac punctures. In rats, deaths were mainly due to intercurrent infection. Lung weights increased during exposure, but returned to normal ranges after exposure. Particle-phagocytosing macrophages accumulated in alveoli, bronchioles and lymphoid tissue. Hilar lymph nodes became enlarged. This remained in mild reaction in rats, but was more evident in guinea pigs and rabbits. This disappeared on cessation of exposure. Epithelial proliferation was minimal. Mild deposition of reticulin fibers occurred in alveoles, but there was no evidence of collagen formation. Bronchial and tracheal epithelia remained intact. No epithelization or pleural changes were noted, and no neoplasia occurred. The type of emphysema that predominated during the exposure phase was diffuse hypertrophic vesicular distention, but apparently did not result from destructive effects on the mucosa of terminal brochioles and disruption of the continuity of alveolar walls as noted from other silaceous particles (p. 158). Acc. to the author, it could not be ruled out that the emphysematous effect in rats was mainly due to aging and recurrent epizootic pneumonitis . The tuberculogenic response (guinea pig) was limited to a slight increase in size of some lesions and slightly longer persistence of the active cellular proliferation phase of the tubercles. No extrapulmonary spread of the tuberculosis occurred. SILICA BURDEN: 12-Months exposure to HI-SIL 233 resulted in only 10 mg SiO2 per lung ash in guinea pigs and progressed only slowly thereafter. After discontinuation of exposure, the silica content of the lung approximated that of the non-treated controls (0.6 mg) after 6 months recovery (Fig. 10).
Test substance	:	Hi-Sil 233, 85-88 % SiO2, approx. 3.5-4 % other metal oxides, >= 5% hydration water: CAS-Name: Silica, precipitated, crystalline-free, CAS-No.:

112926-00-8

Conclusion : Virtual complete reversibility of silica retention in guinea pigs along with almost complete regression of inflammatory responses within 6-months recovery after cessation of 12-months exposure was noted. Silicotic processes are completely absent, which - by contrast - are characteristic of crystalline silica and quartz even post-exposure (p. 160).

On this basis by comparison with 24 other varieties of silica previously studied in comparable fashion, the precipitated, synthetic amorphous silica of the HI-SIL type is the least biologically active of the synthetic silicas (rated at approx. 5 % of the capability of the most injurious siliceous materials) (Fig. 9). [note: The ranking system for comparing pathogenicity is not well defined.]

Reliability : (3) invalid
3a: Significant methodological deficiences

(172)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : 0.033 - 10 mg per plate, suspended in DMSO
Cycotoxic concentr. : None
Metabolic activation : with and without
Result : Negative
Method : other: Ames et al.
Year : 1975
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Method: Standard plate incorporation assay. S9-Mix (Aroclor 1254 induced, rat).
Test substance : Silcron G-190 (SCM Glidden): synthetic amorphous silica
Reliability : (1) valid without restriction
1b: Comparable to guideline study
Flag : Critical study for SIDS endpoint

(154) (162)

Type : Escherichia coli reverse mutation assay
System of testing : Escherichia coli WP 2
Test concentration : 0.033 - 10 mg per plate, suspended in DMSO
Cycotoxic concentr. : None
Metabolic activation : With and without
Result : Negative
Method : Other: analogous Ames et al.
Year : 1975
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Method: Standard plate incorporataion assay. S9-Mix (Aroclor 1254 induced, rat).
Test substance : Silcron G-190 (SCM Glidden): synthetic amorphous silica
Reliability : (1) valid without restriction
1b: Comparable to guideline study
Flag : Critical study for SIDS endpoint

(154) (162)

Type : Ames test
System of testing : Salmonella typhimurium TA98, TA100, TA1535, TA1537,TA1538
Test concentration : 667 -10000 ug/plate

Cycotoxic concentr.	:	None
Metabolic activation	:	with and without
Result	:	Negative
Method	:	Other: Ames test
Year	:	1989
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Plate incorporation assay, metabolic activation: Aroclor induced rat liver S9; test material suspended in DMSO.
Remark	:	Method: metabolic activation: Aroclor induced rat liver S9; plate incorporation assay
Test condition	:	Metabolic activation: Aroclor induced rat liver S9; plate incorporation assay
Test substance	:	Cab-O-Sil EH-5: CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(11)

Type	:	Cytogenetic assay
System of testing	:	Human embryonic lung cells (Wi-38)
Test concentration	:	1 - 1000 ug/ml
Cycotoxic concentr.	:	no data
Metabolic activation	:	Without
Result	:	Negative
Method	:	Other
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Mutations were quantified by counting anaphase aberrations. Negative (0.85 % saline) and positive (0.1 ug/l triethylene melamine) controls were run in parallel.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(143)

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster ovary (CHO) cells
Test concentration	:	19 - 300 ul/ml (without S9) and 250 - 1000 ul/ml (with S9)
Cycotoxic concentr.	:	see Result
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: established methodology
Year	:	1990
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Metabolic activation: Aroclor induced rat liver S9; solvent for test article DMSO. Triethylenemelamine served as pos. control substance under non-activated condition, cyclophosphamide under activated condition.
Result	:	The test substance was partially insoluble in solvent and treatment medium at all concentrations tested. Toxicity (reduction in the mitotic index) was 92% (without S9) and 63% (with S9).
Test substance	:	Cab-O-Sil EH-5 (>99 % SiO2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Reliability	:	(1) valid without restriction 1b: Comparable to guideline study, well documented.
Flag	:	Critical study for SIDS endpoint

(12)

Type	:	HGPRT assay
System of testing	:	Chinese hamster ovary (CHO) cells
Test concentration	:	10 - 250 ug/ml (without S9) and 100 - 500 ug/ml (with S9)
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: acc. to publ. methodology
Year	:	1990
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Metabolic activation: Aroclor induced rat liver S9; solvent for test article DMSO. EMS served as pos. control substance under non-activated condition, B(a)P under activated condition.
Test substance	:	Cab-O-Sil EH-5: CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1b: Comparable to guideline study, well documented.
Flag	:	Critical study for SIDS endpoint

(14)

Type	:	Unscheduled DNA synthesis
System of testing	:	Primary rat hepatocytes
Test concentration	:	0.3 - 1000 ug/ml (5 concentrations tested)
Cycotoxic concentr.	:	260 - 500 ug/ml: rel. tox. approx. 50 %
Metabolic activation	:	Without
Result	:	Negative
Method	:	other: William, G. M.: Chemical Mutagens, 4, 61-79, 1979
Year	:	1989
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Test material was suspended in DMSO, cells were incubated in the presence of silica for 18 to 20 h. As pos. control substance served 7,12-DMBA. Cytotoxicity was evaluated on the basis of LDH release from cells.
Test substance	:	Cab-O-Sil EH-5: CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(16)

Type	:	Gene mutation in Saccharomyces cerevisiae
System of testing	:	Saccharomyces cerevisiae D-3
Test concentration	:	not stated
Cycotoxic concentr.	:	not stated
Metabolic activation	:	Without
Result	:	Negative
Method	:	other: Ames et al.
Year	:	1975
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(3) invalid 3a: Significant methodological deficiences

(143)

Type : Ames test
System of testing : Salmonella typhimurium TA 1530 and G-46
Test concentration : not stated
Cycotoxic concentr. : not stated
Metabolic activation : Without
Result : Negative
Method : other: Ames et al.
Year : 1975
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Test substance : Syloid 244 = FDA-Compound 71-48: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No.: 112926-00-8
Reliability : (3) invalid
3a: Significant methodological deficiences

(143)

Type : Micronucleus test in vitro
System of testing : Chinese hamster lung fibroblasts (V79)
Test concentration : 20, 40, 80 and 160 ug/cm2 (= 0.12, 0.23, 0.46, and 0.93 mg/ml test medium)
Cycotoxic concentr. : >= 80 ug/cm2
Metabolic activation : Without
Result : Ambiguous
Method : Other
Year : 1996
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Weak but significant, dose-dependent induction of micronuclei at cytotoxic concentrations; however, no clastogenicity in sub-cytotoxic doses in neither medium. No effects were noted at doses lower than 40 ug/cm2 (= approx. 0.23 mg/ml test medium).
Test condition : 24-h treatment of cell culture in culture medium and in simulated pulmonary surfactant: Given area-specific doses can be transformed into corresponding concentrations of the test media by means of the data stated. MNNG served as pos. control substance.
Test substance : Spherisorb (95 % <5um) from Phase Sep/Norwalk, CT, amorphous silica
Conclusion : Clastogenic effect is likely to be secondary to cytotoxic activity or may be artefactual.
Reliability : (4) not assignable

(144)

Type : other: DNA damage: Single-cell gel/Comet Assay
System of testing : Chinese hamster fibroblasts (V79) and human embryonic lung fibroblasts (HEL 299)
Test concentration : 68.9 and 137.9 ug/cm2
Cycotoxic concentr. : no data
Metabolic activation : Without
Result : Positive
Method : Other
Year : 1997
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study including amorphous and crystalline silica: 3-h treatment of cells with autoclaved test substance.
Remark : The biological relevance of this genotoxic effect is unclear, because cytotoxicity as well as programmed cell death (apoptosis) may cause DNA

fragmentation, too.

Result : There was a significant dose-related increase in DNA migration in the gel in both target cell types to a similar extent. The effect appeared to be more pronounced for crystalline silica. A medium control, but no pos. control substance was included.

Test substance : Spherisorb (95 % <5um) from Phase Sep/Norwalk, CT, amorphous silica

Reliability : (4) not assignable
Meets generally accepted scientific standards, sufficiently documented, but not appropriate for assessment of mutagenic mechanisms.

(207)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : Rat
Sex : Male
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : single administration (acute) and repeated administration (5 times, subacute)
Doses : acute and subacute: 1.4, 14.0, 140, 500 and 5000 mg/kg, suspended in 0.85 % saline
Result : Negative
Method : other: see Remark
Year : 1974
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : 15 animals per dose group. Observation 6, 24 and 48 hours, resp., after administration (single dose) and 6 hours after last administration (5 doses). Bone marrow cell preparations were made and 50 cells per animal were counted in metaphase for chromosomal aberrations. Negative (0.85 % saline) and positive (0.3 mg/kg triethylene melamine) controls were run in parallel.

Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessment

Flag : Critical study for SIDS endpoint

(143)

Type : Dominant lethal assay
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : single administration (acute) and repeated administration (5 times, subacute)
Doses : 1.4, 14.0, 140, 500 and 5000 mg/kg suspended in 0.85 % saline
Result : Negative
Method : other
Year : 1974
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Chemical treatment of male rats only (10 per group). To cover a complete cycle of spermatogenesis the male rats were mated to virgin females at weekly intervals (8 times in the acute and 7 times in the subacute study). Per male two female mice were used. The females were sacrificed 14 days

after mating, and at necropsy the uterus was examined for deciduomata, late fetal deaths and total implantations. Negative (0.85 % saline) and positive (0.3 mg/kg triethylene melamine, i.p.) controls were run in parallel.

Result : acute: Some changes were observed in the low and mid dose group. In the high dose, no significant changes were seen. Sub acute: In the high dose groups significant decreases were seen in fertility index and number of implants in week 5. Dose releated decreases were observed in corpora lutea (week 5) and dead implants/pregnant female in week 4. Dose releated increases were seen in corpora lutea (week 3), preimplantation loss (week 2, 3). A time trend pattern was not found.

Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented, acceptable for assessment

Flag : Critical study for SIDS endpoint

(143)

Type : Somatic mutation assay
Species : Rat
Sex : Male
Strain : Fischer 344
Route of admin. : Inhalation
Exposure period : 13 wks, 6 h/d, 5 d/wk
Doses : 50 mg/m3
Result : Negative
Method : other: ex-vivo/in-vitro HPRT assay
Year : 2000
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Comparative study including synthetic amorphous and crystalline silica: Whole-body exposure. The testing programme included cellular and biochemical Bronchoalveolar Lavage Fluid Analysis (BLA) on inflammatory markers, histopathology, inflammatory cytokine gene expression, immunohistochemisty for DNA damage, and mutagenesis in alveolar epithelial cells (see other entry: 5.4).
Alveolar type-II cells were isolated from BAL after 13 wks of dust exposure and subjected to the HPRT gene-mutation assay. The cells were cultured for 14 - 21 days selective medium prior to fixation.

Result : There was no increase in 6TG-resistant mutants vs. control (7.6 +-3.4 mutants/10exp6 cells in control), whereas after exposure to crystalline silica, the mutant frequency was significantly enhanced (approx. 30 mutants/10exp6 cells) (Fig. 4).

Test substance : Aerosil 200: CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5 (note: specified as "precipitated" in the report, apparently erroneous).

Reliability : (2) valid with restrictions
2: Comparable to guideline study, containing scientifically justified modifications, no validated standard test in vivo (see: Method).

Flag : Critical study for SIDS endpoint

(123)

Type : other: Host mediated assay
Species : Rat
Sex : Male
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : single application (acute) and repeated application (5 times, subacute)
Doses : acute and subacute: 1.4, 14, 140, 500 and 5000 mg/kg suspended in 0.85 % saline

Result	:	Negative
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Type: Mitotic recombination in Saccharomyces cerevisiae D-3 Method: From the test protocol the used host animal species (mouse or rat) is not quite clear, likely rat. The test substance was administered orally to 10 host animals per dose. In the acute study the yeast (Saccharomyces cerevisiae D-3) was inocculated i. p. after the administration of the test substance. In the subacute study the yeast was injected ater the last administration of the test substance. Negative (0.85 % saline) and positive (350 mg/kg ethyl methane sulfonate, i. m.) controls were run in parallel. The animals were killed three hours after administration and the yeast cells were removed from the peritoneal cavity.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

(143)

Type	:	other: Host mediated assay
Species	:	Rat
Sex	:	Male
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	single application (acute) and repeated application (5 times, subacute)
Doses	:	acute and subacute: 1.4, 14, 140, 500 and 5000 mg/kg suspended in 0.85 % saline
Result	:	Negative
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Type: Salmonella typhimurium reverse mutation assay Method: From the test protocol the used host animal species (mouse or rat) is not quite clear, likely rat. The test substance was administered orally to 10 host animals per dose. In the acute study the bacteria (Salmonella typhimurium strains TA 1530 and his G-46) were inocculated i. p. after the administration of the test substance. In the subacute study the bacteria were injected after the last administration of the test substance. Negative (0.85 % saline) and positive (100 mg/kg dimethylnitrosamine) controls were run in parallel. The animals were sacrificed three hours after administration and the bacteria were removed from the peritoneal cavity. The induction of reverse mutation was quantified on agar plates.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

(143)

5.7 CARCINOGENICITY

Species	:	Mouse
Sex	:	male/female

Strain : other: "mixed strain", increased sensitivity to tumorigenesis in all organs (about 10 %), highest in the lung
Route of admin. : Inhalation
Exposure period : 1 year
Frequency of treatm. : 1x/h for 10 min, 6 consecutive hours, 5 d/wk
Post exposure period : observation for the whole life-span
Doses : Unspecified
Result : Positive
Control group : yes, concurrent no treatment
Method : other:
Year : 1940
GLP : No
Test substance : other TS: precipitated, unspecified

Method : Two groups of mice, untreated (75 m/f), treated (74 m/f). Whole-body exposure system: Clouds of dust were produced by means of a foot-bellow connected with a bottle containing the silica, concentration of particles not controlled and regulated, therefore undefined: Estimated amount of dust based upon measurements was about 0.5 g/d, including the heavier particles which tended to precipitate quickly. By microscopic analysis of particles, "many appeared to be about 5 um and less in diameter".

Histopathology: on lung tissue with tumours.

Remark : Shortcomings in test design: Test material not specified, exposure conditions not defined: absence of particle concentration and size distribution, experimental techniques and technical equipment not adequate.

Result : Survival at 600 days (of treatment = approx. 690 days lifespan) was 12/74 in treated vs. 17/75 in control animals.

There was a significant increase in primary lung tumours (adenomas + carcinomas), 21.3 % (13/61) vs. 7.9 % (5/63) in controls after approx. 700 days in mice living 10 months or longer (see Tab. VII: experimental day 200 plus 90 days of age at the start of the experiment).

At termination of the study (some 900 d), 8 treated animals with carcinoma and 5 treated animals with adenoma were found, while in the control, 2 animals with carcinoma and 3 with adenoma were identified (Tab. I).

Days (Exp.)	Number of mice		Mice with lung tumours alive total(malign.) [Tab.VII]	
	Control	SiO2	Control	SiO2
0	75	74	0(0)	0(0)
200	63	61	1(1)	0(0)
300	57	55	1(1)	0(0)
400	36	39	1(1)	1(0)
500	29	24	2(1)	3(2)
600	17	12	3(2)	5(3)
700	7	6	5(2)	9(5)
800	4	3	5(2)	11(6)
900	0	1	5(2)	12(7)
917	0	0	5(2)	13(8)

Non-neoplastic effects: No obvious fibrosis in lung tissue, but in 50 % of the treated animals vs. 10 % of the controls, nodular fibrotic overgrowth of the mediastenal connective tissue covering the tracheobronchial nodes. In about 30 % of treated animals vs. 14.3 % of controls, overgrowth or hyperplasia of the tracheobronchial lymph nodes.

The incidence of pneumonia appeared to be somewhat increased in treated animals (21.3 % vs. 15.9 % the control) [Tab. VII], in comparison to the other control groups more pronounced.

Conclusion : Amorphous silica have been studied less than crystalline silica. They are generally less toxic than crystalline silica and are cleared more rapidly from the lung (IARC, 1997, p. 210).
According to IARC (1997, p. 210/211), there is inadequate evidence in humans and animals for the carcinogenicity of synthetic amorphous silica. Amorphous silica is not classifiable as to its carcinogenicity in humans (Group 3).

Reliability : (4) not assignable
3a: Significant methodological deficiences (test substance unclear, probably not as described)

Flag : Critical study for SIDS endpoint

29.09.2004 (17)

Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 weeks
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	1.25, 2.5 and 5 %
Result	:	Negative
Control group	:	Yes
Method	:	other: see Remark
Year	:	1986
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Remark : Method: Test procedure comparable to OECD-Guideline, interim kill after 6 and 12 months.

Four groups with 40 male and 40 female animals each.

20 animals per group were reserved for 21 months.

Result : The mean cumulative intake was 143.46, 179.55 and 581.18 g/rat in males and 107.25, 205,02 and 435.33 g/rat in females, resp.

No significant variations in survival rats were observed in males, while the female survival rats were decreased but not statistic significant different from the control group. In body weight, food intake behaviour or in hematology and clinical chemistry parameters no relevant changes were seen. Lower liver weights were noted from 12 to 24 months in the 2.5 and 5 % female dose group.

In histopathological examination the tumor incidence was the greatest in testes, mammary gland (incidence in the controls higher than in the treatment groups) and prepuce (males) and mammary gland and clitoris (incidence in the controls higher than in the treatment groups) in females. (see also IARC 1997)

Test substance : Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8, produced by Fuji Davidson Chemical Ltd., Lot No. JC-2108

Conclusion : In relation to the low -if any- effects to be expected, the test design cannot be satisfactory with respect to biostatistics: The group sizes are too low to discriminate small effects.

Reliability : (2) valid with restrictions
2b: Comparable to guideline study with acceptable restrictions (but see Conclusions)

Flag	:	Critical study for SIDS endpoint
24.09.2004		(107) (185)
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	93 weeks
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	1.25, 2.5 and 5 %
Result	:	
Control group	:	Yes
Method	:	other: see Remark
Year	:	1986
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Method: Test procedure comparable to OECD-Guideline, interim kill after 6 and 12 months. Four groups with 40 male and 40 female animals each: 20 animals per group were reserved for 21 months.
Result	:	The mean cumulative intake after 93 weeks was 38.45, 79.78 and 160 g/mouse in males and 37.02, 72.46 and 157.59 g/mouse in females, respectively. In the 2.5 and 5 % groups the food consumption increased, but this was accompanied by a decreased body-weight gain in the 5-% group from week 15 through 50 (males, <0.01) and from week 30 through 50 (females, p<0.05). No significant difference in survival rats or behaviour was observed. No dose-related alteration in hematologic parameters was evident. None of the changes in organ weights were sex- or dose related. At the histopathological examination tumors were found in the hematopoietic organs, particularly malignant lymphoma/leukemia, which occurred in 7/20 (38 %) in the female groups of the 2.5 % dose group. The results of the Cochran-Armitage test for positive dose-related trends in the incidence of tumors were not significant. Females: In the lungs, the frequency of adenocarcinomas was 1/16 (6.25 %) for the control, 1/19 (5.3 %) for the 1.25-%, 0/20 for the 2.5-%, and 1/20 (5 %) for the 5-% dosage groups of females (no adenomas). Males: In the lungs, the frequency of adenocarcinomas was 1/16 (6.25) for the control, 2/17 (11.8 %) for the 1.25-%, 3/14 (21.4 %) for the 2.5-%, and 3/16 (18.8 %) for the 5-% dosage groups of males. In the liver, the correlation of hyperplastic nodules/hepatocellular carcinoma/hemangioma/fibrosarcoma in the treated groups, as compared with the control group, was relatively low. Non-neoplastic lesions were observed in the subcutis, lungs, kidneys, and liver in the treated groups. But these were considered to be of no toxicological significance.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8, produced by Fuji Davidson Chemical Ltd. Lot No. JC-2108
Conclusion	:	The tumour responses in the silica-fed mice were not statistically significantly different from the controls (Fisher´s exact test and Cochran-

Armitage test for trend) (see also: IARC 1997, p. 171).

Note - limitation: In relation to the low -if any- effects to be expected, the test design cannot be satisfactory with respect to biostatistics: The group sizes are too low to discriminate small effects.

Reliability : (2) valid with restrictions
2b: Comparable to guideline study with acceptable restrictions (but see Conclusions)

Flag : Critical study for SIDS endpoint

24.09.2004 (107) (185)

5.8.1 TOXICITY TO FERTILITY

Type : One generation study
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 6 months
Frequency of treatm. : Daily
Premating exposure period
Male : 4.5 month
Female : 4.5 month
Duration of test : 6 months
No. of generation studies : 1
Doses : 497 mg/kg (m); 509 mg/kg (f)
Control group : Yes
NOAEL parental : = 497 mg/kg bw
NOAEL F1 offspring : = 497 mg/kg bw
Result : Negative
Method : other: see Method
Year : 1962
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Screening test:
Parents (40 m / 40 f), treatment started at a mean weight of 90 - 110 g; mating procedure (14 d): 5 treated and 5 control females (mated to 1 male, resp.) after 4 1/2 months of exposure.
The test-substance dose was adjusted to the body-weight gain.
Hematology carried out in 5 animals of each group prior to exposure, each month and at the end of the study. Histopathology only in parent animals.
Pups were examined for external appearance and development.

Note: As compared to current standards, number of pregnant animals was too low (5 instead of 20 females), mating ratio was 1:5 instead of 1:2; only 1 male used per treated and control group; one dose tested, not at the limit as recommended in the guideline 415.

Result : Parents: No clinical symptoms; no mortality, no abnormalities in body-weight gain and feed consumption, no haematological findings. In pups during lactation [total: 45 and 37 (control), resp.], no behavioral or developmental or structural abnormalities.

Test substance : Aerosil (not further specified)

Reliability : (3) invalid
3a: Significant methodological deficiences (no complete one generation study according to current standards: too low number of animals and examinations)

Flag : Critical study for SIDS endpoint

(70)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	Gavage
Exposure period	:	from day 6 to day 15 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	20 days
Doses	:	0, 13.5, 62.7, 292 and 1350 mg/kg bw/day
Control group	:	Yes
NOAEL maternal tox.	:	= 1350 mg/kg bw
NOAEL teratogen.	:	= 1350 mg/kg bw
Method	:	
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The administration of up to 1350 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well documented (though with deficiencies in description of test design) acceptable for assessment of mechanisms.
Flag	:	Critical study for SIDS endpoint

(88)

Species	:	Mouse
Sex	:	Female
Strain	:	CD-1
Route of admin.	:	Gavage
Exposure period	:	from day 6 to day 15 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	20 days
Doses	:	0, 13.4, 62.3, 289 and 1340 mg/kg
Control group	:	Yes
NOAEL maternal tox.	:	= 1340 mg/kg bw
NOAEL teratogen.	:	= 1340 mg/kg bw
Method	:	other
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The administration of up to 1340 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well documented (though with deficiencies in description of test design) acceptable for assessment of mechanisms.

Flag	:	Critical study for SIDS endpoint (88)
Species	:	Rabbit
Sex	:	Female
Strain	:	Dutch
Route of admin.	:	Gavage
Exposure period	:	from day 6 to day 18 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	29 days
Doses	:	0, 16.0, 74.3, 345 and 1600 mg/kg
Control group	:	Yes
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 mg/kg bw
Method	:	other
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham treated controls.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well documented (though with deficiencies in description of test design) acceptable for assessment of mechanisms.
Flag	:	Critical study for SIDS endpoint (88)
Species	:	Syrian hamster
Sex	:	Female
Strain	:	other: (outbred)
Route of admin.	:	Gavage
Exposure period	:	from day 6 to day 10 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	14 days
Doses	:	0, 16.0, 74.3, 345 and 1600 mg/kg
Control group	:	Yes
NOAEL maternal tox.	:	>= 1600 mg/kg bw
NOAEL teratogen.	:	>= 1600 - mg/kg bw
Method	:	other
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occuring spontaneously in the sham-treated controls.
Test substance	:	Syloid 244: CAS-Name: Silica gel, precipitated, cryst.-free; CAS-No. 112926-00-8
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well documented (though with deficiencies in description of test design) acceptable for assessment of mechanisms.
Flag	:	Critical study for SIDS endpoint

(88)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

Endpoint	:	Mechanistic Studies
Study descr. in chapter	:	
Reference	:	
Type	:	
Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	Intratracheal
No. of animals	:	
Vehicle	:	Water
Exposure period	:	
Frequency of treatm.	:	20 instillations with 2-wk intervals between the treatments
Doses	:	
Control group	:	
Observation period	:	
Result	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Comparative mechanistic study with various particulate matters (quartz, amorphous silica, carbon black and coal dust). Various examinations included: histopathology, cell differentiation in the bronchiolar lavage, and characterization of the cellular immunogenic responsiveness of lavage cells to a LPS (E. coli antigen) or zymosan stimulus 9 months after first instillation (see also for Pathology: other entry this chapter). Immunobiological endpoints, such as generation of reactive nitrogen and oxygen species and production of TNF-alpha (tumor necrosis factor) served as markers to further characterize the inflammatory reaction.
Result	:	Acc. to authors, among the particles tested, only synthetic amorphous silica failed to impair the natural cellular responsiveness to LPS stimulation, while all others more or less suppressed this function. (Note: The concurrent treatment of the animals with a protective agent, PVNO, largely restored the cellular responsive capacity despite exposure to quartz.). The high number of PMN in the synthetic amorphous silica group correlates with the reactivity of the cells to produce TNF upon stimulation (note: TNF plays a major role in recruitment of neutrophils into the lung.). Furthermore, the relatively high protein content in lungs after treatment with amorphous silica may account for the enhanced production of reactive species. Although the implication of these findings for pulmonary cytotoxicity are yet obscure, the histopathological observations clearly demonstrate that exposure to synthetic amorphous silica is less damaging than exposure to quartz and other tested materials.
Test substance	:	Aerosil 150: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well documented, acceptable for assessment of mechanism

Flag	:	Critical study for SIDS endpoint (83)
Endpoint	:	Cytotoxicity
Study descr. in chapter	:	
Reference	:	
Type	:	
Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	Intratracheal
No. of animals	:	
Vehicle	:	Water
Exposure period	:	
Frequency of treatm.	:	1x
Doses	:	2 mg Aerosil/animal (as aqueous suspension)
Control group	:	
Observation period	:	1 or 3 months
Result	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	LUNG EFFECTS: Multifocal, dose-dependent, moderate to severe alveolar and interstitial accumulations of particle-laden macrophages were observed in the lungs. Although macrophages often had a foamy appearance, there were no or only very few signs of degeneration or necrosis as well as no evidence of lipoproteinosis with synthetic amorphous silica (p. 123), contrary to treatment with quartz or carbon black (p. 118). A specific finding in the 4-wk experiment was multifiocal moderate to severe granulomatous alveolitis (Fig. 1)(p. 118) characterized by abundant macrophages (Fig. 2), lesser number of fibroblasts and T-lymphocytes and only a few granulocytes. With increasing time after instillation, the majority of these inflammatory foci had progressed to very localized, "scar-like" interstitial fibrotic granulomas. The fibrotic lesions are considered to represent chronic stages of alveolitis induced by (also single doses of) synthetic amorphous silica, which may arise from acute alveolitis. Lung-associated LYMPH NODES: Moderate to severe chronic granulomatous inflammation was noted after either treatment time, associated with significant infiltration of granulocytic cells as well as focal development of fibrosis.
Test substance	:	Aerosil 150: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5
Conclusion	:	The fibrotic lesions seen after single and repeated intratracheal administration of synthetic amorphous silica are considered to represent chronic stages of alveolitis (p.120), which may arise from acute alveolitis. Pathogenically, they are thought to have resulted from acute epithelial damage at the sites of particle deposition with subsequent (granulomatous) inflammation and production of granulomatous tissue, primarily consisting of macrophages and later on mostly of fibroblasts. Probably due to the high removal of synthetic amorphous silica from the lung, the granulomatous inflammation becomes progressively "interstitialized" and resolves by leaving only focal fibrotic scar tissue.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well documented, acceptable for assessment of mechanism
Flag	:	Critical study for SIDS endpoint

(83)

5.10 EXPOSURE EXPERIENCE

Type of experience : other: Human - Epidemiology / Inhalation Hi-Sil, Silene

Remark : Occupational exposure:
78 workers (age 21 - 67 years, average age 34 1/4 years; exposure time 1 - 16.6 years, average 4 3/4 years) who were employed in the manufacturing and processing of Hi-Sil (precipitated silica) and Silene (Calcium silicate) were examined from 1941 to 1959. The medical examination was complemented by chest x-rays. The dust concentration ranged from 0.35 to 204 mg/m3. No evidence of silicosis or other pulmonary disease was found.

Test substance : Hi-Sil, Silene (not further specified), CAS-Name: Silica, submicron amorphous, precipitated, crystalline-free, CAS-No.: 112926-00-8

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

(161)

Type of experience : other: Human - Medical Data / skin contact

Remark : From 1972 - 2000 more than 200 workers had intensive and regular contact with silica. During this time, there was no evidence of skin allergy caused by amorphous silica.

The only signs seen on workers´skin were signs of irritation due to the desiccative and defatting property of amorphous silica which resulted in skin dryness.

This adverse effect was reversible and could be controlled by regular use of skin-protection ointment.

Reliability : (2) valid with restrictions

Flag : Risk Assessment

(197)

Type of experience : other: Human - Epidemiology / Inhalation HIL-SIL, Silene

Remark : Epidemiology:
The authors reviewed serial spirograms, respiratory questionnaires, and chest radiographs of 165 workers at two plants exposed for a mean of 8.6 years to precipitated amorphous silica (PAS). 44 workers had been exposed on the average 18 years (range 10-35 years). Dust levels varied between <1 - 10 mg/m3 with some higher intermittent levels.

Cough and dyspnea correlated with mean pack-years of smoking but not PAS exposure. Linear regression analysis of yearly change of all pulmonary function variables showed no correlation with either the dose of PAS nor total years of exposure. Among 44 workers with a mean exposure time of 18 years, yearly decline of pulmonary function variables were similar to the overall group.

Eleven workers had minimal radiographic evidence of minimal pneumoconiosis, but this effect was biased by prior occupational exposure to limestone.

Of 143 workers with serial radiographs and exposure to only PAS, none had radiographic pneumoconiosis. Respiratory symptoms in PAS workers correlate with smoking but not with PAS exposure, while serial pulmonary

function values and chest radiographs are not adversely affected by long-term exposure.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
(203) (204) (205)

Type of experience : Other: Human - Epidemiology / Inhalation Aerosil

Remark : Occupational exposure:
143 workers were involved in an occupational study (1959 - 1985). The exposure time ranged from 1 to 34 years. 54/143 workers (36 %) complained of some disorder or exhibited abnormalities in lung function or histology. 34/54 (63%) suffered from dry cough, expectoration or dyspnoea. A total of 42/54 affected workers (78 %) had some characteristic that could confound any effect from AEROSIL exposure (pre-existing disorder and/or previous confounding exposure: 32/54 = 59 %, smoking: 30/59 = 56 %), only 12/54 (22 %) had neither, which represents 8 % of the cohort. Radiological examination did not show any signs of fibrotic disease. A spirometric examination showed obstructive and/or restrictive ventilation disturbances in 24 workers. Most of the observed findings in this study occurred in connection with confounding factors (smoking) or case histories.

No control group was included.

Flag : Critical study for SIDS endpoint
(60) (86) (146)

Type of experience : other: Human - Epidemiology / Inhalation Aerosil

Remark : Occupational exposure:
In a production plant of amorphous silica, in total 215 workers were examined during 1947 and 1959 and in total 720 chest X-rays were made. The only significant observation was the hairline accentuation of the interlobar fissures, suggesting slight interlobar pleuritis. No signs of silicosis could be observed. The dust concentrations to which the workers were exposed, varied with the place of work and the job. The following air concentrations were measured: Immediately at the filling station 15 - 100 mg/m3, in the baggaging room 2 - 6 mg/m3 and in the production room 3 - 7mg/m3.

Test substance : Aerosil (not further specified)
Flag : Critical study for SIDS endpoint
23.09.2004 (196)

Type of experience : other: Human - Oral ingestion / Excretion

Method : TEST: Controlled human stress test
To 5 m / 1 f persons (age 22 - 28), Aerosil 175 was administered in two portions of 1.25 g (suspended in 250 ml apple juice each time) at day 4 of an experimental period of 7 days.

Six other volunteers (also 5 m /1 f) received the same amount FK 700 suspended in 250 ml apple juice each time, at day 4 of an experimental period of 7 days.

The total urine was collected daily and analysed for the mononomer SiO_2-content.

Individual changes of the SiO_2 excretion were determined (comparison SiO_2 before and after silica application).

ANALYSIS

SiO2 according to Baumann (determination after alkaline hydrolysis with molybdate).

Result : During the four days post-treatment, significant changes of the renal SiO2 secretion were not seen. Daily SiO2 increments in urine after ingestion ranged between 7 and 23 mg.

Aerosil:
The individual baseline values of the pre-test phase were very variable and individually different, mean excretion rates ranging from 25 to 87 mg/day.

In the post-treatment phase, individual mean excretion rates ranged from 32 to 61 mg/day.

FK 700:
The individual baseline values of the pre-test phase were very variable and individually different, mean excretion rates ranging from 16 to 71 mg/day.

In the post-treatment phase, individual mean excretion rates ranged from 20 to 81 mg/day.

Overall, increases in excretion were not unequivocally detectable. The small apparent increases were in marked contrast to the high dose of 2500 mg SiO2 applied.

Test substance : Aerosil 175, CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5

FK 700, Silica, precipitated, crystalline-free, CAS No. 112926-00-8

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

Flag : Critical study for SIDS endpoint
22.09.2004 (71) (139)

Type of experience : other: Worker exposure

Remark : Detailed information see Chapter 1.10
Flag : Risk Assessment
23.09.2004 (28)

Remark : Renal SiO2-secretion after oral administration in humans:
To 5 m / 1 f persons (age 22 - 28), precipitated, amorphous silica was administered in two portions of 1.25 g (suspended in apple juice). The total urine was collected and analysed for the mononomer SiO2-content. In 5/6 persons the renal SiO2 secretion was increased by 7 to 23 mg. In 1/6 persons it was decreased (26 mg), the medium daily SiO2 secretion of the following 3 days was increased by 4 to 20 mg (5/6 persons) and slightly decreased by 1/6 persons.
23.09.2004 (71) (139)

Remark : Occupational exposure:
A single chest X-ray was made from 99 workers who had been involved in the manufacture of synthetic silicates (Gasil and Sorbsil/Lucilite) for varying periods of time. The X-ray films were each read independently by two readers. No evidence of any occupational disease (silicosis, etc.) was found.
(20)

Remark : Occupational exposure:

41 workers exposed to amorphous silica (precipitated, amorphous silica) dust were compared with a control group. From a questionary blood gas analysis or chest radiographs a differentiation was not possible. Test of respiratory function showed a decrease in forced expiratory flow in the exposed groups, althought no correlation between the exposure index and polmonary function was found. The authors concluded that smoking and exposure to amorphous silica synergise to induce small airway disease.
(19)

Remark : Occupational exposure:
Light- and scanning electron microscopical studies with energy dispersive X-ray microanalysis were performed on biopsy material obtained from two patients with longstanding occupational exposure to amorphous silica, in whom radiologically interstitial pulmonary fibrosis in vicinity of dust deposits, which could be identified as amorphous and rarely as crystalline silica, was found. The analytical examination of the dust samples showed, that these contained 1 - 3 % crystalline silica (alpha-quartz).
(160)

Remark : Human-lipids:
The short-term safety and efficacy of Syloid HC was studied in six adults (aged 20 to 51 years) with primary type II hyperlipoproteinemia. Three men and three women were admitted to a metabolic unit for three weeks. Four subjects were studied on a liquid formula diet containing 100 mg cholesterol/day and a ratio of polyunsaturated to saturated fat (P/S) of 1.0, while the other two were ingesting a solid food diet containing 200 mg cholesterol/day and a P/S of 2.0. Sufficient calories were provided to keep the weight constant (+- 1 kg). Syloid HC was administered with the morning and evening feeding, starting with an oral dose of 1.0 g/d that increased by 1.0 g daily up to a final dose of 16 g/d. Syloid HC was given in two equally divided doses with the morning and evening feeding. No statistically significant effect of Syloid HC on the plasma levels of total cholesterol, low density (beta) lipoprotein (LDL) cholesterol, high density (alpha) lipoprotein (HDL) cholesterol or total triglycerides was found. In one subject, bile acid excretion increased somewhat but not markedly so. There was no significant increase in the serum or urinary levels of silica after Syloid HC administration. As judged by clinical and chemical criteria, no significant adverse effects of Syloid HC were observed on hepatic or renal function. The number of white and red blood cells and platelets were unaffected. Two subjects had a fall in serum iron levels, one a fall in hemoglobin concentration, two had falls in carotene, one a fall in serum folate and another in the vitamin A level.
Clinical side effects include constipation in half the subjects, an unusual aftertaste in all 6, and one patient suffered gastritis.

Several conclusions may be made from the study:
1.) In doses up to 16 g/d Syloid HC did not have a significant effect on the plasma lipid and lipoprotein levels in subjects with primary type II hyperlipoproteinemia;
2.) Syloid HC did not markedly enhance bile acid excretion, suggesting that it was not binding bile acids as efficiently in vivo, as it did in vitro (previous studies of W. R. Grace and Co);
3.) Syloid HC, as ecpected, was not absorbed significantly from the intestine;
4.) No marked untoward side effects were observed; however, at higher doses, Syloid HC is unpleasant to take and produces constipation.
(96)

Remark : Skin sensitization (patch test):
Patches were applied for six days to the arms of 10 men and the arms or legs of 10 women. After a two-week interval, new patches were applied for 48 hours as a challenge test. Skin under the patches was examined at one, two, three and six days after the first application and on removal of the challenge patch. No skin reactions were seen at any examination on any subject.

Test substance : Silica, colloidal and vitreous (active incredient SiO2: 45 % w/w)

(75)

Remark : Subcutaneous administration: Twenty-eight men were given 2 to 8 intradermal injections of 1 to 4 mg Ludox colloidal silica in saline. Granulomatous inflammation were observed within a few days and persisted for months.

(82)

Remark : Blood level:
SiO2 levels in blood were determined in 264 humans. The mean value was 8.3 +- 24 gamma SiO2 per ml (total) blood. There was no significant influence in sex, age, employment, lung disease (dust lung) or other disease. After oral administration of Silicol (a colloidal silica protein) or Silistren (silica acid, tetraglycol ester) a rapid increase of SiO2 blood levels and a rapid elimination with the urine (approx. 8-24 hours) was seen.

(206)

Remark : Silicosis with silica (comment):
The inhalation of crystalline silica can cause nodular fibrosis in lung tissue and in lymph nodes. Such severe effects were not seen, when workers were exposed to dusts which contain only non crystalline silica. In nearly all papers describing silicosis to exposure to amorphous silica, also the presence of crystalline silica at the workplace or in the examine biopsy material is reported. Unfortunately not all authors gave data or details to the conditions at the workplace of the exposed workers (see also Ruehl et al., 1990; Ferch and Habersang, 1982).
In ferroproducing plants dust and smoke occurring at the operating site of the ferrosilicon furnaces mainly contain amorphous silica. Peak concentrations reached 100 mg/m3 and more (total dust). In these dust samples also crystalline silica was found in a range between 2 to 21 % (see also Jung and Drees, 1960; Prochazka, 1971).

(87) (124) (163) (169)

Remark : Occupational exposure:
In 4 of 28 workers, which were exposed to amorphous silica during 2 - 32 years (mean 8.9 years) findings in X-ray exa-minations were observed indicating to silicotic changes. The measured fine dust concentrations were between 0.8 and 1.9 mg/m3 with a crystalline silica part of < 1 - 2%. The causality between amorphous silica exposure and X-ray findings is something questionable, because the air concentration and exposure time (7 - 10 years) does not correlate with the development of silicosis. Also an anamnesis (exposure before employment) and confounding factors were not considered in this study.

(153) (169)

Remark : The medical supervision in amorphous silica (precipitated) producing factories (during 1952 to 1981) showed no indications to silicosis in workers which were employed between one or more than 20 years (mean

13.2 years). The medical check performed from time to time contained hematology, urine analysis, lung functions and X-ray of chests. Negative results were also seen in another production plant producing fumed silica during 1959 and 1981. The employment time was between 2 and 22 years (mean 9.1 years).

(39) (42) (43) (87)

Remark : The role of the amorphous silica in the so-called Ferro-Alloy worker`s disease is discussed controverse by several authors.

(7) (8) (23) (91) (168) (184) (186)

Remark : Occupational exposure:
In 11 out of 40 workers exposed to amorphous silica. In a production plant of silicon metal crystalline silica (quartz) is vaporized by heating and on cooling condensed to a fine powder. Roentgenographic abnormalities were noted in 11 of 40 men who were exposed for 11 to 18 years in this plant. Findings from 3 cases were presented. They had wide-spread pulmonary disease with granulomatous nodules and fibrosis but there was no demonstrable restrictive impairment of pulmonary function. In biopsy material 6.7 % silica was found. All three workers smoked cigarettes, and this may be cause of the obstructive emphysema observed.

(193)

Remark : Occupational exposure:
The complete health records of 78 men employed in the manufacture and processing of Hi-Sil, an amophous, hydrated silica pigment, and silene (calcium silicate) in the period from 1941 to 1959 were reviewed. Dust concentrations ranged from 0.35 to 205 mg/m3. No evidence of silicosis or other pulmonary disease was observed. The incidences of illnesses and injuries were similar to those of other workers in this plant.

(122)

Remark : A cohort mortality study of white men employed for at least one year between 1939 and 1966 at three U.S. plants was done to evaluate the risk of lung cancer and nonmalignant respiratory disease among workers exposed to silica dust. A follow-up of 2055 men through January 1, 1981, indicated a substantial excess of nonmalignant respiratory disease among those with high levels of exposure to silica dust and rose with the number of years exposed. The levels appeared much lower among those exposed in more recent time periods. For lung cancer, men exposed to high levels of silica dust had a non-significant standardized mortality ratio of 1.37.

(187)

Remark : Occupational exposure:
In workers exposed only to amorphous silica dust for five years or more, only doubtful linear-nodular changes were found. Concentrations of dust containing amorphous silica were above 20 million particles per cubic foot in 30 to 51 % of the samples taken during the first year of the study and in 0 to 9 % three years later.

(125)

Remark : Occupational exposure:
The role of amorphous (fumed) silica on 14 workers (Portuguese factory of ferrosilicon alloy and of silicon metal) with X-ray alterations was

determined. Six of the workers had no other occupational lung aggressions and had 12 - 18 years of exposure to amorphous silica. The remaining eight workers had other occupational lung aggressions and had silica exposures of 7 to 21 years. Raw data only is given, and the authors state that "the probability of the lung pathogenic action of this inhaled silica is very suggestive". The authors did not consider the exposure situation (no data to air concentration at the work place).

(168)

Type of experience : other: Human - Epidemiology: Allergy case report

Result : A case of allergic dermatitis developing after a contact exposure of the skin to Aerosil is described. The authors suppose that violated intactness of the skin integument is largely responsible for the allergic reaction.

Test substance : Aerosil (not further specified)

Reliability : (4) not assignable
4d: Reference in foreign language.

23.09.2004 (145)

5.11 ADDITIONAL REMARKS

Type : other: Biochemical or cellular interactions / inflammatory response (see entry 5.4)

Method : Comparative study including amorphous and crystalline silica: Whole-body exposure. The testing programme included cellular and biochemical Bronchoalveolar Lavage Fluid Analysis (BAL) on inflammatory markers, histopathology, inflammatory cytokine gene expression, immunohistochemistry for DNA damage (terminal transferase dUTP nick-end-labeling = TUNEL staining), and mutagenesis in alveolar epithelial cells.

Particle size of dust in exposure chamber: mass median aerodynamic diameter = 0.81 um; Chamber concentration: 50.4 +-19 mg/m3 (note: Crystalline silica was administered only at 3 mg/m3, based on the expected lung burden and pulmonary reaction.) Silica burden was measured after 6.5 and 13 weeks of exposure and 3 and 8 months of recovery.

For pathological effect see 5.4; mutagenic assay: see other entry 5.6.

Result : M-RNA synthesis of the cytokine MIP-2 could be shown to be operative in rat lungs during the presence of either silica, i.e. after elimination of amorphous silica in the recovery phase, the expression of MIP-2 ceased, whereas being continued in the recovery groups of crystalline silica.

Test substance : 1. Aerosil 200: CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5 (note: specified as "precipitated" in the report, apparently erroneous)
2. cristalline silica (cristobalite)

Conclusion : The concurrence between increased MIP-2 levels and proliferation of neutrophils further support a role for this chemokine in the inflammatory response to particle exposure.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessement

Flag : Critical study for SIDS endpoint

(123)

Type : other: Elimination after sc. Application

Remark : Species: rat
Strain: albino, in-bred
Sex: female
Route of admin.: subcutaneous
a) suspension in water and 0.5 % Tween 80
b) dry powder (operative subcutaneous administation)
Exposure period:
Freq. of treatment:
Post. obs. period:
Doses: 30, 40 and 50 mg
Control Group:
Method: examination times 45 min (control value), 3 and 6 weeks
Year: no data
GLP: no
Results: after 6 weeks 95 - 97 % of the substance was eliminated; local tumefaction, slightly inflammatory reaction

Test substance : Aerosil 150 (not further specified): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Reliability : (4) not assignable
Abstract only

(51) (131)

Type : Behaviour

Remark : After inhalative exposure of rabbits (681 days) or intratra-cheal administration of different amount of silica with different particle size (0.2 - 5.0 um) the lungs were examined.
It was shown that not only the solubility of the SiO2 was responsible for formation of nodular fibrotic or diffuse-fibrotic changes in the lungs. Concentration of the dissolved SiO2, the surface forces of the colloidal particles, mechanical and physio-chemical conditions were regarded as important for the observed changes.

(121)

Type : Biochemical or cellular interactions

Remark : Surface equal probes of amorphous silica showed a higher hemolytic activity than quartz. Interaction with biological membranes (erythrocytes, liver cell lysosomes) were responsible for the cytotoxic effect.

Test substance : Aerosil 200 (CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5), and other types of silica

(180)

Type : Cytotoxicity

Remark : Fumed silicas and micronised silica gels (Aerosil OX 50, Aerosil 200, Cab-O-Sil M5 and micronised silica gel) were cytotoxic to mouse peritoneal macrophages in in vitro tests.
The precipitated silica was less cytotoxic. In comparison of the results with crystalline silica the author stated that the in vitro experiments are too sensitive (no significant difference between amorphous and crystalline silica) and not in accordance with the results of in vivo studies.

Test substance : Aerosil 200: CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5
Aerosil OX 50, Aerosil 200, Cab-O-Sil M5(CAS Name: Silica, amorphous, fumed (pyrogenic), cryst.-free, CAS No. 112945-52-5), and micronised silica gel

(24)

Type : other: adjuvant effect

Remark : Amorphous silica (Aerosil) s. c. injected to guinea pigs enhanced the humoral immune response to particulate and soluble antigens. Dependent on the system used adsorption of antigen on silica particles is not absolutely required for its adjuvanticity.

Test substance : Aerosil

(148)

Type : other: silicotic effect

Remark : Species: rat
Strain: SPF-Sprague-Dawley
Sex: female
Route of admin.: i. p.
Exposure period:
Freq. of treatment:
Post. obs. period: 3 month
Doses: 10 mg/rat
Control Group:
Method: 15 f rats; the test substance was injected in 0.9 % NaCl-solution, the animals were histological and enzymological examined; in addition animal- and organ weights and SiO2-contend in organs were determined
Year: no data
GLP: no
Results: abdominal organs were adhered (only few animals); enlarged lymphatic nodes; increased weights of liver, spleen, kidney, network and lymphatic nodes; small granulomata in the network amd few quartz-typical foci in the lymphatic nodes (only few animals); no changes in liver and spleen

Test substance : Wessalon S: amorphous precipitated silica, 98 % SiO2, BET surface 190 m2, mean aggregate size 7 µm

(202)

Type : other: tissue reaction

Remark : Results:
Macroscopically quartz and quartz glass causes comparable changes, but the progression was more pronounced with quartz. Histopathologically with quartz glass a retardation of progress was seen between 4 and 8 months, but not with quartz. The administration of amorphous (pyrogenic) silica causes very rapid onset of the tissue reaction in the lungs, which afterwards does not show any tendency to progress. After one month 60 % of the administered dose was eliminated.
With the ferro silicon smelting furnace tissue reactions mainly developed during the first month, subsequently there is a very little progress. When Kieselguhr containing no crystalline components is heated to 800 °C for 24 h its fibrogenic tendency increases markedly although this heating is insufficient to cause demonstrable transformation to crystalline silica forms. Thus, in the animal experiment, it is possible to demonstrate that there are different types of amorphous silica as regards their fibrogenic potency.
Species: rat
Strain:
Sex: female
Route of admin.: intratracheal
Freq. of treatment: single administration
Post. obs. period: up to 8 month
Doses: 40 mg/rat
Control Group: yes
Method: particles were suspended in physiological saline. 1 ml containing 40 mg of silica was injected into the trachea.

Animals were grouped 10 to 20 animals and were killed 1, 2, 4 and 8 month after injection.
Year: no data
GLP: no

Test substance : - Pyrogenic amorphous silica
- Quartz
- Quartz-glass (particles 0 - 3 µm)
- Silicon dioxide from the smoke of a ferrosilicon smelting furnace (1 % crystalline silica)
- Kieselguhr
- Kieselguhr heated to 800 °C for 24 h, no crystalline components demonstrable

(183)

Type : other: tissue reaction

Remark : Species: mouse/rat
Strain:
Sex:
Route of admin.: i. p.
a) moistened with water and 0.5 % tween 80
b) dry powder
c) aqueous suspension (1:1)
Exposure period: -
Freq. of treatment: single administration
Doses: mice 15 mg, rats 60 to 100 mg (not specified: mg/kg or mg/animal) and additional "subletal" dosage
Control Group:
Method: no further data
Year: no data
GLP: no
Results: the mice and rats died within 2 to 5 or 3 to 5 days, resp., after application. Following the "subletal" dosage, the animals showed after 2, 4 or 8 weeks, resp., a diffuse fibrosis in the abdominal region.

Test substance : Aerosil 150 : CAS-Name: Silica, amorphous, fumed (pyrogenic), CAS No.: 112945-52-5

(51) (131)

Type : other: tissue reaction

Remark : Species: rabbit
Strain: New Zealand
Sex: no data
Route of admin.: implantation into the paravertrebral musculature
Exposure period: -
Freq. of treatment: single implantation
Post. obs. period: up to 6 month
Doses: 100 mg
Control Group: yes
Method: The animals were sacrified 2, 4 and 6 month after application and histologically examined. Year: no data
GLP: no
Results: The histopathological examination showed granulation tissue, fatty macrophages and foreign matter. To the end of the study, the changes were reduced. In controls smaller granulation foci were observed.

Test substance : Syloid 244 and Aerosil 200

(94)

Type : other: tissue reaction

Remark : After administration of 1, 2.5, 5, 10 and 50 mg Aerosil per rat (Wistar), the

animals were sacrified after 3, 6 and 12 months. One animal was killed in extremis in week 44 (2.5 mg dose group). In all test groups the body weight gain was not influenced. After 3 months a slightly increase of the lymph nodes was seen in doses of 2.5 mg and higher. This effect was more pronounced in doses of 5 and 10 mg. Fibrotic effects were seen after 3 months (in 50 mg dose group) and after 6 months in the 10 and 50 mg dose groups. At the end of the study, fibrotic effects were also seen in some animals of the 5 mg dose group. In the abdomen cavity adhesion with connective tissue, perihepatitis, perinephritis and agglomeration of macrophages (spleen, liver) were observed. In the lymph nodes agglomeration of macrophages and a tendency to cellular necrobiosis were observed. The alteration did not show a silicotic-like progression.

Test substance : Aerosil 200 (not further specified): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No.: 112945-52-5

(105)

Type : other: tissue reaction

Remark : Different samples of amorphous silica were intraperitoneally administrated to guinea pigs. Ludox, a colloidal silica type caused death, dependend on the size of the silica particles.
On autopsy after one or two months, resp., necrosis with acute inflammatory reaction, scan like lesions, enclosing injected materials were seen. The occurence of proliferative type of reaction were inconsistent in these studies. Esterified and resuspended silica powders (Ludox) reduced the severity of the immediate reactions. Other types of amorphous silica showed apparently inert tissue effects and did not produce proliferative reactions after intraperitoneal injection.

(76) (77) (78) (79)

Type : other: tissue reactions

Remark : The intratracheal administration of a solution with 0.2 % molecular-soluted silicious acid (mono and oligomers) caused death within 24 hours (lung edema) in rats. In inhalation experiments using solutions with the same concentration no clinical signs were reported and after 300 days of inhalation exposure no pathological changes were seen.

After intratracheal administration of amorphous silica (primary particle size 10 - 20 um) 10 mg and more death occurred. After injection of 5 mg, the animals survived and in the lungs necrosis, cell damage, macrophages but no nodular fibrosis were seen. In the alveolar septes the connective tissue was increased. After intraperitoneal injection of 50 mg SiO2, the surviving animals did not show any pathological findings after one year

After a fractionated administration small nodules with a little dust were seen, which contained a lot of cells, reticulin and collagen.

After intratracheal injection of 50 mg silica gel in rats small foci of macrophages with minimal reticulin formation were observed in the lungs. Also pneumonia and desquamative catarrh occured, but up to 15 months no progress in fibrosis was seen.

(127) (137)

Type : other: tissue reactions

Remark : The intratracheal administration of SiO2 samples of various origin and types had different effect to the lung tissue. After heating of amorphous silica samples (8 h, 800 degree C) quartz-like tissue reaction were seen. Not in all of these heated probes a crystaline part could be detected with the used analytical method.

(128)

Remark : After i. p. injection of Aerosil 200 in rats within 3 months conglutinations in the peritoneum, increased organ weights and silicotic changes were seen in tissues and organs in the peritomeum. With Wessalon S (precipitated silica) the changes were much milder.

(202)

Remark : In the range of 1 - 15 x 10 exp 6 particles of amorphous silica the number of particles phagocytized per macrophage was increased, but the intraphagosomal pH was not influenced. When the particles were instilled intratracheally to rabbits 24 hours or 1 week before lavage and pH-measurement, the intraphagosomal pH values in the macrophages were lower.

Test substance : no data

(158)

Remark : Not all used mice strains produced IgG1 and/or IgE antibodies when Aerosil was used as adjuvant but a booster effect (secondary effect) was seen in all strains. The adjuvant effect was more selectively directed to the production of IgE than to IgG1 antybodies.

Test substance : Aerosil

(149)

Remark : Cab-O-Sil showed more pronounced hemolytic activities in comparison to crystalline silica (Min-U-Sil) on a per mass basis. The opposite was the case when the hemolytic activity was measured per unit surface area (The surface structure (silanol groups) is involved in cell lysis).

Test substance : Cab-O-Sil

(159)

Remark : In each three rats 1 ml of a suspension with amorphous silica (derived from the smoke of a ferrosilicon smelting furnace, less than 1 % crystalline SiO2) or quartz with a concentration of 40 mg/ml were injected. After 4 months the rats were killed. In BAL the recovery of alveolar cells was most pronounced in the rats exposed to quartz. Also in these rats lymphocytes and neutrophils and the hyaluronate level (biochemical marker of fibrosis?) were increased. In the amorphous silica rats in one animal slight changes in recovered BAL cells were seen.

(191)

Remark : Rats inhaled 30 mg/m3 amorphous silica (TK 800 and VN 3, resp.) about 5 hours at three days.
Results for TK 800:
20 hours after the last exposure 0.31 mg SiO2/lung were found and after 1 month 0.11 mg and after 3 months 0.06 mg
SiO2. In the mediastinal lymph nodes 0.009 - 0.012 mg SiO2 were found.
Results for VN 3:
20 hours after the last exposure 0.21 mg SiO2/lung were found and after 1 month 0.07 mg and after 3 months 0.06 mg
SiO2. In the mediastinal lymph nodes 0.005 - 0.013 mg SiO2 were found.

Test substance : Mattierungsmittel TK 800 and Ultrasil VN 3

(38)

Remark : Rats were intraperitoneally injected 50, 100 or 200 mg amorphous silica (TK 800) as an aqueous suspension. These doses were lethal and at autopsy reddening of the peritoneous and of the net work was seen. With another substance type (VN3) death occurred only in some animals and the survivors were sacrificied 3.5 months later. In the peritoneal cavity no dust cell foci or other macroscopically changes were observed.

Test substance : Mattierungsmittel TK 800 and Ultrasil VN 3

(38)

Remark : Female rats were exposed by inhalation 4 hours/day up to 6 days to various amorphous SiO2 types (A: pyrogen, surface area 150 m2/g; B: pyrogen Aerosil OX 50, surface area 50 m2/g; C: amorphous; D: precipitated, surface area 140 m2/g). Within 3 months in the average of several experiments 73.8 % SiO2 were eliminated from the lungs. In the mediastinal lymph nodes only small amounts of SiO2 were found (0.6 to 3.5 % of the SiO2 eliminated from the lungs and 0.2 to 2.8 % of the total retained amount).

(136)

Remark : After intratracheal administration of 50 mg condensed silica (no further details) to rats the collagen content increased. After 6 months there was a decrease of the collagen content. The total observation time was 17 months.

(6)

Remark : After inhalative exposure of female rats to various silica samples the elimination rate of SiO2 from the lungs were examined. The amorphous silica dusts were eliminated rapidly in comparison with quartz. A great influence of the particle size was not observed. The lymphatic glands were moderately enlarged and the silica content was less than 2 % of the amount eliminated. These results differ considerably from those obtained with quartz or other unsoluble dusts. Most of the amorphous SiO2 species were eliminated within 1 - 2 months and in the lymphnode relatively small amounts were detected. The less soluble amorphous SiO2 dusts were eliminated mor slowly than the more soluble types.

Test substance : - Aerosil: 40 - 45 µg/ml water soluble within 24 h
- Precipitated amorphous silica: 76 µg/ml water soluble
- Precipitated amorphous silica: 90 µg/ml water soluble
- Quartz

(134) (135)

Remark : Amorphous silica was i. p., intratracheal and i. v. injected in rats, guinea pigs and rabbits. The intraperitoneal introduction of 200 mg of dust in guinea pigs caused death.
For the majority of the rats the dust also proved lethal when administered intratracheally in a 37.5 mg dose. Guinea pigs, on the contrary, tolerated an intratracheal dose of 75.0 mg fairly well. Of 5 rabbits 3 died of doses of 100 mg to 1000 mg of the dust introduced i. v., while two survived injections of 1000 mg. In rats the main features were diffuse pulmonary granulomata in which necrosis ocurred and collagen formed later. In guinea pigs the lesions remained pre-dominantly cellular, and these lesions were partly or wholly reversible. On i. v. injections in rabbits, cor pulmonale, hepatic cell atrophy and interstitial nephrosclerosis were significant findings. All lesions except the renal damage proved to be reversible.

(171)

Result	:	Six h after instillation of a particle suspension containing 2 mg SiO2, 82 % was retained within the lungs and decreased to 18 % after 2 d. This amount was slowly eliminated with a half-life of about 11 d, i.e. 2 weeks after instillation, the retention was 10 % (p. 111).
Test substance	:	Aerosil 150: >99.8 % (SiO2): CAS-Name: Silica, amorphous, fumed (pyrogenic), cryst.-free; CAS-No. 112945-52-5
Reliability	:	(2) valid with restrictions

(83)

6.1 ANALYTICAL METHODS

Test substance : Pyrogenic (fumed) silica
Method : Various methods: Field Emission Scanning Microscopy (SEM), Laser Light Diffraction (LD), Time-and-Flight Particle Size Analysis (TOF), Cascade impactor (CI)

Method : Comparative analytical studies, objective: to investigate particle sizes of pyrogenic silica grades, to compare different measurement techniques and, thereby, describe structural parameters such as shape and internal structure of aggregates and agglomerates, in particular in relation to shear and dispersion forces.

For comparison, a silica product exhibiting a near monodisperse size distribution with a modal value of 1.5 µm, Silica Monospheres 1500 (Geltech), was included. This stable reference material is expected to reflect the typical but small deviations between applied methods.

The technical limitations of analytical techniques are being discussed.

Aerodynamic diameters below 20 µm were determined by CI, larger particles according to free settling behaviour in air.
Geometrical diameters below 70 µm were obtained from SEM and above using light optical images.

The following methods of aerosol generation were applied:
- Fluidized bed dispersion using injection nozzles (high shear stress)
- Pulsating air flow dispersion (lower shear stress)
- Free settling (simulation of settling in air).

Remark : Using conventional particle sizing techniques, pyrogenic amorphous silica shows large particles in the µm-size range, markedly larger than expected from the high surface area.

The macroscopic appearance is that of a white, fluffy powder-like solid with an extremely low bulk density of down to 0.03 g/cm3 (Barthel et al. 1998, p. 745).

Aerodynamic diameters of most silica types, ranging from 0.45 - 85 µm correlated in linear manner with geometrical diameters from 1 - 250 µm (Stintz 2001, Fig. 1.3.2; Barthel et al. 1998, Fig. 6): This indicates a uniform structure concerning the aerodynamic behaviour of the silica agglomerates, independent of the size and shear stress applied during generation (Bartelt et al. 1998, p. 749).
The best fit of the functional relationship between both parameters was a linear regression-plot with a slope of 3.6 (conversion factor), i.e. an MMAD of 1 µm corresponded to 3.6 µm (geometric) (Stintz 2001, Fig. 1.3.2, p. 5).

Based on above measured data, the effective microscopic particle density of the agglomerates of low-bulk silicas could be calculated to be at 0.075 g/cm3, which is close to the bulk density of 0.05 g/cm3 for various pyrogenic silica samples and well fitted the broad particle-size range under investigation (from 1 - 250 µm geometric diameter).

Assuming the agglomerates to be spheres, this apparent density could be related to a porosity of 96.6 %.

For two silica types diverging values were found, effective particle size 0.25 g/cm3 and a conversion factor of 2 instead of 3.6.

Shear forces cause a breakdown of agglomerates as well as dilution tends to prevent the formation of larger agglomerates due to the larger interparticle distances and low collision frequencies.
But irrespectice of test conditions, the fraction of particles having a low MMAD was always very small, shown with HDH H15: Even under worst-case conditions, i.e. single particle settling (low aerosol concentration range), not more than 2 vol% of particles of <30 µm have been measured.

With respect to respirable fractions of the aerosols, 1 % and generally significantly less is potentially able to reach the alveolar region when inhaled (Stintz 2001, Tab. 6.4, p. 30 and p. 32): "The thoracic and alveolar fractions of the whole size range according to EN/DIN481 have been calculated for the silica analyzed; they are on a very low level of <1 vol% = wt%."

Test substance : HDK Types: >99,8 % SiO2, approx. 130-380 m2/g (BET), bulk density 33-48 g/l, CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Reliability : (1) valid without restriction
1c: Meets national and international standard methods

Flag : Critical study for SIDS endpoint

(5) (181)

Test substance : Silicas and silicates
Method : Determination of particle size

Method : GENERAL METHODOLOGY:
A. Determination of the average size of AEROSIL:
The average size of agglomerates of pyrogenic silicas is difficult to determine because of chain formation of primary particles. Therefore, the average primary particle size is the preferred parameter to be analysed by electron microscopic visualisation: The diameters of 3000 - 5000 particles are semiautomatically measured, and the arithmetic mean represents the average size of the primary particle. For the measurements of the diameter, only those primary particles are considered where at least one half of the circumference is recognisable (Degussa 1992).

B. Determination of the average size of precipitated silicas/silicates:

Unlike AEROSIL, the agglomerate particle size of precipitated products is relatively easy to determine.

For that purpose, a Coulter Counter is used in an aqueous solution. Before measuring in aqueous suspension, the material under analysis is dispersed with the aid of ultrasonics. Depending on the particle size resulting from the experiment, measuring capillaries ranging from 30 to 400 µm are inserted.

For agglomerate particle sizes which are more than 1 µm, IR laser apparatus can also be used.

For coarse silicas with an agglomerate particle size of 100 or 50 µm, it is the best to use the airjet sieve (Alpine).

Remark : COMMON METHOD (particle size):
Multisizer, 100 µm capillary according to ASTM C690-1992 (see also Chapter 2.14).

Methodological variants are: Multisizer, 50, 140, and 200 µm capillary according to ASTM C690-1992;
Particle size d50, Cilas 1064 G, following ISO 13320-1;
Particle size d50, Malvern, following ISO 13320-1;
Alpine air-jet sieve, following ISO 8130-1.

Remark:
Primary particles are not existent as individual units (compare IARC, 1997, Tab. 7, p. 57). Therefore, primary particle size is generally not accounted because of the particles aggregate.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

(33) (34)

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I U C L I D

Data Set

Existing Chemical	:	ID: 1344-95-2
CAS No.	:	1344-95-2
EINECS Name	:	Silicic acid, calcium salt
EC No.	:	215-710-8
TSCA Name	:	Silicic acid, calcium salt

Producer related part

Company	:	Association of Synthetic Amorphous Silica Producers (ASASP)
Creation date	:	29.06.2004

Substance related part

Company	:	Association of Synthetic Amorphous Silica Producers (ASASP)
Creation date	:	29.06.2004
Status	:	
Memo	:	Origin Degussa AG, 11 Oct. 2002, Rev. 5
Printing date	:	06.12.2004
Revision date	:	21.09.2004
Date of last update	:	29.09.2004
Number of pages	:	43
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : other: consortium
Name : ASASP (Association of Synthetic Amorphous Silica Producers) [CEFIC Sector Group]
Contact person :
Date :
Street : Avenue E. van Nieuwenhuyse 4
Town : B-1160 Brussels
Country : Belgium
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint

Type : lead organisation
Name : Degussa AG
Contact person : Dr. Rudolf Weinand
Date :
Street : Rodenbacher Chaussee 4
Town : D-63457 Hanau-Wolfgang
Country : Germany
Phone : +49 6181 59 4787
Telefax : +49 6181 59 2180
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint

Type : cooperating company
Name : Huber Engineered Materials
Contact person :
Date :
Street : Strandesplanaden 110
Town : DK-2665 Vallensbaek Strand
Country : Denmark
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

Flag : Critical study for SIDS endpoint

Type : cooperating company
Name : INEOS Silicas Ltd
Contact person : Dr. P.A. Hunt
Date :
Street : 4 Liverpool Road
Town : Warrington, Cheshire, WA5 1AB
Country : United Kingdom

Phone	:	+44 1925 416292
Telefax	:	+44 1925 416113
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Flag	:	Critical study for SIDS endpoint
Type	:	cooperating company
Name	:	RHODIA Silica Systems
Contact person	:	Marie-Christine Rosset (see Remark)
Date	:	
Street	:	La Danica - 21, avenue Georges Pompidou
Town	:	F-69006 Lyon
Country	:	France
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	marie-christine.rosset@eu.rhodia.com
Homepage	:	
Remark	:	contact point: RHODIA SERVICES Etoile Part-Dieu 190, Avenue Thiers F-69006 LYON France Tel: +33 4 37 24 88 63 Fax: +33 4 37 24 88 81
Flag	:	Critical study for SIDS endpoint

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Silicic acid, Calcium salt
Smiles Code	:	
Molecular formula	:	
Molecular weight	:	
Petrol class	:	

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	inorganic
Physical status	:	solid

Purity : >= 98 % w/w
Colour :
Odour :

Remark : In this dossier only data about industrially produced, amorphous calcium silicates with a high grade of dispersity are listed. Naturally occurring crystalline calcium silicates and man-made fibrous calcium silicates are not considered.
Precipitated synthetic amorphous calcium silicate is a synthetic amorphous form of the reaction product of calcium chloride or calcium hydroxide with sodium silicate. After ignition the content of the oxides (calcium oxide and silicon dioxide) ranges are described as follows:

Composition of typical Precipitated Synthetic Amorphous Calcium Silicate:

Parameter	wt.%
SiO2	> 50 - < 95
CaO	> 1 - < 35.0
Na2O	< 4.0
Trace oxides	< 0.1

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Silicic acid, calcium salt [IUPAC and CAS name]

Remark : Tradenames: Sipernat 880, Extrusil, Microcal ET, Hubersorb, Zeopharm, Huberderm TM, RxCipients TM, Zeocal, Ultrasil
Flag : Critical study for SIDS endpoint

(2)

Calcium silicate

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :
Remark : Heavy Metal Impurity Data:

Metal Impurity/ppm	Ca Silicates
Antimony	< 5
Barium	< 50
Chromium	< 10
Arsenic	< 3
Lead	< 10
Mercury	< 1

Cadmium < 1
Selenium < 1
==========

The given limits are typical data. The mentioned products are in line with the quality requirements of DIN EN 71/3 (toys), BGVV Recommendation LII (Fillers for Commodities Made of Plastic) and of quality requirements for direct food additive E551, E552 and E554 (2000/63/EU and 2001/30/EU).

Purity : typical for marketed substance
CAS-No : 7647-14-5
EC-No : 231-598-3
EINECS-Name : sodium chloride
Molecular formula :
Value : <= 2 % w/w

Remark : Produced in powder form and may contain up to 15 % (w/w) water
Flag : Critical study for SIDS endpoint

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 40800 - tonnes produced in 2000

Remark : The production volume in Europe comprises all synthetic amorphous silicates.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.09.2004 (3)

1.6.1 LABELLING

Labelling : no labelling required (no dangerous properties)
Specific limits : No

Flag : Critical study for SIDS endpoint

1.6.2 CLASSIFICATION

Classified : no classification required (no dangerous properties)
Class of danger :
R-Phrases :
Specific limits :

Flag : Critical study for SIDS endpoint

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : Type
Category : Use resulting in inclusion into or onto matrix

Remark : As in general the amorphous silicas/silicates become an integral part of a product matrix, the powder form no longer exists in most applications.
Flag : Critical study for SIDS endpoint
29.09.2004

Type of use : Type
Category : Wide dispersive use

Remark : The applications of silicates are versatile, but in general for consumers not freely available as powders, as the silicates are bound in the matrix of an article.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Agricultural industry

Remark : No data on this application is available
24.09.2004

Type of use : Industrial
Category : Leather processing industry

Remark : No data on this application is available.
24.09.2004

Type of use : Industrial
Category : Paints, lacquers and varnishes industry

Remark : Paints: Synthetic amorphous silicas and silicates are used as functional pigments in emulsion paints.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Paper, pulp and board industry

Remark : Paper: Small amounts of synthetic amorphous silicas and silicates added to paper improve printability and opacity. Synthetic amorphous silica is also used in specially coated paper grades for ink jet printing, copying etc.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Polymers industry

Remark : Plastics: Plastic films often tend to stick to each other but this can be prevented by the addition of an synthetic amorphous silicas and silicates as an anti blocking agent. They are also used in polyester and epoxy resins for thixotropy control.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial

Category : Textile processing industry

Remark : No data on this application available
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : other: Rubber industry

Remark : Rubber and Silicones: Synthetic amorphous silicas and silicates are used as reinforcing fillers for many non-staining and colored rubber and silicones products.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Anti-set-off and anti-adhesive agents

Remark : For example, silicates provide thickening in pastes and ointments to inhibit the separation of components.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Fillers

Remark : For example in Rubber and Silicones: Synthetic amorphous silicas and silicates are used as reinforcing fillers for many non-staining and colored rubber and silicones products.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use :
Category : Personal and domestic use

Remark : Consumer Use Products: Due to their inert nature synthetic amorphous silicas/silicates are used in cosmetics (especially tooth paste), pharmaceuticals and foods. They provide thickening in pastes and ointments to inhibit the separation of components and maintain flow properties in powder products. They can also function as a carrier for fragrances or flavors.
Flag : Critical study for SIDS endpoint
24.09.2004

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : Synthetic Amorphous Precipitated Silica/Silicates:
Wet Process
The production processes for precipitated synthetic amorphous silica and silicates can be divided into the following general unit operations: raw material storage, synthesis, washing/solid-liquid-filtration, drying packing and storage. Optionally after the drying step the product can be milled,

granulated or surface treated to promote hydrophobicity. These individual steps may be operated in a continuous or batch process manner.

Raw materials for the production of precipitated synthetic amorphous calcium silicates are aqueous calcium chloride or calcium hydroxide. In case of the production of precipitated sodium-aluminium silicates, aqueous sodium silicate solution (e.g. water glass) and generally aluminium sulphate are used for metal salts.

The reaction and precipitation conditions (e.g. acid:alkali ratio, temperature, concentration, stirring rate, and residence time) determine the size of the silicate particle and the way they bind together to form higher structures like aggregates and agglomerates.

To date, only batch precipitation processes in stirred vessels have attained economic importance, although continuous precipitation techniques have been reported.

The suspension received from precipitation is filtered. For this purpose, usual filter presses, membrane filter presses or belt/drum filters are used. Equipment selection is dependent on the properties and structure of the silica produced. The solid content of the filter cake typically varies between 15 to 35 wt%, depending on the filter technique employed.

After filtration a washing step follows to remove salts (normally done in the filtration equipment). The level of salt retained in the product depends on the intended application of the final silicate. For drying, contact dryers are mostly used (plate, belt, rotary drum) as well as spray dryers are used. After conventional drying, the product has to be milled in jet mills or mechanical mills.
During this process, the particle size distribution and sieve residue characteristics of the product are modified.

Flag : Critical study for SIDS endpoint

(2)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : 3 mg/m3

Remark : "Allgemeiner Staubgrenzwert", related to fine dust (respirable fraction).

(18)

Type of limit : TLV (US)
Limit value : 10 mg/m3

Remark : The value is TWA = Time-Weighted Average (8-Hour Exposure Limit) for total dust containing no asbestos and <1 % crystalline silica.

(1)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: (provisionally) Degussa AG
Labelled by : other: (provisionally) Degussa AG
Class of danger : 0 (generally not water polluting)

Remark : German WGK [Water Endangering Class]
Flag : Critical study for SIDS endpoint

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : EINECS
Additional information :

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Non-occupational exposure:
Levels of addition of calcium silicate to foods (Data for the USA, where calcium silicate has GRAS status, see also sect. 1.13 Additional Remarks):

Food category	Weighed mean percent
baked goods, baking mixes	0.16
grain products, such as pastas or rice dishes	0.05
fats and oils	0.19
meat products	0.01
poultry products	0.01
fish products	0.02
candy, soft	0.01
soups, soup mixes	0.03
snack foods	0.13
beverages, nonalcoholic	< 0.01
nuts, nut products	< 0.01
gravies, sauces	0.03
dairy products analogs	0.49
seasonings and flavours	0.30

Based on this data the NRC subcommittee has calculated the possible average daily intake for calcium silicate to be 300 mg/individual. It was recognized by the NRC subcommittee thas this assumption of possible

intake is likely overestimated.

(21)

Remark : Non-occupational exposure:
Based on the 260 t/a calcium silicate totally used in the USA in 1975 and an U. S. population of 215 million people the per capita daily intake was estimated to be 3 mg.

(21)

1.11 ADDITIONAL REMARKS

Remark : In the USA calcium silicate has GRAS status (generally recognized as save). The following uses in foods are authorized:

use	FDA-reference
- anticaking agent	21 CFR 182.2227 21 CFR 172.410
- pigments and colourants in resinous and polymeric coatings	21 CFR 175.300

The tolerance in table salt is 2 percent and in baking powder 5 percent.

(21)

Remark : Synthetic calcium silicate may be added as an anti-caking agent, release agent, icing sugar or in sweets (EEC-No. 552) to feeding stuffs under the provisions laid down in the directive 70/524/EEC and according to the requirements set out in the annex to the same directive.

(23)

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	ca. 1700 °C
Decomposition	:	no, at °C
Sublimation	:	No
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data avaialble: analogy - it is assumed that the melting point will be si,ilar to that of silica (CAS No. 7631-86-9] (see IUCLID Silicon Dioxide]
Reliability	:	(4) not assignable
Flag	:	Critical study for SIDS endpoint

(6)

2.2 BOILING POINT

Remark	:	>>1700 °C, not relevant for normal and intended use, analogy approach

(9)

2.3 DENSITY

Type	:	Density
Value	:	ca. 2 g/cm³ at 20 °C
Method	:	other: DIN / ISO 787/10
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Density relates to that of the primary particles, not to the silicate in aggregated/agglomerated form as it exists.
Reliability	:	(2) valid with restrictions Meets national/international standards: limited documentation
Flag	:	Critical study for SIDS endpoint

(9)

Type	:	bulk density
Value	:	ca. 230 - 300 kg/m3 at °C
Method	:	other: DIN / ISO 787/11
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	An accurate volume of a sample is measured in a glass cylinder in such a way that no empty space remains and the surface is horizontal. The glass cylinder containing this samples is being tapped (tamped) in a volumeter 1250 times. Then the resulting volume is read off. That means the sample is not pressed to a minimum under high pressure. Tapped/tamped density is the minimum bulk density.
Reliability	:	(2) valid with restrictions Meets national/international standards: limited documentation
Flag	:	Critical study for SIDS endpoint

(9) (13)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Decomposition	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on the structure and nature of this substance, its vapour pressure will be negligible, practically 0 mmHg, at ambient temperature and pressure (compare IUCLID Silicon dioxide, CAS No. 7631-86-9): significant vapour pressure (10 mmHg) only at the melting point.
Flag	:	Critical study for SIDS endpoint

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	at °C
pH value	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	This parameter is not considereed applicable due to its physico-chemical nature (inorganic compound, non-lipophilic).
Flag	:	Critical study for SIDS endpoint

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	ca. 260 at 20 °C
pH value	:	ca. 9.7
concentration	:	6660 mg/l at 30 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	Directive 92/69/EEC, A.6
Year	:	1998
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Elemental analytical method not specified.
Result	:	

	48	72	96 hours	
SiO2	200 +-10	190 +-10	190 +-10	mg/l
Na	61 +-3	60 +-3	60 +-3	mg/l
Ca	8.6 +-0.5	9.7 +-0.5	10.7 +-0.6	mg/l

Overall solubility is about 260 mg/l.

Test condition : Approx. 1 g was stirred at 30 °C in 150 ml water (purissima) for 48, 72, and 96 h. After settling for 24 h at 20 °C, the suspension was membrane-filtered (pore size= 0.45 µm). Elements were determined in the filtrate.
Test substance : Calsil B
Reliability : (2) valid with restrictions
2b: Guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint

(10)

Solubility in : Water
Value : at °C
pH value : = 7 - 11
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Reliability : (2) valid with restrictions
Meets national/international standards: limited documentation
Flag : Critical study for SIDS endpoint

(2)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(5)

2.8 AUTO FLAMMABILITY

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(5)

2.9 FLAMMABILITY

Result : non flammable
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(5)

2.10 EXPLOSIVE PROPERTIES

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable, note - amorphous silica, related compounds, can be used as a fire-extinguishing agent.
Reliability : (4) not assignable
Manufacterer data / data from handbook or collection of data.

(8)

2.11 OXIDIZING PROPERTIES

Result : other: not expected
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(5)

2.12 DISSOCIATION CONSTANT

Acid-base constant : no data
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Particle size

Remark : Value: mean size of agglomerates: 5 um
Method: coulter counter, 100 um capillary, ASTM C 690-1992
Reliability : (2) valid with restrictions
Meets national/international standards: limited documentation
Flag : Critical study for SIDS endpoint

(7) (13)

Memo : Particle size

Remark : Average value: 7.5 µm
Reliability : (4) not assignable
Manufacturer data
(20)

Memo : Surface

Method : Specific Surface Area (N2): today ISO 5794-1, Annex D
Remark : Value: BET surface area: 35 m2/g
Method (BET surface area): Brunauer, Emmet, Teller (BET); J. Amer. Chem. Soc., 60, 309 (1938) (DIN 66 131)
Reliability : (4) not assignable
Manufacturer data
Meets national/international standards: limited documentation
(7) (13)

Memo : Surface

Remark : Value: 60 m2/g, method no data
Reliability : (2) valid with restrictions
Meets national/international standards: limited documentation
Flag : Critical study for SIDS endpoint
(20)

3.1.1 PHOTODEGRADATION

Type	:	other: air, water
Light source	:	
Light spectrum	:	Nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no light-induced transformation expected.
Flag	:	Critical study for SIDS endpoint

3.1.2 STABILITY IN WATER

Type	:	Abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable towards acids and alkali), no chemical transformation under environmental conditions significant and relevant; ion exchange possible.
Flag	:	Critical study for SIDS endpoint

3.1.3 STABILITY IN SOIL

Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	"SiO2" is a stable substance. In the environment, it occurs in different forms (as amorphous and crystalline silica, as silicates complexed with metals), and it is one of the most abundant materials on the earth's surface (see also Sec. 3.2). Whatever its origin, man-made or natural silicates, and whatever their structure, crystalline or amorphous, once released and dissolved into the environment, no distinction can be made between the initial forms of silicates. Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable towards acids and alkali), silicates are considered as an inert substance, and no chemical transformation under environmental conditions is expected to be significant

and relevant. Ion exchange possible.
Flag : Critical study for SIDS endpoint

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : Volatility
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : Silicates are not volatile under environmental conditions due to their chemical nature and inherent physical properties: Due to low water solubility and extremely low vapour pressure, silicates are expected to be distributed mainly into soils/sediments, weakly into the water and probably not at all in the air.

Type : other: deposition
Media : other: water, soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : There is a mixing up between the natural cycle of silicon, where transport of siliceous material by air is important (the eolian erosion of land surfaces, particularly desert), and the releases and the transport of man-made silicates.

If silicates are released into the air or into water, the ultimate compartment will always be soils or sediments due to their physico-chemical properties (vapour pressure, water solubility, density, chemical structure).

Silicates are expected to combine undistinguishably with the soil layer or sediment due to its chemical identity with inorganic soil matter and will be subjected to slow natural transformation processes of weathering and corrosion.
Flag : Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

Memo : Stability

Remark : Amorphous silicates are not degraded in actual use.

3.5 BIODEGRADATION

Deg. product :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 – 1.4

Remark : Due to the chemical nature (inorganic structure) biodegradation is not applicable.
Flag : Critical study for SIDS endpoint

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Elimination :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 – 1.4

Remark : Due to their inherent chemico-physical properties, such as absence of lipophilicity, as well as the capability of the organism to excrete absorbed SiO2 components, bioaccumulation of silicates can be disregarded.

But silica can be actively accumulated by terrestrial plants (e.g. grass) and some marine organisms (e.g. diatoms, radiolarians, and sponges), which are normal natural processes.
Flag : Critical study for SIDS endpoint

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	> 10000 measured/nominal
LC50	:	> 10000 measured/nominal
LC100	:	> 10000 measured/nominal
Limit test	:	Yes
Analytical monitoring	:	No
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1998
GLP	:	Yes
Test substance	:	other TS
Remark	:	No data on calcium silicate available: Analogy! Toxicity to fish is not expected (see dossier on Na-Al silicate, CAS No. 1344-00-9, also dossier on silicon dioxide, chemically prepared, CAS-No. 7631-86-9).
Result	:	No deaths occurred during testing. Concentrations are described as loadings (nominal concentrations).
Test condition	:	In a pre-test, the water-soluble fractions of the nominal concentrations of 100, 1000 and 10000 mg/l has been tested. In the main test, only the highest concentration was examined (limit test). The water extracts were prepared by stirring corresponding suspensions for 24 h at 25 °C with subsequent filtration of the suspensions (saturated solution). Test solutions were then adjusted to pH 7.00. Concentrations are described as loadings (nominal concentrations).
Test substance	:	Other TS: SIPERNAT 820A, sodium aluminium silicate (Degussa) [CAS No. 1344-00-9]
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(14)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	> 10000 measured/nominal
Method	:	OECD Guide-line 202
Year	:	
GLP	:	Yes
Test substance	:	other TS
Remark	:	A. No data on calcium silicate available: Analogy! Toxicity to daphnia is not expected. There is a corresponding study performed with Aerosil 200, another amorphous silica, with a similar result: see IUCLID 7631-86-9, 4.2.
Result	:	After 24 h of exposure 7.5 % and 2.5 % of the daphniae were immobile at test concentrations of 1000 and 10000 mg/l, resp. The observed effects were not dose related. Therefore, the effects can be attributed to physical

hampering of the daphnias.

(note: There is a corresponding study performed with Aerosil 200, another amorphous silica, where the physical effect was apparently more marked: see IUCLID 7631-86-9, 4.2.)

Test condition : Concentrations of 1000 and 10000 mg/l were tested, and results refer to loading. Because of the poor solubility of the test substance the test solution was stirred for 20 hours. The test media remained turbid throughout the test and starchy particles were observed on the bottom of the test vessels.

Concentrations can be described as loading rate. Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).

Test substance : Other TS: ULTRASIL VN 3 (>98 % SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: 24 h instead of 48 h applied.

Flag : Critical study for SIDS endpoint

(17)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	other: biomass and growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 10000 measured/nominal
EC10	:	> 10000 measured/nominal
EC50	:	> 10000 measured/nominal
Limit test	:	
Analytical monitoring	:	No
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1998
GLP	:	Yes
Test substance	:	other TS

Remark : No data on calcium silicate available: Analogy! Toxicity to algae is not expected.

Result : Results are given in nominal concentrations (loadings). After 72 h, an increase in biomass at a factor of >30 was achieved in all tests without significant difference of the highest concentration from the control run, while at the lower concentrations results may indicate slight stimulation of growth.

Test condition : Preparation of test solutions:
Water extracts from 6250, 630, and 60 mg/l silica were produced by stirring the suspensions for 24 h in 0.5 l ultrapure water, followed by filtration through paper filter.

The final nominal concentrations in the test media were obtained by addition of the algal preculture and the mineral salt concentrate to the filtrated extract, corresponding to 10000, 1008, and 96 mg/l nominal.

Empty controls ("blanks") without the algae suspension were prepared for each concentration with the suitable water-silica extract.

Temperature was 24.9 +-0.3°C;
Illumination: approx. 8000 lux (>= 120 uE/m2sec).

3 to 5 parallel tests were prepared for each concentration and respective

controls. Initial cell concentration: approx. 8.5 x10exp4 cells.

Extinction differences were determined at 24, 48, and 72 h at 578 nm.
Initial pH: 8.00 (control); between 8.12 and 8.58 (tests).

Test substance : Other TS: SIPERNAT 820A, sodium aluminium silicate (Degussa) [CAS No. 1344-00-9]

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(15)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	Aquatic
Species	:	
Exposure period	:	
Unit	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	no data - assumed to be not toxic, based on inherent physico-chemical substance properties and ubiquitous nature of this compound
Flag	:	Critical study for SIDS endpoint

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	ca. 3400 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Number of animals	:	40
Vehicle	:	physiol. Saline
Doses	:	100 - 5000 mg/kg
Method	:	other
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The substance was suspended in 0.85 % saline. 5 animals per test group, 10 in the 5000-mg group. Observation period 10 days. (Method p. 118- 120; Results p. 5 and 9 - 11)
Remark	:	The result of this test is questionable, because in other acute and subacute toxicology studies (in vivo genetic toxicity tests, see chapter 5.6). 5000 mg/kg did not cause lethality. It is assumed that probably the alkalinity of the test solution caused the deaths.
Result	:	At doses of >= 2000 mg/kg, deaths occurred within 24 hours. Stomach mucosa bloody with distension, pleural fluid present, lungs congested. 10/10 animals died at 5000 mg/kg.
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

(22)

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Number of animals	:	
Vehicle	:	physiol. Saline
Doses	:	5000 mg/kg
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Method: The substance was suspended (24.1 % (w/v)) in 0.85 % saline. Observation period 7 days.
Result	:	No clinical symptoms or other findings contrary to previous entry.
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(22)

Type	:	LD0
Value	:	> 10000 mg/kg bw
Species	:	Rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	
Vehicle	:	other: oral feed
Doses	:	10 g/kg bw
Method	:	
Year	:	1979
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The product was mixed with stock diet at a ratio of 1:4 (w/w) and fed to the trained animals during a 24 h period.
Result	:	Most animals consumed the supplemented diet quantitatively. No clinical symptoms or other pathological findings following autopsy. No diarrhea, stool changed colour to grey, but showed normal consistency with faecal pellets considerably bigger than normal.
Test substance	:	Amorphous silicates including Ca-Silicate, Extrusil [CAS No. 1344-95-2], not further specified
Reliability	:	(2) valid with restrictions 2b: Comparable to guideline study with acceptable restrictions (only summary report)
Flag	:	Critical study for SIDS endpoint

(12)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data - assumed to be non-toxic within the scope of technical feasability, based on analogy: see IUCLID Silicon Dioxide (SAS) [CAS No. 7631-86-9]
Flag	:	Critical study for SIDS endpoint

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	

Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data - assumed to be non-toxic based on analogy: see IUCLID Silicon Dioxide (SAS) [CAS No. 7631-86-9] and Na-Al-Silicate [CAS No. 1344-00-9]
Flag	:	Critical study for SIDS endpoint

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	
Classification	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data - assumed to be not irritating, based on analogy: see IUCLID Silicon Dioxide (SAS) [CAS No. 7631-86-9] and Na-Al-Silicate [CAS No. 1344-00-9]
Flag	:	Critical study for SIDS endpoint

5.2.2 EYE IRRITATION

Species	:	
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data - assumed to be not irritating, based on analogy: see IUCLID Silicon Dioxide (SAS) [CAS No. 7631-86-9] and Na-Al-Silicate [CAS No. 1344-00-9]
Flag	:	Critical study for SIDS endpoint

5.3 SENSITIZATION

Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data - assumed to be not sensitizing, based on analogy: see IUCLID Na-Al-Silicate [CAS No. 1344-00-9]
Flag	:	Critical study for SIDS endpoint

5.4 REPEATED DOSE TOXICITY

Type	:	Chronic
Species	:	Rat
Sex	:	male/female
Strain	:	other: "albino"
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	1.0, 5.0, 7.5 and 10 % (w/w) in feed
Control group	:	Yes
NOAEL	:	7.5 %
Method	:	other
Year	:	1957
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No deaths and no gross signs of toxicity; at 10% in diet growth suppression; slight elevation of organ weights at the higher dose levels; no significant changes of hematological and biochemical values; slightly elevated pH of the urine; no tumors are observed. NOAEL estimated to be about 5000 mg/(kg*d) (dietary level of 7.5 %).
Test substance	:	Silenen EF = calcium silicate (acc. to Plunkett and de Witt 1962)
Reliability	:	(4) not assignable A final report summary of Hazleton Laboratories, the original study was reported to the FDA.
Flag	:	Critical study for SIDS endpoint

23.09.2004 (4) (25)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	13 wks
Frequency of treatm.	:	6 h/d, 5 d/wk
Post exposure period	:	up to 52 wks
Doses	:	1.3, 5.9 or 31 mg/m3 (mean analytical values)
Control group	:	yes, concurrent no treatment
NOAEL	:	= 1 mg/m³
LOAEL	:	= 5.9 mg/m³
NOEL	:	< 1
Method	:	other: acc. to OECD Guide-line 413, see Method
Year	:	1985
GLP	:	Yes

Test substance : other TS

Method : Comparative study including Aerosil R974 (fumed, hydrophobic), Sipernat 22S (precipitated, hydrophil) as well as quartz (crystalline).
Special modifications as compared with standard study:
Examinations primarily focused upon changes in the lung, respiratory tract, and regional (hilus and mediastinal) lymph nodes, including collagen and silica determinations in the lung.

Post-exposure recovery period up to one year was enclosed:
10 m / 10 f animals per group sacrificed after 13 wks, 50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks).

Haematology and urinalysis were conducted 5x periodically up to week 65 (including recovery). Blood chemistry was carried out group-wise on autopsy after defined intervals up to week 66 (including recovery).

Remark : No data on calcium silicate available: Analogy! No higher toxicity expected from exposure to the Ca salt than to silicon dioxide (see also dossier on silicon dioxide CAS-No. 7631-86-9).

Result : The respiration rate showed a concentration-related increase when compared to the controls (only qualitatively evaluated); the body-weight gain was slightly depressed.

Red blood cell count and hemoglobin were statistically higher in males exposed to 30 mg/m3, but not in females.

White blood cell count due to increases in the numbers of neutrophilic leukocytes were elevated in both males and females of the 6- and 30-mg groups, but concentration-response relationship was poor.

After 3 months recovery, these blood parameters normalized. Blood chemistry and urine analysis were without significant findings. At autopsy after exposure, swollen and spotted lungs and enlarged mediastinal lymph nodes were observed, the degree of severity being treatment-related. At 6 and 30 mg/m3, the lung weights and the collagen content in the lungs were clearly increased, most pronounced in males showing this effect also at 1 mg/m3. The above-mentioned effects gradually subsided after the exposure period, but in males exposed to 6 and 30 mg/m3 the collagen content was still above control values at the end of the study.

Silica could be detected in lungs only in relatively small amounts at the end of the exposure period, on the average 0.2 mg in all animals of the 30-mg groups. Only one male exposed to 30 mg/m3 showed a small amount of silica in the regional lymph node. During the post-exposure observation period, no silica could be recovered from any animal.

The microscopic examination at the end of exposure period showed accumulation of alveolar macrophages and granular material, cellular debris, polymorphonuclear leucocytes, increased septal cellularity, alveolar bronchialisation, focal interstitial fibrosis, cholesterol clefts and granuloma-like lesions in the lung. The granuloma-like lesions did not show fibroblastic activity and hyalinization and regressed during recovery.

Accumulation of macrophages were seen in the mediastinal lymph node (disappeared after wk 39 post-exposure). Treatment-related, microscopic changes in the nasal region were occasionally found at the end of exposure period such as focal necrosis slight atrophy of the olfactory epithelium. All types of pulmonary lesions were more marked in males than in females.

A level of 1 mg/m3 induced only slight changes, which generally recovered quickly, therefore the NOEL is lower than 1 mg/m3.

During the post-exposure observation period the changes in lungs and lymph nodes recovered totally or partly (see conclusions). Interstitial fibrosis was not noted directly after the exposure period, but appeared with a delay, for the first time observed after 13 wks post-exposure: increasing incidence especially in 30-mg rats, and a few in the 6-mg group (p. 44), but decreased in severity and frequency until the end of the study (p. 51).

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.

Particle size distribution:
No MMAD range given because of analytical limitations (see below):
The very small primary particles (<6 - approx. 45 nm, calculated as the arithmetic mean of transmission electron micrograph magnification) [comp. Degussa AG 1987, part I, p. 62] form agglomerates and aggregates. Because of the weakness of bonds and the electrostatic charge of particles, it was impossible to determine the aerodynamic agglomerate/aggregate size distribution in the test atmosphere.
The range of the geometric agglomerate/aggregate size distribution was 1 to about 120 µm for the amorphous silicas with a maximum at approx. 10 µm (Degussa 1987, p. 13)

Test substance : Other TS: Aerosil 200: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Conclusion : The NOEL is <1.3 mg/m3 based on the pulmonary response (collagen stimulation and increase in lung weight: not statistically significant).

At the 1 mg-level, the effects were mild, completely cured after 13 wks recovery. There were no histologically manifested tissue changes. Therefore, depending on the pathological relevance placed on observed effects, this exposure concentration may also be defined as NOAEL.

Inhaled amorphous silica provokes an inflammatory response in the respiratory tract of rats, in particular the lung, at low concentration.

A progression process of any lesion was not observed like that seen after quartz exposure, i.e. all observations suggest reversibility, although rather slow.

All synthetic amorphous silica was completely cleared from the lung, but clearance is different for various silica (see also other entries): for Aerosil very quickly.

The granuloma-like lesions were not progressive, i.e. no silicogenic nodules formed (no silicosis).

Mortality was not affected in any of the groups. The only clinical sign noted with Aerosil 200 was increased respiration rate.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint

23.09.2004 (16) (26)

Type : Sub-chronic
Species : Rat
Sex : male/female
Strain : Wistar
Route of admin. : Inhalation
Exposure period : 13 wks

Frequency of treatm.	:	6 hours/day, 5 days/week
Post exposure period	:	up to 52 weeks
Doses	:	35 mg/m3 (mean analytical value)
Control group	:	Yes
Method	:	other: see Method
Year	:	1984
GLP	:	Yes
Test substance	:	other TS
Method	:	Comparative study including Aerosil R 974 (fumed, hydrophobic), Sipernat 22S (precipitated, hydrophil) as well as quartz (crystalline). Special modifications as compared with standard study OECD Guide-line 413: One high-dosed group only within a combined study (see above). Examinations primarily focussed upon changes in the lung, respiratory tract, and regional (hilus and mediastial) lymph nodes, including collagen and silica determinations in the lung. Post-exposure recovery period up to one year was enclosed: 10 m / 10 f animals per group sacrificed after 13 wks, 50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks). Haematology and urinalysis were conducted 5x periodically up to week 65 (including recovery). Blood chemistry was carried out group-wise on autopsy after defined intervals up to week 66 (including recovery).
Remark	:	No data on calcium silicate available: Analogy! No higher toxicity expected from exposure to the Ca salt than to silicon dioxide (see also dossier on CAS-No. 7631-86-9).
Result	:	Slightly decreased body weight; the organ weights of lung and thymus were increased. At autopsy swollen and spotted lungs and enlarged mediastinal lymph nodes were observed. Microscopic changes in lungs were accumulation of alveolar macrophages, intra-alveolar leucocytes and increased septal cellularity. Accumulation of macrophages were seen in the lymph nodes. The collagen content in lungs was slightly increased. Greater amounts of silica could be detected in lungs and lymph nodes. During the recovery period the changes disappeared mostly within 26 weeks. Only in the mediastinal lymph nodes slight accumulation of macrophages and the presence of silica could be found during the total observation period.
Test condition	:	Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically. Particle size distribution: No MMAD range given because of analytical limitations (see below): The very small primary particles (5 - approx. 30 nm, calculated as the arithmetic mean of transmission electron micrograph magnification) [comp. Degussa AG 1987, part I, p. 65] form agglomerates and aggregates. Because of the weakness of bonds and the electrostatic charge of particles, it was impossible to determine the aerodynamic agglomerate/aggregate size distribution in the test atmosphere. The range of the geometric agglomerate/aggregate size distribution was 1 to about 120 µm for the amorphous silicas with maxima at approx. 10 and 100 µm (Reuzel et al. 1991, p. 342).
Test substance	:	Other TS: SIPERNAT 22S >98 % (SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8
Conclusion	:	SIPERNAT 22S (35 mg/m3) induced changes that were similar to those of Aerosil 200 (see also IUCLID on Silicon Dioxide, CAS No. 7631-86-9). The

changes quickly recovered, although silica was still detectable in the lungs after 26 weeks of recovery, and in the lymph nodes even at the end of the observation period.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint
23.09.2004 (16) (26)

Type	:	Chronic
Species	:	Dog
Sex	:	male/female
Strain	:	other: mongrel
Route of admin.	:	oral feed
Exposure period	:	1 year
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	1.0, 3.0 and 5.0 % (w/w) in feed
Control group	:	Yes
LOAEL	:	>= 5 %
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 – 1.4

Result : No deaths and no gross signs of toxicity; slightly elevated pH of the urine; small calculi in the pelvis of the kidneys, urinary bladder and urethra.
Test substance : Silenen EF = calcium silicate (acc. to Plunkett and de Witt 1962)
(4)

Type	:	Sub-acute
Species	:	Rat
Sex	:	Male
Strain	:	Sprague-Dawley
Route of admin.	:	oral unspecified
Exposure period	:	5 days
Frequency of treatm.	:	Daily
Post exposure period	:	
Doses	:	5000 mg/kg suspended in 0.85 % saline
Control group	:	Yes
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 – 1.4

Result : No deaths occurred, no other data (see also chapter 5.6)
Test substance : FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
(22)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Cytogenetic assay
System of testing	:	Human embryonic lung cells (Wi-38)
Test concentration	:	1, 10 and 100 ug/ml
Cycotoxic concentr.	:	>= 150 ug/ml (p. 6/7)
Metabolic activation	:	Without
Result	:	Negative
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Mutations were quantified by counting anaphase aberrations. Negative (0.85 % saline) and positive (0.1 ug/l triethylene melamine) controls were run in parallel (see Method p. 126-128; Results p. 71 + 75).
Remark	:	Basis of selection of test concentrations was "cytopathic" effects in relation to mitotic index (see p. 126-128 and p. 5-7).
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(22)

Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	Salmonella typhimurium TA 1530 and his G-46, see p. 123
Test concentration	:	Unclear
Cycotoxic concentr.	:	
Metabolic activation	:	Without
Result	:	Negative
Method	:	Other
Year	:	1975
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(4) not assignable 4e: Documentation insufficient for assessment
Flag	:	Critical study for SIDS endpoint

(22)

Type	:	Gene mutation in Saccharomyces cerevisiae
System of testing	:	Saccharomyces cerevisiae D-3, see p. 123/124
Test concentration	:	Unclear
Cycotoxic concentr.	:	
Metabolic activation	:	Without
Result	:	Negative
Method	:	Other
Year	:	1975
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(4) not assignable 4e: Documentation insufficient for assessment

(22)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic assay
Species	:	Rat
Sex	:	Male
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	single administration (acute) and repeated administration (5 times, subacute)
Doses	:	acute and subacute: 15, 150, 1500 and 5000 mg/kg suspended in 0.85 % saline
Result	:	Negative
Method	:	other: see Method

Year : 1974
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : 15 animals per dose group. Observation 6, 24 and 48 hours, resp., after administration (acute study) and 6 hours after last administration (subacute study). Bone-marrow cell preparations were made and 50 cells per animal were counted in metaphase for aberrations. Negative (0.85 % saline) and positive (0.3 mg/kg triethylene melamine) controls were run in parallel. (Method p. 124 - 126; Results p. 71 - 79)
Test substance : FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag : Critical study for SIDS endpoint

(22)

Type : Dominant lethal assay
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : single administration (acute) and repeated administration (5 times, subacute)
Doses : acute and subacute: 15, 150, 1500 and 5000 mg/kg suspended in 0.85 % saline
Result : Negative
Method : other: see Remark
Year : 1974
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Method : Chemical treatment of male rats only (10 per group). To cover a complete cycle of spermatogenesis, the male rats were mated to virgin females at weekly intervals (8 times in the acute and 7 times in the subacute study). Per male two female mice were used. The females were sacrified 14 days after mating, and at necropsy the uterus was examined for deciduomata, late fetal deaths and total implantations. Negative (0.85 % saline) and positive (0.3 mg/kg triethylene melamine, i. p.) controls were run in parallel. (Method p. 128/129; Results p. 82 - 117)
Remark : Method: Chemical treatment of male rats only (10 per group). To cover a complete cycle of spermatogenesis the male rats were mated to virgin females at weekly intervals (8 times in the acute and 7 times in the subacute study). Per male two female mice were used. The females were sacrified 14 days after mating, and at necropsy the uterus was examined for deciduomata, late fetal deaths and total implantations. Negative (0.85 % saline) and positive (0.3 mg/kg triethylene melamine, i. p.) controls were run in parallel.
Test substance : FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag : Critical study for SIDS endpoint

(22)

Type : other: Host mediated assay
Species : Mouse
Sex : Male
Strain : ICR
Route of admin. : Gavage

Exposure period	:	single administration (acute) and repeated administration (5 times, subacute)
Doses	:	acute and subacute: 15, 150, 1500 and 5000 mg/kg suspended in 0.85 % saline
Result	:	Negative
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Remark	:	A. Type: Salmonella typhimurium reverse mutation assay Method: The test substance was administered orally to 10 host animals per dose. In the acute study the bacteria (Salmonella typhimurium TA 1530 and his G-46) were inocculated i.p. after the administration of the test substance. In the subacute study the bacteria were injected after the last administration of the test substance. Negative (0.85 % saline) and positive (100 mg/kg dimethylnitrosamine) controls were run in parallel. The animals were sacrificed three hours after administration and the bacteria were removed from the peritoneal cavity. The induction of reverse mutation was quantified on agar plates. (Method: p. 120/121; Results p. 52 - 70) B. There was a high increase in mutants following oral treatment with DMN, but no significant increases in mutation rates at any dose and dose regimen.
Result	:	There was a high increase in mutants following oral treatment with DMN, but no significant increases in mutation rates at any dose and dose regimen.
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)

(22)

Type	:	other: Host mediated assay
Species	:	Mouse
Sex	:	Male
Strain	:	ICR
Route of admin.	:	Gavage
Exposure period	:	single administration (acute) and repeated administration (5 times, subacute)
Doses	:	acute and subacute: 15, 150, 1500 and 5000 mg/kg suspended in 0.85 % saline
Result	:	Negative
Method	:	other: see Remark
Year	:	1974
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Remark	:	Type: Mitotic recombination in Saccharomyces cerevisae D-3 Method: The test substance was administered orally to 10 host animals per dose. In the acute study the yeast (Saccharomyces cerevisiae D-3) was inocculated i. p. after the administration of the test substance. In the subacute study the yeast was injected after the last administration of the test substance. Negative (0.85 % saline) and positive (350 mg/kg ethyl methane sulfonate, i. m.) controls were run in parallel. The animals were killed three hours after administration and the yeast cells were removed from the peritoneal cavity.
Result	:	negative (The results with D-3 were unusual, because a reduction in recombinant activity was seen (anti-recombinogenic activity ?) There was a high increase in mutants following oral treatment with EMS.
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)

(22)

5.7 CARCINOGENICITY

Species	:	Rat
Sex	:	male/female
Strain	:	other: "albino"
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	1.0, 5.0, 7.5 and 10 % (w/w) in feed
Result	:	Negative
Control group	:	Yes
Method	:	
Year	:	1957
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Result : No deaths and no gross signs of toxicity; highest dose group: growth suppression; slightly elevated pH of the urine; slight elevation of organ weights. No tumors are observed.

The NOAEL is considered to be the 7.5-% dietary level, which is estimated to correspond to about 5000 mg/(kg bw*d).

Test substance : Silenen EF = calcium silicate (acc. to Plunkett and de Witt 1962)

Reliability : (4) not assignable
A final report summary of Hazleton Laboratories, the original study was reported to the FDA.

Flag : Critical study for SIDS endpoint

23.09.2004 (4)

5.8.1 TOXICITY TO FERTILITY

Type	:	other: Dominant lethal test
Species	:	Rat
Sex	:	Male
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	
Frequency of treatm.	:	
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	
Control group	:	

Remark : A series of dominant lethal tests in rats (doses up to 5000 mg/kg) (see entry 5.6).

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

23.09.2004 (22)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	Gavage

Exposure period	:	from day 6 to day 15 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/kg
Control group	:	Yes
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 mg/kg bw
Method	:	
Year	:	1972
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	21 - 22 dams were used per sham control and test groups. Aspirin (250 mg/kg) served as pos. control substance. 1/3 of fetuses of each litter was subjected to detailed microscopic visceral examination, 2/3 to examination of skeletal defects.
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on implantation or on maternal or fetal survival. The number of abnormalities seen in either soft of skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(19)

Species	:	Mouse
Sex	:	Female
Strain	:	CD-1
Route of admin.	:	Gavage
Exposure period	:	from day 6 to day 15 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/kg
Control group	:	Yes
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 mg/kg bw
Method	:	
Year	:	1972
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	21 to 23 dams were used per sham control and test groups. Aspirin (150 mg/kg) served as pos. control substance. 1/3 of fetuses of each litter was subjected to detailed microscopic visceral examination, 2/3 to examination of skeletal defects.
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on implantation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls (see Tab. 1 - 4).
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(19)

Species	:	Syrian hamster
Sex	:	Female
Strain	:	other: (outbred)
Route of admin.	:	Gavage
Exposure period	:	from day 6 of day 10 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/kg
Control group	:	Yes
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 - mg/kg bw
Method	:	
Year	:	1972
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	19 - 22 pregnant dams were used per sham control and test groups. Aspirin (250 mg/kg) served as pos. control substance. 1/3 of fetuses of each litter was subjected to detailed microscopic visceral examination, 2/3 to examination of skeletal defects.
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on implantation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	FDA-Compound 71-41 = Silene, calcium silicate (hydrated)
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(19)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience	:	Human – Epidemiology
Remark	:	Occupational exposure: 78 workers (age 21 - 67 years, average age 34 1/4 years; exposure time 1 - 16.6 years, average 4 3/4 years) who were employed in the manufacturing and processing of Hi-Sil and Silene EF (Calcium silicate) were examined from 1941 to 1959. The medical examination was complemented by chest X-rays. The dust concentration ranged from 0.35 to 204 mg/m3. No evidence of silicosis or other pulmonary disease was found.
Test substance	:	Silenen EF = calcium silicate (acc. to Plunkett and de Witt 1962)
Flag	:	Critical study for SIDS endpoint

(24)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

Test substance : Silicates
Method : Determination of particle size

Method : Determination of the average size of precipitated silicas/silicates:

The agglomerate particle size of precipitated products is relatively easy to determine.

For that purpose, a Coulter Counter is used in an aqueous solution. Before measuring in aqueous suspension, the material under analysis is dispersed with the aid of ultrasonics. Depending on the particle size resulting from the experiment, measuring capillaries ranging from 30 to 400 µm are inserted.

For agglomerate particle sizes which are more than 1 µm, IR laser apparatus can also be used.

For coarse silicas with an agglomerate particle size of 100 or 50 µm, it is the best to use the airjet sieve (Alpine).

Remark : Common method (particle size): Multisizer, 100 µm capillary according to ASTM C690-1992.

Methodological variants are:
Multisizer, 50, 140, and 200 µm capillary according to ASTM C690-1992;
Particle size d50, Cilas 1064 G, following ISO 13320-1;
Particle size d50, Malvern, following ISO 13320-1;
Alpine air-jet sieve, following ISO 8130-1.

Remark: Primary particles are not existent as individual units (compare IARC, 1997, Tab. 7, p. 57). Therefore, primary particle size is generally not accounted because of the particles aggregate.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

(11) (13)

6.2 DETECTION AND IDENTIFICATION

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I U C L I D

Data Set

Existing Chemical	:	ID: 1344-00-9
CAS No.	:	1344-00-9
EINECS Name	:	Silicic acid, aluminum sodium salt
EC No.	:	215-684-8
TSCA Name	:	Silicic acid, aluminum sodium salt

Producer related part

Company	:	Association of Synthetic Amorphous Silica Producers (ASASP)
Creation date	:	29.06.2004

Substance related part

Company	:	Association of Synthetic Amorphous Silica Producers (ASASP)
Creation date	:	29.06.2004
Status	:	
Memo	:	Origin Degussa AG, 11 Oct. 2002, Rev. 7
Printing date	:	17.06.2005
Revision date	:	17.06.2005
Date of last update	:	17.06.2005
Number of pages	:	43
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	Other: consortium
Name	:	ASASP (Association of Synthetic Amorphous Silica Producers) [CEFIC Sector Group]
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Flag	:	Critical study for SIDS endpoint

Type	:	lead organisation
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Flag	:	Critical study for SIDS endpoint

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Email	:	
Homepage	:	

Flag	:	Critical study for SIDS endpoint

Type	:	cooperating company
Name	:	Huber Engineered Materials
Contact person	:	
Date	:	
Street	:	Strandesplanaden 110
Town	:	DK-2665 Vallensbaek Strand
Country	:	Denmark

Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Flag	:	Critical study for SIDS endpoint
Type	:	cooperating company
Name	:	INEOS Silicas Ltd
Contact person	:	Dr. P.A. Hunt
Date	:	
Street	:	4 Liverpool Road
Town	:	Warrington, Cheshire, WA5 1AB
Country	:	United Kingdom
Phone	:	+44 1925 416292
Telefax	:	+44 1925 416113
Telex	:	
Cedex	:	
Email	:	paul.a.hunt@ineossilicas.com
Homepage	:	
Flag	:	Critical study for SIDS endpoint
Type	:	cooperating company
Name	:	RHODIA Silica Systems
Contact person	:	Marie-Christine Rosset (see Remark)
Date	:	
Street	:	La Danica - 21, avenue Georges Pompidou
Town	:	F-69006 Lyon
Country	:	France
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	e.mail: marie-christine.rosset@eu.rhodia.com
Homepage	:	
Remark	:	contact point: RHODIA SERVICES Etoile Part-Dieu190, Avenue Thiers F-69006 LYON France Tel: +33 4 37 24 88 63 Fax: +33 4 37 24 88 81
Flag	:	Critical study for SIDS endpoint

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : Silicic acid, aluminum sodium salt
Smiles Code :
Molecular formula :
Molecular weight :
Petrol class :

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : Inorganic
Physical status : Solid
Purity : > 95 % w/w
Colour : White
Odour : Odourless

Remark : A. NOTE: For this CAS-Number, 1344-00-9, an additional dataset has been submitted by Henkel KGaA, Duesseldorf (as lead company) and Enichem Augusta (as cooperating company). This is a dataset which includes crystalline zeolites (NaA-zeolite), the CAS No. of which is 1318-02-1, which are not identical with the amorphous sodium aluminum silicate mentioned in the dataset submitted by Degussa AG, Frankfurt (as lead company).

In addition, a IUCLID on crystalline silicates, CAS No. 1318-02-1, exists.

The data presented here are limited to synthetic amorphous Na-Al-silicates which are produced or imported by the industrial companies which prepared this data set.

It is to comprise also aluminium silicates which are allocated to CAS No. 1327-36-2 and 1335-30-4.

B. Precipitated sodium aluminum silicates (silicic acid, aluminum sodium salt) are non-stoichiometric amorphous forms of the precipitated synthetic reaction product of aluminum sulfate and sodium silicate with varying contents of sodium oxide, aluminum oxide and silicon dioxide. After ignition the content of the oxide ranges are described as follows:

Composition of typical Precipitated Synthetic Amorphous Sodium Aluminum Silicate:

Parameter	wt.%
SiO2	> 42 - < 85
Na2O	> 0.2 - < 22.0
Al2O3	> 0.2 - < 36.0
Trace oxides	< 0.1

Flag : Critical study for SIDS endpoint

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Silicic acid, aluminium sodium salt (9CI) [IUPAC and CAS names]

Remark : Tradenames: Sipernat, Alusil ET, Zeolex, Hydrex, Huberfil, Durabrite, Zeocopy, Tixolex, Rhodoxane
Flag : Critical study for SIDS endpoint

Aluminiumsilikat / aluminium silicate / Silicic acid, aluminium salt

Remark : Tradename: Davicat, Tixolex, Rhodoxane
Flag : Critical study for SIDS endpoint

Aluminosilicic acid sodium salt (8CI)

Silicoaluminate de sodium

Sodium aluminum silicate

Sodium silico aluminate

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Remark : Heavy Metal Impurity Data

Metal Impurity/ppm	Al-Na Silicates
Antimony	< 5
Barium	< 50
Chromium	< 10
Arsenic	< 3
Lead	< 10
Mercury	< 1
Cadmium	< 1
Selenium	< 1

The given limits are typical data. The mentioned products are in line with the quality requirements of DIN EN 71/3 (toys), BGVV Recommendation LII (Fillers for Commodities Made of Plastic) and of quality requirements for direct food additive E551, E552 and E554 (2000/63/EU and 2001/30/EU).

Purity : typical for marketed substance
CAS-No : 7757-82-6
EC-No : 231-820-9
EINECS-Name : sodium sulphate

Molecular formula :
Value : < 5 % w/w

Flag : Critical study for SIDS endpoint

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 40800 - tonnes produced in 2000

Remark : The production volume in Europe comprises all synthetic amorphous silicates.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.09.2004 (6)

1.6.1 LABELLING

Labelling : no labelling required (no dangerous properties)
Specific limits : No

1.6.2 CLASSIFICATION

Classified : no classification required (no dangerous properties)
Class of danger :
R-Phrases :
Specific limits :

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : Type
Category : Use resulting in inclusion into or onto matrix

Remark : As in general the amorphous silicas/silicates become an integral part of a product matrix, the powder form no longer exists in most applications.
Flag : Critical study for SIDS endpoint
29.09.2004

Type of use : Type
Category : Wide dispersive use

Remark : The applications of silicates are versatile, but in general for consumers not freely available as powders, as the silicates are bound in the matrix of an article.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial

Category : Agricultural industry

Remark : No data on this application available
24.09.2004

Type of use : Industrial
Category : Leather processing industry

Remark : No data on this application available
24.09.2004

Type of use : Industrial
Category : Paints, lacquers and varnishes industry

Remark : Paints: Synthetic amorphous silica and silicates are used as functional pigments in emulsion paints.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Paper, pulp and board industry

Remark : Paper: Small amounts of synthetic amorphous silica and silicates added to paper improve printability and opacity. Synthetic amorphous silica is also used in specially coated paper grades for ink jet printing, copying etc.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Polymers industry

Remark : Plastics: Plastic films often tend to stick to each other but this can be prevented by the addition of an synthetic amorphous silica or silicates as an anti blocking agent. They are also used in polyester and epoxy resins for thixotropy control.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Industrial
Category : Textile processing industry

Remark : No data on this application available
24.09.2004

Type of use : Use
Category : Absorbents and adsorbents

Remark : No data on this application available
24.09.2004

Type of use : Use
Category : Anti-set-off and anti-adhesive agents

Remark : Silicas and silicates provide thickening in pastes and ointments to inhibit the separation of components and maintain flow properties in powder products.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use

Category : Colouring agents

Remark : For example, in paints: Synthetic amorphous silicas and silicates are used as functional pigments in emulsion paints.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Cosmetics

Remark : Due to their inert nature, synthetic amorphous silicas/silicates are used in cosmetics (especially tooth paste). They can also function as a carrier for fragrances or flavors.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Fillers

Remark : For example in Rubber and Silicones: Synthetic amorphous silica and silicates are used as reinforcing fillers for many non-staining and colored rubber and silicones products.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use : Use
Category : Food/foodstuff additives

Remark : Animal Feed: Synthetic amorphous silicas and silicates serve as carriers and anticaking agents in vitamins and mineral premixes.
Flag : Critical study for SIDS endpoint
24.09.2004

Type of use :
Category : Personal and domestic use

Remark : Consumer Use Products: Due to their inert nature synthetic amorphous silicas/silicates are used in cosmetics (especially tooth paste), pharmaceuticals and foods. Synthetic amorphous silicas for pharmaceutical use meet the requirements of international pharmacopoeias, such as DAB 10, USP/NF XXIV/ 19, and the European Pharmacopoeia 1997 2002(Add. 2001). They provide thickening in pastes and ointments to inhibit the separation of components and maintain flow properties in powder products. They can also function as a carrier for fragrances or flavors.
Flag : Critical study for SIDS endpoint
24.09.2004

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : Synthetic Amorphous Precipitated Silica: Wet Process
The production processes for precipitated synthetic amorphous silica and

silicates can be divided into the following general unit operations: raw material storage, synthesis, washing/solid-liquid-filtration, drying packing and storage. Optionally after the drying step the product can be milled, granulated or surface treated to promote hydrophobicity. These individual steps may be operated in a continuous or batch process manner.

Raw materials for the production of precipitated synthetic amorphous sodium-aluminium silicates are aqueous sodium silicate solution (e.g. water glass) and metal salts, generally aluminium sulphate. In case of the production of precipitated calcium silicate calcium chloride or calcium hydroxide is used for metal salts.

The reaction and precipitation conditions (e.g. acid:alkali ratio, temperature, concentration, stirring rate, and residence time) determine the size of the silicate particle and the way they bind together to form higher structures like aggregates and agglomerates.

To date, only batch precipitation processes in stirred vessels have attained economic importance, although continuous precipitation techniques have been reported.

The suspension received from precipitation is filtered. For this purpose, usual filter presses, membrane filter presses or belt/drum filters are used. Equipment selection is dependent on the properties and structure of the silica produced. The solid content of the filter cake typically varies between 15 to 35 wt%, depending on the filter technique employed.

After filtration a washing step follows to remove salts (normally done in the filtration equipment). The level of salt retained in the product depends on the intended application of the final silicate.

For drying, contact dryers are mostly used (plate, belt, rotary drum) as well as spray dryers are used. After conventional drying, the product has to be milled in jet mills or mechanical mills. During this process, the particle size distribution and sieve residue characteristics of the product are modified.

Flag : Critical study for SIDS endpoint

(5)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : 3 mg/m3

Remark : "Allgemeiner Staubgrenzwert", related to fine dust (respirable)
Flag : Critical study for SIDS endpoint

(20)

Type of limit : TLV (US)
Limit value : 10 mg/m3

Remark : TWA = Time-Weighted Average (8-Hour Exposure Limit): The value is for total dust containing no asbestos and <1 % crystalline silica.
Flag : Critical study for SIDS endpoint

(1)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: (provisionally) Degussa AG
Labelled by : other: (provisionally) Degussa AG
Class of danger : 0 (generally not water polluting)

Remark : Kenn-Nummer: 1393 (Katalog wassergefährdender Stoffe) [Water Endangering Class]

(2)

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Non-occupational exposure:
Levels of addition of sodium aluminosilicate to foods (Data for the USA, where sodium aluminosilicate has GRAS status, see also sect. 1.13 Additional Remarks):

Food category	Weighed mean percent
baked goods, baking mixes	0.68
breakfast cereals	< 0.01
grain products, such as pastas or rice dishes	0.04
fats and oils	0.04
milk, milk products	0.04
frozen dairy deserts, mixes	< 0.01
meat products	< 0.01
poultry products	0.01
fish products	< 0.01
condiments, relishes, salt substitutes	0.17
sweet sauces, toppings, syrups	0.39
gelatins, puddings, fillings	0.03
soups, soup mixes	0.42
snack foods	0.63
beverages, nonalcoholic	0.08
gravies, sauces	0.06
diary products analogs	0.88

seasonings and flavours 0.54

Based on this data the NRC subcommittee has calculated the possible daily intake for sodium aluminosilicate to be 150 mg/individual. It was recognized by the NRC subcommittee that this assumption of possible intake is likely overestimated.

(27)

Remark : Non-occupational exposure:
Based on the 1400 t/a sodium aluminumsilicate totally used in the USA in 1975 and an U. S. population of 215 million people the per capita daily intake was estimated to be 18 mg.

(27)

1.11 ADDITIONAL REMARKS

Memo : Nutritional application

Remark : Synthetic sodium aluminosilicate may be added as a binder, anti-caking agent, and coagulant (EEC-No. E 554) to feeding stuffs under the provisions laid down in the directive 70/524/EEC and according to the requirements set out in the annex to the same directive.

(28)

Remark : The acceptable daily intake of sodium aluminosilicate is not limited by the FAO/WHO.

(32)

Remark : In the USA sodium aluminosilicate has GRAS status (generally recognized as save). Up to 2 % can be added as an anticaking agent to foodstuff. Regulation: FDA paragraph 121.101 and 21 CFR 182.2727.

(22) (27) (31)

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	ca. 1700 °C
Sublimation	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data available: analogy - assumed to be similar to silica [CAS no. 7631-86-9]
Flag	:	Critical study for SIDS endpoint

(10)

2.2 BOILING POINT

Decomposition	:	Yes
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	>>1700 °C: not relevant for normal and intended use

(10)

2.3 DENSITY

Type	:	Density
Value	:	ca. 2.1 g/cm³ at 20 °C
Method	:	other: DIN / ISO 787/11
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Density relates to that of the primary particles, not to the silicate in aggregated/agglomerated form as it exists.
Test substance	:	SIPERNAT 820A
Reliability	:	(2) valid with restrictions 2d: Meets national and international standards: limited documentation
Flag	:	Critical study for SIDS endpoint

(14)

Type	:	bulk density
Value	:	220 - 300 kg/m3 at °C
Method	:	other: DIN / ISO 787/11
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	An accurate volume of a sample is measured in a glass cylinder in such a way that no empty space remains and the surface is horizontal. The glass cylinder containing this sample is being tapped (tamped) in a volumeter 1250 times. Then the resulting volume is read off. That means the sample is not pressed to a minimum under high pressure.

Tapped/tamped density is the minimum bulk density.

Remark : Density relates to tapped density.
Reliability : (2) valid with restrictions
2d: Meets national and international standards: limited documentation
Flag : Critical study for SIDS endpoint

(11) (14)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Decomposition :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Based on the structure and nature of this substance, its vapour pressure will be negligible, practically 0 mmHg, at ambient temperature and pressure (compare IUCLID Silicon dioxide, CAS No. 7631-86-9): significant vapour pressure (10 mmHg) only at the melting.
Flag : Critical study for SIDS endpoint

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : at °C
pH value :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : This parameter is not considered applicable to this compound due to its physico-chemical nature (inorganic compound, not lipophilic).
Flag : Critical study for SIDS endpoint

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 48 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : Method of determination and measured part not specified.
Test substance : SIPERNAT 820A
Reliability : (2) valid with restrictions
Study without detailed documentation: data generated within the performance of a GLP guideline study.

(16)

Solubility in : Water
Value : ca. 68 - 79 mg/l at 20 °C
pH value : ca. 9
concentration : 6660 mg/l at 30 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : Directive 92/69/EEC, A.6
Year : 1998
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Elemental analytical method not specified.
Result :

	48	72	96 hours	
SiO2	35 +- 2	42 +-3	42 +-3	mg/l
Na	33 +- 2	35 +-2	36 +-2	mg/l
Al	0.33 +-0.04	0.58 +-0.06	0.61 +-0.07	mg/l

The indicated value range is the total of measured elements.

Test condition : Approx. 1 g was stirred at 30 °C in 150 ml water (purissima) for 48, 72, and 96 h. After settling for 24 h at 20 °C, the suspension was membrane-filtered (pore size= 0.45 µm). Elements were determined in the filtrate.
Test substance : SIPERNAT 820A: SiO2 approx. 82 %, Al approx. 5.6 % (as element), Na approx. 5.9 % (as element)
Reliability : (2) valid with restrictions
2b: Guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint

(12) (26)

Solubility in : Water
Value : at °C
pH value : 5 - 11
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: acc. to ISO 787/IX, ASTM D 1208, JIS K 5101/24
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

(5)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Method :

Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(7)

2.8 AUTO FLAMMABILITY

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(7)

2.9 FLAMMABILITY

Result : non flammable
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(7)

2.10 EXPLOSIVE PROPERTIES

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable: note - amorphous silica can be used as a fire-extinguishing agent.
Reliability : (4) not assignable
Manufacturer data / data from handbook or collection of data.

(9)

2.11 OXIDIZING PROPERTIES

Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Remark : Non-combustible, stable
Reliability : (4) not assignable
Data from handbook or collection of data.

(7)

2.12 DISSOCIATION CONSTANT

Acid-base constant : no data
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Particle size

Remark : Value: mean size of agglomerates: 5 - 9 um
Method: coulter counter, 100 um capillary, ASTM C 690-1992
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

(11)

Memo : Surface area

Method : Specific Surface Area (N2): today ISO 5794-1, Annex D
Remark : Value: BET surface area: 85 - 110 m2/gMethod (BET surface area): Brunauer, Emmet, Teller (BET); J. Amer. Chem. Soc., 60, 309 (1938) (DIN 66 131)
Reliability : (2) valid with restrictions
Meets national/international standards: limited documentation
Flag : Critical study for SIDS endpoint

(11)

3.1.1 PHOTODEGRADATION

Type	:	other: air, water
Light source	:	
Light spectrum	:	Nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable), no light-induced transformation expected.
Flag	:	Critical study for SIDS endpoint

3.1.2 STABILITY IN WATER

Type	:	Abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable towards acids and alkali), no chemical transformation under environmental conditions significant and relevant; ion exchange possible.
Flag	:	Critical study for SIDS endpoint

3.1.3 STABILITY IN SOIL

Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	"SiO2" is a stable substance. In the environment, it occurs in different forms (as amorphous and crystalline silica, as silicates complexed with metals), and it is one of the most abundant materials on the earth's surface (see also Sec. 3.2). Whatever its origin, man-made or natural silica/silicates, and whatever its structure, crystalline or amorphous, once released and dissolved into the environment, no distinction can be made between the initial forms of silicates. Based on the chemical nature (inorganic structure and chemical stability of the compound: Si-O bond is highly stable towards acids and alkali), silicates are considered as inert substances, and no chemical transformation under environmental conditions is expected to be significant

and relevant. Ion exchange possible.

Flag : Critical study for SIDS endpoint

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : Volatility
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : Silicates are not volatile under environmental conditions due to its chemical nature and inherent physical properties.

SiO2/silicates are not volatile under environmental conditions due to their chemical nature and inherent physical properties: Due to low water solubility and extremely low vapour pressure, silicates are expected to be distributed mainly into soils/sediments, weakly into the water and probably not at all in the air.

Type : other: Deposition
Media : other: water, soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Remark : Silicates are expected to combine undistinguishably with the soil layer or sediment due to their chemical identity with inorganic soil matter and will be subjected to slow natural transformation processes of weathering.

Flag : Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

Memo : Stability

Remark : Amorphous silicates are not degraded in actual use.

3.5 BIODEGRADATION

Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Due to the chemical nature (inorganic structure) biodegradation is not applicable.
Flag	:	Critical study for SIDS endpoint

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Elimination	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Due to their inherent chemico-physical properties, such as absence of lipophilicity, as well as the capability of the organism to excrete absorbed SiO2 components, bioaccumulation of silicates can be disregarded. But silica can be actively accumulated by terrestrial plants (e.g. grass) and some marine organisms (e.g. diatoms, radiolarians, and sponges), which are normal natural processes.
Flag	:	Critical study for SIDS endpoint

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	= 10000 measured/nominal
Limit test	:	Yes
Analytical monitoring	:	No
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1998
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No deaths occurred during testing.
Test condition	:	Concentrations are described as loadings (nominal concentrations). In a pre-test, the water-soluble fractions of the nominal concentrations of 100, 1000 and 10000 mg/l has been tested. In the main test, only the highest concentration was examined (limit test). The water extracts were prepared by stirring corresponding suspensions for 24 h at 25 °C with subsequent filtration of the suspensions. Test solutions were then adjusted to pH 7.00. Concentrations are described as loadings (nominal concentrations). Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).
Test substance	:	SIPERNAT 820A, sodium aluminium silicate (Degussa) [CAS No. 1344-00-9]
Reliability	:	(1) valid without restriction 1a: GLP guideline study
Flag	:	Critical study for SIDS endpoint

(15)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	> 10000 measured/nominal
Analytical monitoring	:	No
Method	:	OECD Guide-line 202
Year	:	1992
GLP	:	Yes
Test substance	:	other TS
Remark	:	A corresponding test was performed with Aerosil 200, another amorphous silica, with similar result: see IUCLID 7631-86-9, 4.2. No data on Al-Na silicate available: Analogy! Toxicity to daphnia is not expected [see IUCLID silicon dioxide CAS No. 7631-86-9]
Result	:	After 24 h of exposure 7.5 % and 2.5 % of the daphniae were immobile at test concentrations of 1000 and 10000 mg/l, resp. The observed effects were not dose related. Therefore, the effects can be attributed to physical hampering of the daphnias. (note: A corresponding test was performed with

Aerosil 200, another amorphous silica, where the physical effect was apparently more marked: see IUCLID 7631-86-9, 4.2)

Test condition : Concentrations of 1000 and 10000 mg/l were tested, and results refer to loading. Because of the poor solubility of the test substance the test solution was stirred for 20 hours. The test media remained turbid throughout the test and starchy particles were observed on the bottom of the test vessels.
Concentrations can be described as loading rate. Analytical determination was not meaningful due to concomitance of dissolved and undissolved particles (saturated conditions).

Test substance : Other TS: ULTRASIL VN 3 (>98 % SiO2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: 24 h instead of 48 h applied.

Flag : Critical study for SIDS endpoint

(19)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	other: biomass and growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 10000 measured/nominal
EC10	:	> 10000 measured/nominal
Limit test	:	
Analytical monitoring	:	No
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1998
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4

Result : Results are given in nominal concentrations (loadings).
After 72 h, an increase in biomass at a factor of >30 was achieved in all tests without significant difference of the highest concentration from the control run, while at the lower concentrations results may indicate slight stimulation of growth.

Test condition : Preparation of test solutions: Water extracts from 6250, 630, and 60 mg/l silica were produced by stirring the suspensions for 24 h in 0.5 l ultrapure water, followed by filtration through paper filter.
The final nominal concentrations in the test media were obtained by addition of the algal preculture and the mineral salt concentrate to the filtrated extract, corresponding to 10000, 1008, and 96 mg/l nominal.
Empty controls ("blanks") without the algae suspension were prepared for each concentration with the suitable water-silica extract.

Temperature was 24.9 +-0.3°C;
Illumination: approx. 8000 lux (>= 120 uE/m2sec) 3 to 5 parallel tests were prepared for each concentration and respective controls.

Initial cell concentration: approx. 8.5 x10exp4 cells.
Extinction differences were determined at 24, 48, and 72 h at 578 nm.
Initial pH: 8.00 (control); between 8.12 and 8.58 (tests).

Test substance : SIPERNAT 820A, SIPERNAT 820A, sodium aluminium silicate (Degussa) [CAS No. 1344-00-9]

Reliability : (1) valid without restriction
1a: GLP guideline study

Flag : Critical study for SIDS endpoint

(17)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	Water
Doses	:	5000 mg/kg (aqueous slurry 10 ml/kg, 50 % w/v)
Method	:	other: U.S. Fed. Hazardous Substance Act, Section 101.1 (f)
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No mortality during 14-d posttreatment observation period. No pathological findings on autopsy (Huber 1973, Tab. 1).
Test substance	:	ZEOLEX 23A and ZEOLEX 7
Reliability	:	(2) valid with restrictions 2d: Meets national standards with acceptable restrictions: short documentation, sufficient for assessment
Flag	:	Critical study for SIDS endpoint

(25) (27)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data - assumed to be non-toxic within the scope of technical feasibility, based on analogy: see IUCLID Silicon Dioxide (SAS) [CAS No. 7631-86-9]
Flag	:	Critical study for SIDS endpoint

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	Rabbit
Strain	:	New Zealand white
Sex	:	
Number of animals	:	16

Vehicle	:	Water
Doses	:	2000, 3000, 4000, and 5000 mg/kg as aqueous paste
Method	:	
Year	:	1978
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No pathological findings. Dermal reactions were limited to slight erythema and edema.
Test condition	:	The TS was applied as paste to the intact and abraded skin. 4 animals per dose. Occlusive exposure for 24 h. Post-treatment observation 14 d.
Test substance	:	ZEOLEX 23A
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(23) (27)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	Rabbit
Concentration	:	.5 g
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	other: none
PDII	:	0
Result	:	not irritating
Classification	:	
Method	:	other: U.S. Fed. Hazardous Substances Act, Section 101.11
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No evidence of erythema or edema on either application site (Huber 1973, Tab. 2 + 3).
Test condition	:	Treatment of the intact and abraded skin. Scoring after 24 and 72 h after test initiation.
Test substance	:	ZEOLEX 23A and ZEOLEX 7
Reliability	:	(2) valid with restrictions 2d: Meets national standards with acceptable restrictions: short documentation, sufficient for assessment
Flag	:	Critical study for SIDS endpoint

(25) (27)

5.2.2 EYE IRRITATION

Species	:	Rabbit
Concentration	:	100 % active substance
Dose	:	100 other: mg
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	6

Vehicle	:	None
Result	:	not irritating
Classification	:	
Method	:	other: FDA guideline, likely acc. to Draize Test
Year	:	1979
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Only slight erythema (score <1) after 24 h in 4/6 animals, after 48 h 1/6 animals still exhibited some effect. No signs of irritation after 72 h (Tab. 41).
Test substance	:	Sodium aluminium silicate, amorphous, size of particle aggregates: 3.5-65 um (based on SEM), not further specified
Reliability	:	(2) valid with restrictions 2d: Meets national standards with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

(8)

Species	:	Rabbit
Concentration	:	50 % active substance
Dose	:	.2 ml
Exposure time	:	24 hour(s)
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	Water
Result	:	not irritating
Classification	:	
Method	:	other: no data
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	ZEOLEX 7 produced no irritation response, while ZEOLEX 23A induced slight, transient erythema and edema in 3 to 5 of 6 animals after 24 h which had subsided after 48 h.
Test substance	:	ZEOLEX 23A and ZEOLEX 7
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

(25) (27)

Species	:	Rabbit
Concentration	:	
Dose	:	100 other: mg
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	None
Result	:	not irritating
Classification	:	
Method	:	other: Fed. Hazardous Substance Act 1973
Year	:	1978
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Only on day one transient slight erythema and edema were noted in all animals (score 1), in one animal score 2 for erythema.
Test substance	:	ZEOLEX 23A
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

(24) (27)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	13 wk
Frequency of treatm.	:	6 h/d, 5 d/wk
Post exposure period	:	up to 52 wks
Doses	:	1.3, 5.9 or 31 mg/m3 (mean analytical values)
Control group	:	yes, concurrent no treatment
NOAEL	:	= 1.3 mg/m³
LOAEL	:	= 5.9 mg/m³
NOEL	:	< 1.3
Method	:	other: acc. to OECD Guide-line 413, see Method
Year	:	1985
GLP	:	Yes
Test substance	:	other TS

Method :

Comparative study including Aerosil R974 (fumed, hydrophobic), Sipernat 22S (precipitated, hydrophil) as well as quartz (crystalline).
Special modifications as compared with standard study:
Examinations primarily focused upon changes in the lung, respiratory tract, and regional (hilus and mediastinal) lymph nodes, including collagen and silica determinations in the lung.

Post-exposure recovery period up to one year was enclosed:
10 m / 10 f animals per group sacrificed after 13 wks,
50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks).

Haematology and urinalysis were conducted 5x periodically up to week 65 (including recovery). Blood chemistry was carried out group-wise on autopsy after defined intervals up to week 66 (including recovery).

Remark : No data on sodium aluminium silicate available: Analogy! No higher toxicity expected from exposure to the Na-Al salt than to silicon dioxide (see also dossier on CAS-No. 7631-86-9).

Result :

The respiration rate showed a concentration-related increase when compared to the controls (only qualitative clinical observation without relation to the exposure levels); the body-weight gain was slightly depressed.

Red blood cell count and hemoglobin were statistically higher in males exposed to 30 mg/m3, but not in females.
White blood cell count due to increases in the numbers of neutrophilic leukocytes were elevated in both males and females of the 6- and 30-mg groups, but concentration-response relationship was poor.

After 3 months recovery, these blood parameters normalized.
Blood chemistry and urine analysis were without significant findings. At autopsy after exposure, swollen and spotted lungs and enlarged mediastinal lymph nodes were observed, the degree of severity being treatment-related.

At 6 and 30 mg/m3, the lung weights and the collagen content in the lungs were clearly increased, most pronounced in males showing this effect also at 1 mg/m3.

The above-mentioned effects gradually subsided after the exposure period, but in males exposed to 6 and 30 mg/m3 the collagen content was still above control values at the end of the study.

Silica could be detected in lungs only in relatively small amounts at the end of the exposure period, on the average 0.2 mg in all animals of the 30-mg groups. Only one male exposed to 30 mg/m3 showed a small amount of silica in the regional lymph node. During the post-exposure observation period, no silica could be recovered from any animal.

The microscopic examination at the end of exposure period showed accumulation of alveolar macrophages and granular material, cellular debris, polymorphonuclear leucocytes, increased septal cellularity, alveolar bronchialisation, focal interstitial fibrosis, cholesterol clefts and granuloma-like lesions in the lung. The granuloma-like lesions did not show fibroblastic activity and hyalinization and regressed during recovery.

Accumulation of macrophages were seen in the mediastinal lymph node (disappeared after wk 39 post-exposure).

Treatment-related, microscopic changes in the nasal region were occasionally found at the end of exposure period such as focal necrosis slight atrophy of the olfactory epithelium.

All types of pulmonary lesions were more marked in males than in females. A level of 1 mg/m3 induced only slight changes, which generally recovered quickly, therefore the NOEL is lower than 1 mg/m3.

During the post-exposure observation period the changes in lungs and lymph nodes recovered totally or partly (see conclusions). Interstitial fibrosis was not noted directly after the exposure period, but appeared with a delay, for the first time observed after 13 wks post-exposure: increasing incidence especially in 30-mg rats, and a few in the 6-mg group (p. 44), but decreased in severity and frequency until the end of the study (p. 51).

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.

Test substance : Other TS: Aerosil 200: >99.8 % (SiO_2): CAS-Name: Silica, amorphous, fumed, cryst.-free; CAS-No.: 112945-52-5

Conclusion : The NOEL is <1 mg/m3 based on the pulmonary response (collagen stimulation and increase in lung weight).

At the 1 mg-level, the effects are mild, completely cured after 13 wks recovery.

Inhaled amorphous silica provokes an inflammatory response in the respiratory tract of rats, in particular the lung, at low concentration.

A progression process of any lesion was not observed like that seen after quartz exposure, i.e. all observations suggest reversibility, although rather slow.

All synthetic amorphous silica was completely cleared from the lung, but clearance is different for various silica (see also other entries): for Aerosil very quickly.

The granuloma-like lesions were not progressive, i.e. no silicogenic

nodules formed (no silicosis).

Mortality was not affected in any of the groups. The only clinical sign noted with Aerosil 200 was increased respiration rate.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint

22.09.2004 (18) (29)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	Inhalation
Exposure period	:	13 wk
Frequency of treatm.	:	6 hours/day, 5 days/week
Post exposure period	:	up to 52 weeks
Doses	:	35 mg/m3 (mean analytical value)
Control group	:	Yes
Method	:	other: see Method
Year	:	1985
GLP	:	Yes
Test substance	:	other TS

Method : Comparative study including Aerosil R 974 (fumed, hydrophobic), Sipernat 22S (precipitated, hydrophil) as well as quartz (crystalline).

Special modifications as compared with standard study: One high-dosed group only within a combined study (see above).

Examinations primarily focussed upon changes in the lung, respiratory tract, and regional (hilus and mediastinal) lymph nodes, including collagen and silica determinations in the lung.

Post-exposure recovery period up to one year was enclosed: 10 m / 10 f animals per group sacrificed after 13 wks, 50 m / 50 f animals per group were kept for a recovery period of at most 52 wks (13, 26, 39, and 52 wks).

Haematology and urinalysis were conducted 5x periodically up to week 65 (including recovery). Blood chemistry was carried out group-wise on autopsy after defined intervals up to week 66 (including recovery).

Remark : No data on sodium aluminium silicate available: Analogy! No higher toxicity expected from exposure to the Na-Al salt than to silicon dioxide (see also dossier on CAS-No. 7631-86-9).

Result : Slightly decreased body weight; the organ weights of lung and thymus were increased. At autopsy swollen and spotted lungs and enlarged mediastinal lymph nodes were observed.
Microscopic changes in lungs were accumulation of alveolar macrophages, intra-alveolar leucocytes and increased septal cellularity. Accumulation of macrophages was seen in the lymph nodes. The collagen content in lungs was slightly increased. Greater amounts of silica could be detected in lungs and lymph nodes. During the recovery period the changes disappeared mostly within 26 weeks. Only in the mediastinal lymph nodes slight accumulation of macrophages and the presence of silica could be found during the total observation period.

Test condition : Inhalation chamber: Single housing during exposure, whole-body exposure. Dust generator with compressed air atomizer producing an aerosol which was mixed with air to achieve desired silica levels. Silica concentration was measured gravimetrically.

Particle size distribution:

No MMAD range given because of analytical limitations (see below):
The very small primary particles (5 - approx. 30 nm, calculated as the arithmetic mean of transmission electron micrograph magnification) [comp. Degussa AG 1987, part I, p. 65] form agglomerates and aggregates. Because of the weakness of bonds and the electrostatic charge of particles, it was impossible to determine the aerodynamic agglomerate/aggregate size distribution in the test atmosphere.
The range of the geometric agglomerate/aggregate size distribution was 1 to about 120 µm for the amorphous silicas with maxima at approx. 10 and 100 µm (Reuzel et al. 1991, p. 342).

Test substance : SIPERNAT 22S >98 % (SiO_2): CAS-Name: Silica, precipitated, cryst.-free; CAS-No.: 112926-00-8

Conclusion : SIPERNAT 22S (35 mg/m3) induced changes that were similar to those of Aerosil 200 (see also IUCLID on Silicon Dioxide, CAS No. 7631-86-9). The changes quickly recovered, although silica was still detectable in the lungs after 26 weeks of recovery, and in the lymph nodes even at the end of the observation period.

Reliability : (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions

Flag : Critical study for SIDS endpoint

(18) (29)

Type : Sub-acute
Species : Rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 14 d
Frequency of treatm. : Continuous
Post exposure period : None
Doses : 0.625, 1.25, 2.5, 5, and 10 % in the diet
Control group : yes, concurrent no treatment
NOAEL : ca. 2500 mg/kg bw
Method : other: screening, range-finding for 90-d study
Year : 1979
GLP : No
Test substance : no data

Method : 5 male and 5 female rats were used, histopathology was comprehensive, but only carried out on 3/10 rats in the control group and the top-dose group each.

Result : There were no substance-related clinical findings at any dose level. Only male rats showed a significantly lower bw gain (-39 %). No deaths occurred during testing. Otherwise, no significant influence on food consumption and body-weight gain was observed.

At autopsy, no evidence of gross tissue/organ changes noted that could be attributable to the treatment.

Comprehensive histopathology revealed no treatment-related effects.

The NOAEL can be estimated to be approx. 2500 mg/(kg bw*d) (at 5-% dietary level).

Test substance : Sodium aluminosilicate, not further specified

Conclusion : There were 30 animals (2.5, 5, and 10 % level) that received a dose of more than 1000 mg/(kg*d), which is a reasonable high number of high-dosed animals to draw firm conclusion on effects.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

Flag	:	Critical study for SIDS endpoint

22.09.2004 (3)

Type	:	Sub-acute
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	14 d
Frequency of treatm.	:	Continuous
Post exposure period	:	None
Doses	:	0.625, 1.25, 2.5, 5, and 10 % in the diet
Control group	:	
NOAEL	:	> 5000 mg/kg bw
Method	:	other: screening, range-finding for 90-d study
Year	:	1979
GLP	:	No
Test substance	:	no data
Method	:	5 male and 5 female rats were used, histopathology was comprehensive, but only carried out on 3/10 rats in the control group and the top-dose group each.
Result	:	There were no substance-related clinical findings at any dose level. No treatment-related deaths occurred during testing. No significant influence on body-weight gain was observed. At autopsy, no evidence of gross tissue/organ changes noted that could be attributable to the treatment. Comprehensive histopathology revealed no treatment-related effects. The NOAEL can be estimated to be >5000 mg/(kg bw*d) (at 10-% dietary level).
Test substance	:	Sodium aluminosilicate, not further specified
Conclusion	:	There were 30 animals (2.5, 5, and 10 % level) that received a dose of more than 1000 mg/ (kg*d), which is a reasonable high number of high-dosed animals to draw firm conclusion on effects.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(4)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Other
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data on sodium-aluminium silicates available: see entries in IUCLID 7631-85-9 (silicon dioxide) and 1344-95-2 (silicic acid, calcium salt): Analogy: Based on negative results from these compounds, no genotoxicity is expected from sodium-aluminium silicates.

Flag : Critical study for SIDS endpoint

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Other
Species	:	
Sex	:	
Strain	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Result	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No data on sodium-aluminium silicates available: see entries in IUCLID 7631-85-9 (silicon dioxide) and 1344-95-2 (silicic acid, calcium salt): Analogy: Based on negative results from these compounds, no genotoxicity is expected from sodium-aluminium silicates.
Flag	:	Critical study for SIDS endpoint

5.7 CARCINOGENICITY

Species	:	Rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	other: intra-pleural
Exposure period	:	
Frequency of treatm.	:	single dose
Post exposure period	:	
Doses	:	20 mg/animal
Result	:	Negative
Control group	:	Yes
Method	:	other: special test design, whole-life study
Year	:	1983
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Comprehensive test programme and comparative study including various silicates (crystalline and amorphous) as well as quartz and TiO2. Fibrous minerals, UICC crocidolite (blue asbestos) and Oregon erionite (fibrous zeolite) served as positive control substances. The objective was to investigate the carcinogenic potential of non-fibrous crystalline zeolites and an amorphous sodium aluminosilicate (ASA) and the influence of these compounds on known inducers of mesotheliomas. Intrapleural treatment in rats was applied as test model known to positively respond on a single dose of fibrous minerals. A score, according to Peto et al. 1980, was assigned to all tumors, a means of expressing degree of malignancy and the degree to which tumor contributed to the death of the animal.
Result	:	SURVIVAL (Tab. 2 and 4): ASA-treated animals as well as all other groups having been treated with non-fibrous material showed normal survival as compared to the saline

control.

CAUSES of MORTALITY (Tab. 7 and 8):
There was no shift towards neoplastic lesions as primary cause of mortality due to treatment with non-fibrous material, while an increased fraction of the crocidolite-treated groups died of cancer.

MESOTHELIOMAS (Tab. 10)
No pleural mesotheliomas appeared in the saline group. No pleural mesotheliomas were induced by ASA and the other non-fibrous minerals including TiO2 and quartz, apart from a single benign testicular mesothelioma. The application of asbestos material distinctly produced pleural mesotheliomas in 71 - 93 % of the animals.

ACTION in COMBINATION with fibrous mineral ASA given in conjunction with UICC crocidolite provided no evidence of a co-carcinogenic potential: no increase in asbestos-induced mesotheliomas and reduction of the latency period. The same applies to the other non-fibrous minerals.
There was some evidence of fibrous materials to slightly reduce the age-adjusted incidences of mesotheliomas.

OTHER TUMORS (Tab. 9)
The treatment with the test minerals, irrespective of the fibrous or non-fibrous nature, did not influence the pattern of prevalence of isolated spontaneous tumors other than mesotheliomas (most of them thyroid follicular tumors).

LOCAL NON-NEOPLASTIC, REACTIVE REPONSE
Test material was occasionally present intra-thoracically.
There was infrequent slight pleural/pericardial thickening composed of macrophages with or without connective tissue. (p. 15), occasionally associated with slight intra-thoracic adhesions (p. 12). There was a trend to form nodules (Tab. 5/6).

On the other hand, quartz elicited much more extensive granulomatous, fibroblastic reactions with dense deposition of collagen forming nodules, also involving the mediastinal lymph nodes which were enlarged, intra-thoracic adhesions, hydrothorax and accumulation of macrophages and mononuclear cells (p. 12/15).

Test condition : ADMINISTRATION of TEST MATERIALS:
Test materials were administered as suspensions in sterile saline by single intra-pleural injection under halothane anaesthesia. The animals were allowed to live their whole life-span or maximally 3 years.

TEST GROUPS (s. Tab. 1)
consisting of
- negative controls [saline, TiO2 (20 mg), Dorentrup quartz (20 mg)
- positive controls including crocidolite(20+40 mg) and erionite(20 mg)
- several single test compounds including ASA.
Furthermore, individual combinations of test substances, TiO2, and quartz with crocidolite were formed.

Test substance : Amorphous sodium aluminosilicate: Crosfield ASA

Conclusion : There was no evidence that ASA and the other test materials acted as carcinogen or as co-carcinogens together with crocidolite, in comparison with the groups treated with crocidolite alone or in combination with TiO2 or Dorentrup quartz.

ASA and the other non-fibrous test materials produced a low-grade foreign-body type response, similar to that associated with TiO2 which is considered not to produce significant toxic effects under realistic exposure.

The non-neoplastic tissue response caused by ASA and others could

clearly be distinguished from the more marked reaction produced by quartz.

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, comparable to guidelines, well documented (not all volumes available), acceptable for assessment

Flag : Critical study for SIDS endpoint

(30)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	Gavage
Exposure period	:	6-15 gd
Frequency of treatm.	:	1x/d
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/(kg*d) (as aqueous suspension)
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 mg/kg bw
Result	:	no adverse effects
Method	:	other: no data
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4

Method : The study comprised a positive control group receiving 250 mg/(kg*d) Aspirin. 21 to 24 pregnant dams resulted per group.

Result : The administration of up to 1600 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Test substance : Sodium aluminium silicate, FDA-compound 71-45, not further specified

Reliability : (2) valid with restrictions
2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment

Flag : Critical study for SIDS endpoint

(21) (27)

Species	:	Mouse
Sex	:	Female
Strain	:	CD-1
Route of admin.	:	Gavage
Exposure period	:	6-15 gd
Frequency of treatm.	:	1x/d
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/(kg*d) (as aqueous suspension)
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 mg/kg bw
Result	:	no adverse effects
Method	:	other: no data
Year	:	1973

GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The study comprised a positive control group receiving 150 mg/(kg*d) Aspirin. 19 to 24 pregnant dams resulted per group.
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	Sodium aluminium silicate, FDA-compound 71-45, not further specified
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(21) (27)

Species	:	Rabbit
Sex	:	
Strain	:	Dutch
Route of admin.	:	Gavage
Exposure period	:	6-18 gd
Frequency of treatm.	:	1x/d
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/(kg*d) (as aqueous suspension)
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 mg/kg bw
Result	:	no adverse effects
Method	:	other: no data
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The study comprised a positive control group receiving 2.5 mg/(kg*d) 6-aminonicotinamide dosed on day 9. 10 to 16 pregnant dams resulted per group.
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	Sodium aluminium silicate, FDA-compound 71-45, not further specified
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(21) (27)

Species	:	Hamster
Sex	:	Female
Strain	:	no data
Route of admin.	:	Gavage
Exposure period	:	6-10 gd
Frequency of treatm.	:	1x/d
Duration of test	:	
Doses	:	0, 16, 74, 350 and 1600 mg/(kg*d) (as aqueous suspension)
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1600 mg/kg bw
NOAEL teratogen.	:	= 1600 - mg/kg bw
Result	:	no adverse effects

Method	:	other: no data
Year	:	1973
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The study comprised a positive control group receiving 250 mg/(kg*d) Aspirin. 20 to 22 pregnant dams resulted per group.
Result	:	The administration of up to 1600 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test substance	:	Sodium aluminium silicate, FDA-compound 71-45, not further specified
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, sufficiently documented, acceptable for assessment
Flag	:	Critical study for SIDS endpoint

(21) (27)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

Test substance : Silicates
Method : Determination of particle size (aggregates): ASTM C690-1992 / ISO 13320-1 / ISO 8130-1

Method : Determination of the average size of precipitated silicas/silicates:

The agglomerate particle size of precipitated products is relatively easy to determine.

For that purpose, a Coulter Counter is used in an aqueous solution. Before measuring in aqueous suspension, the material under analysis is dispersed with the aid of ultrasonics. Depending on the particle size resulting from the experiment, measuring capillaries ranging from 30 to 400 µm are inserted.

For agglomerate particle sizes which are more than 1 µm, IR laser apparatus can also be used.

For coarse silicas with an agglomerate particle size of 100 or 50 µm, it is the best to use the airjet sieve (Alpine).

Remark : Common method (particle size): Multisizer, 100 µm capillary according to ASTM C690-1992.

Methodological variants are:
Multisizer, 50, 140, and 200 µm capillary according to ASTM C690-1992;
Particle size d50, Cilas 1064 G, following ISO 13320-1;
Particle size d50, Malvern, following ISO 13320-1;
Alpine air-jet sieve, following ISO 8130-1.

Remark: Primary particles are not existent as individual units (compare IARC, 1997, Tab. 7, p. 57). Therefore, primary particle size is generally not accounted because of the particles aggregate.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

(11) (13)

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