# Final Safety Assessment

## Silylates and Surface Modified Siloxysilicates As Used in Cosmetics

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## ABSTRACT

*The Cosmetic Ingredient Review (CIR) Expert Panel assessed the safety of silica silylate, silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/trimethylsiloxysilicate as used in cosmetics. These silylates and surface modified siloxysilicates function in cosmetics as antifoaming agents, anti-caking agents, bulking agents, binders, skin-conditioning agents-emollient, skin-conditioning agents-occlusive, slip modifiers, suspension agents-nonsurfactant, and viscosity increasing agents-nonaqueous. The Expert Panel reviewed available animal and clinical data, as well as information from a previous CIR safety assessment of amorphous silica. The CIR Expert Panel concluded that silica silylate, silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/trimethylsiloxysilicate are safe as used when formulated and delivered in the final product to be not irritating or sensitizing to the respiratory tract.*


## INTRODUCTION

This safety assessment addresses the use of silica silylate, silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/ trimethylsiloxysilicate in cosmetics. These ingredients function in cosmetics as: antifoaming agents, anti-caking agents, bulking agents, binders, skin-conditioning agents-emollient, skin-conditioning agents-occlusive, slip modifiers, suspension agents-nonsurfactant, and viscosity increasing agents-nonaqueous.

Amorphous silica, which is the core of silica silylate and silica dimethyl silylate, has been reviewed by the Cosmetic Ingredient Review Expert Panel and was found to be safe as a cosmetic ingredient in the practices of use and concentrations as described in that safety assessment.[1]

The ingredients in this safety assessment also are based on amorphous (synthetic amorphous silica and silicates), not crystalline silica. The ingredients in this safety assessment are organo-silane hybrid materials, modified to have desired properties for their use in cosmetics.

Data on silane, dichlorodimethyl-, reaction products with silica (CAS No. 68611-44-9) are also included in this literature review, since these chemicals are the same as silica dimethyl silylate. Data from a mixture, siloxanes and silicones, di-me, hydroxyl-terminated (as Antifoam M) was also included because the data may also be relevant to the individual ingredients.

### Definition and Structure

The cosmetic ingredient definitions, functions in cosmetics, and structures of silica silylate, silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/trimethylsiloxysilicate are provided in Table 1. These four hybrid silica materials can be divided into two distinct types, grafted and co-condensed.

**Grafted silica materials** – These materials consist of silica particles that are surface modified by organo-silanes. For example, dichlorodimethylsilane can be used to produce dimethyl silyl groups on the surface of a particle of fumed silica.[2] Silica silylate and silica dimethyl silylate are grafted silica materials. Silica silylate consists of fumed silica, surface modified with trimethylsilyl groups (Figure 1).

**Co-condensed silica materials -** In contrast to grafted materials, co-condensed silica materials are not surface modified silica particles. Instead, co-condensed materials are prepared by the simultaneous reaction of condensable inorganic silica and silylated organic compounds.[2] This process is similar to random co-polymer synthesis, but is non-linear. Trimethylsiloxysilicate and trifluoropropyldimethyl/trimethylsiloxysilicate are co-condensed silica materials. Trimethylsiloxy silicate is the co-hydrolysis product of a tetraalkoxysilane and a trimethylalkoxysilane.[3] The chemical structure of trimethylsiloxy silicate can be visualized as a three-dimensional network of polysilicic acid units (resultant from the tetraalkoxysilane), which are end-blocked with trimethylsilyl groups (Figure 2).

Trifluoropropyldimethyl/trimethylsiloxysilicate differs from trimethylsiloxy silicate only by the replacement of some of the methyl groups with trifluoropropyl groups.

### Physical and Chemical Properties

These ingredients are amorphous solids, with virtually no water solubility. The water solubility of grafted silica materials is below $10e^{-6}$ g/L. Chemical and physical properties for silica dimethyl silylate and trimethylsiloxysilicate are provided in Table 2. Silica silylate was stable for 24 months when stored at or below 40°C.[4]

One manufacturer reported that less than 0.83% of silica dimethyl silylate had a particle size of < 125 μm and none were < 90 μm.[5] The Synthetic Amorphous Silica and Silicate Industry Association has suggested that this is true industry-wide.[6]

It was reported in a material safety data sheet that trimethylsiloxysilicate dissolves in organic and silicone oils up to concentrations of 50%.[7] No special storage measures are required of trimethylsiloxysilicate when stored at or below 32°C in an unopened container for 24 months, thus, it is considered stable. A manufacturer reported that trimethylsiloxysilicate has a bulk density of ~0.3 g/cm$^3$ and goes through thermal decomposition at > 200ºC.[7] The particle size is ~10 µm. Two other manufacturers report that the average particle size is 10 µm or ranges from 20 – 100 µm.[8,9]

Trimethylsiloxysilicate releases formaldehyde vapors when heated above 150ºC in the presence of air.[10]
Physical and chemical properties were not discovered for silica silylate and trifluoropropyldimethyl/trimethylsiloxysilicate. Trifluoropropyldimethyl/trimethylsiloxysilicate was stable after 5 2-day cycles of -10°C and 45°C for 24 h at each temperature.[11] This ingredient was also stable after 3 months storage at 45°C.

### Analytical Methods

The presence of silylate particles may be quantified and counted by a scanning mobility particle sizer.[12] Gas chromatography (GC) was used to identify fluorine compounds in trifluoropropyldimethyl/trimethylsiloxysilicate.[13] Samples of trifluoropropyldimethyl/trimethylsiloxysilicate were analyzed for stability using infrared (IR) and nuclear magnetic resonance (NMR).[11]

### Impurities

A manufacturer reported that trimethylsiloxysilicate was > 99% pure.[7] Benzene and toluene may be present at < 0.0001% after an extensive drying step. Toluene is safe as a cosmetic ingredient.[14,15]
Another manufacturer reported the only impurity to be alkanes (C7-10-iso) at a maximum of 0.35%, a residual solvent from the production process.[9]

Analysis of trifluoropropyldimethyl/trimethylsiloxysilicate by GC showed that the product does not contain trifluoropropene or initial manufacturing materials.[13]

### UV Absorption

While no data were available, the ingredients included in this review would not be expected to have any significant ultraviolet (UV) absorption because these materials do not contain any of the functional groups commonly associated with UV absorption.

### Method of Manufacture

Grafted material such as silica silylate, and silica dimethyl silylate can be manufactured via reaction of a fumed silica particle with one of an alkoxysilane (e.g. $(CH_3O)_3SiCH_3$), a halosilane (e.g., $ClSi(CH_3)_3$) or an alkylsilazane (e.g., $NH[Si(CH_3)_3]_2$).[2] For example, amorphous silica can be modified by reaction with hexamethyldisilazane (HMDS), in hexanes at 275ºC and 30 atm, to manufacture silica silylate.[16] Solvents are removed by heated evaporation. The degree of surface modification can be adjusted by varying the concentration of the silylating agent (e.g., increasing the amount of HMDS).

Co-condensed silica materials can be manufactured via the co-hydrolysis of a tetraalkoxysilane (e.g., tetraethoxysilane; which result in the inorganic silane groups in the reaction product) and a trialkylalkoxysilane (e.g., trimethylethoxysilane; which will result in the organo-silane groups in the reaction product).[2] Solvents are removed by heated evaporation. Some residual alkoxyl (i.e. leaving groups that did not leave; Si-OR) and hydroxyl (Si-OH) functional groups are likely to be present.[17] The average molecular weight can be adjusted by varying the ratio of the silanes.

## USE

### Cosmetic

According to the Voluntary Cosmetic Registration Program (VCRP) administered by the Food and Drug Administration (FDA), the total number of uses of silica dimethyl silylate was 734 (592 leave-on and 142 rinse-off products).[18] A survey conducted by the Personal Care Products Council (Council) found that silica dimethyl silylate was used at 0.00003% – 10% in leave-on products (highest concentration in lipsticks) and 0.0003% - 4% in rinse-off products (highest concentration in personal cleanliness products; Table 3).[19] There were 633 uses reported of trimethylsiloxysilicate at 0.0001% - 30% in leave-on products (highest in eyeliner and lipsticks) and 0.002% - 5% in rinse-off products (highest in hair straighteners). There were 245 used reported of silica silylate (244 in leave-on and 1 rinse-off product) at 0.2% - 25 in leave-on products.[20] There were no uses reported of trifluoropropyldimethyl/trimetylsiloxysilicate by FDA but the Council reported use at 2% – 20% in leave-on products (highest in eyeliner).

Silica dimethyl silylate is used in perfumes. This product category may include products that are aerosolized or used as powders. In practice, 95% to 99% of the aerosols released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to

110 µm range.[21,22] Therefore, most aerosols incidentally inhaled from these sprays are deposited in the nasopharyngeal region and are not respirable.[23,24] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic diameters in the range considered to be respirable.[25] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

### Non-Cosmetic Use

FDA has approved silicon dioxide (a compound similar to silica dimethyl silylate) to be used as a direct food additive as an anticaking agent up to 2% and in the manufacture of materials that come in direct contact with food in various production, manufacturing, packaging, preparing, transporting, and holding operations.[26]

Silica aerogel (an amorphous silica gel) is generally recognized as safe (GRAS) in dietary supplements.[27]

## TOXICOKINETICS

### Absorption, Distribution, Metabolism, and Excretion

***Oral***

SILICA DIMETHYL SILYLATE

Antifoam M (siloxanes and silicones, di-me, hydroxyl-terminated; 0.5 mg/kg) or silica (6 mg/kg) were orally administered in sesame oil to male Buckberg mice (n = 12) after fasting.[28] Controls were administered sesame oil (0.5 ml). There was no increase in urinary and biliary silicon in both groups. The authors suggested that the source was organosoluble silicon rather than inorganic silica. Antifoam M (21.8 or 41.8 mg/kg) was labeled using randomly radio-labeled [$^{14}$C] polydimethylsiloxane and orally administered to rhesus monkeys (n = 5) that were then observed for 7 days.[28] Antifoam M was expired in the breath (0.1% - 0.2%) and in the urine (0.22%) with a half-life of 24 h. There was 0.1% to 0.9% in the bile in the first 24 h after dosing. Over 92 h, 93% to 97% of the dose was recovered in the feces. There was < 0.01% detected in ~40 tissues examined in the 1 monkey necropsied after 7 days. A range of 93% to 98% was recovered in the feces.

Human subjects were orally administered Antifoam M (100 mg/kg; n = 6) after 5 days of a consistent diet (that continued through the rest of the experiment) on day 6 and data collected through day 7.[28] Increased silicon levels were not detected in urine, feces, or expelled air after oral administration of Antifoam M.

***Inhalation***

SILICA DIMETHYL SILYLATE

Rats (n = 40) were exposed to aerosolized silica dimethyl silylate (200 mg/m$^3$; particle size not provided) for 5 h/d for 3 days.[29] At 24 h after the last exposure there was 0.91 mg test substance in the lung and none at 1 month post exposure. There was 0.383, 0.239, and 0.173 mg in the mediastinal lymph nodes at 1, 2, and 3 months, respectively. At 3 months, 81% of the test substance had been eliminated.

Female Sprague-Dawley rats (n = 50) were exposed to aerosolized silica dimethyl silylate (50 mg/m$^3$; <7 µm) for 5 h.[17] At necropsy, silica deposited in lungs (0.156, 0.034, 0.034 mg at 20 h, 1 and 3 months, respectively) and mediastinal lymph nodes (0, 0.003, 0.004 mg). The test substance was eliminated at 78% and 85% at 1 and 3 months, respectively.
Female Sprague-Dawley rats (n = 30) were exposed to aerosolized silica dimethyl silylate (50 mg/m$^3$; <7 µm) for 5 h for 3 days.[17] At necropsy, silica deposited in lungs (0.34, 0.085, 0.30 mg at 20 h, 1 and 3 months, respectively) and mediastinal lymph nodes (0.34, 0.085, 0.30 mg). Test substance was eliminated at 75% and 92% at 1 and 3 months, respectively.

***Other***

Silica particles (4 nm) placed in simulated physiological conditions dissolve completely in ~32 h.[30]

## TOXICOLOGICAL STUDIES

### Acute Toxicity

***Dermal – Non-Human***

SILICA DIMETHYL SILYLATE

Silica dimethyl silylate (2000 mg/kg in propylene glycol) applied in a single dose to the skin of Wistar rats (n = 5/sex) for 24 h caused no mortality.[31] No clinical signs were observed and necropsies were unremarkable.

TRIMETHYLSILOXYSILICATE

Trimethylsiloxysilicate (100%; 0.5 g) was administered to the intact skin of New Zealand White rabbits (n = 6) under occlusion for 4 h.[32] All rabbits survived and gained weight during the study. There were no signs of toxicity.

Trimethylsiloxysilicate (2 g/kg) was administered to the shaved skin of New Zealand White rabbits (n = 10) under occlusion for 24 h.[32] The patch was then removed and the skin rinsed in corn oil. The rabbits were observed for 14 days. All rabbits gained weight. There were no signs of toxicity. There were no abnormalities observed at necropsy.

***Oral – Non-Human***

SILICA DIMETHYL SILYLATE

The oral $LD_{50}$ of silica dimethyl silylate was > 5000 mg/kg for Sprague-Dawley rats.[33,34] Another study in rats found the oral $LD_{50}$ to be > 7900 mg/kg.[35]

TRIMETHYLSILOXYSILICATE

Trimethylsiloxysilicate (5 g/kg in corn oil) was orally administered to Sprague-Dawley rats (n = 5/sex).[32] There were no clinical signs. All rats gained weight. There were no lesions at necropsy. The observation time was not provided.
The oral $LD_{50}$ of trimethylsiloxysilicate was reported to be > 1 g/kg in mice.[36]

TRIFLUOROPROPYLDIMETHYL/TRIMETHYLSILOXYSILICATE

The oral $LD_{50}$ of trifluoropropyldimethyl/trimethylsiloxysilicate was reported to be > 2 g/kg in mice.[37]

***Inhalation – Non-Human***

SILICA DIMETHYL SILYLATE

Inhalation toxicity studies using rats were conducted. The results are presented in Table 4. There was no mortality up to 520 $mg/m^3$.

***Intraperitoneal – Non-Human***

*SILICA DIMETHYL SILYLATE*

Silica dimethyl silylate (up to 30 mg in water with Tween 80) was administered intraperitoneally (i.p.) to mice (n = 120; strain and sex not provided).[38] All mice survived treatment. The observation period was not provided, but the report stated that at necropsy fibrosis was not observed, although thickening of the liver and spleen capsules were observed. Histopathology showed that the test substance was found in the abdominal cavity in a tight network of reticulin and collagen. Slight phagocyte accumulations and necrosis were observed. Histopathology of the liver showed some evidence of the test substance there, also in a tight network of reticulin and collagen.

Silica dimethyl silylate (up to 200 mg in water with 0.5% Tween) was administered i.p. to female rats (n = 100; strain not provided) as described above.[38] All rats survived treatment. At necropsy, there was no fibrosis observed. Histopathology showed that the test substance was found in the abdominal cavity in a tight network of reticulin and collagen. Slight phagocyte accumulations and necrosis were observed. Histopathology of the liver showed some evidence of the test substance there, also in a tight network of reticulin and collagen.

***Ocular – Non-Human***

Silica dimethyl silylate (0.1 – 0.2 g; 0.1 ml) was applied to one eye of New Zealand white rabbits (n = 3/sex).[39] Three of the treated eyes were not rinsed and 3 rinsed with saline after 20 – 30 sec. Two females had decreased feed consumption as well as soft stool, ano-genital staining, and reduced fecal volume.

**Repeated Dose Toxicity**

***Oral – Non-Human***

SILICA DIMETHYL SILYLATE

Silica dimethyl silylate (500 or 1000 mg/kg) was orally administered to Wistar rats (n = 40/sex) by gavage every other day for 19 or 39 days.[40] Rats were killed and necropsied at the end of the treatment period or after 4 weeks recovery. There were no clinical signs or treatment effects observed. The NOAEL was 1000 mg/kg.

Silica dimethyl silylate (0, 500, 1000, 2000 mg/kg; the high dose groups was gradually increased to 4000, 8000, and 16,000

mg/kg) was orally administered to Wistar rats (n = 40/sex) in feed daily for 5 or 8 weeks for the high dose.[41] Rats were killed and necropsied at the end of the treatment period. Two males and 2 females in the high dose group died after 9 and 13 days of exposure to 16000 mg/kg. Clinical signs in the high dose group after increasing the dose to 16000 mg/kg were apathy and decreased grooming activity. Cachexia and hemorrhagic mucosa of the nose and eyes were observed prior to death. There was severe body weight decrease in males and females following 1 week exposure to 8000 mg/kg and exposure to 16000 mg/kg. Feed consumption severely decreased following exposure to 16000 mg/kg in males and females. There was hemorrhage in the mucous membranes of the eyes and nose in animals exposed to 16000 mg/kg. In 2 females of the mid dose group and 8 animals of the high dose group, atrophic hepatocytes with decreased appearance [sic] and decreased glycogen contents of the cytoplasm were observed. The NOAEL was 500 mg/kg and the LOAEL was 1000 mg/kg.

Silica dimethyl silylate (0, 500 mg/kg) was orally administered to Wistar rats (n = 40/sex) in feed daily for 6 months.[42] Rats were killed and necropsied at the end of the treatment period or after 3 weeks recovery. There were no clinical signs or treatment effects observed. The NOAEL was 500 mg/kg.

Silica dimethyl silylate (100 mg/kg) was orally administered to Wistar rats (n = 20/sex) in feed daily for 24 months.[43] Rats were killed and necropsied at the end of the treatment period or after 3 weeks recovery. There were no clinical signs or treatment effects observed. The NOAEL was 100 mg/kg.

***Inhalation – Non-Human***
SILICA DIMETHYL SILYLATE

Repeated dose inhalation studies from 1 week to 1 year are presented in Table 4. In rats, clinical signs included crusty eyes, muzzle, and nose; crust around ear tags; closed eyes; irregular breathing; irritable disposition; lacrimation and salivation; scabs; and red and yellow/brown stained fur. At 2 weeks, there was an increase in lymphocytes and neutrophils. Reduced body weights were observed. Silica was deposited in the lungs and lymph nodes, but the deposits cleared over time. At necropsy, focal bronchiolar mucus proliferation, intraluminal mucus deposition, granulomata, focal increased septal cellularity, and accumulation of alveolar macrophages were observed in the lungs. One study noted slight necrosis or atrophy of the olfactory epithelium after a year at 35 $mg/m^3$. Shorter exposure times did not generate remarks on the nasal area. A LOAEL of 31 $mg/m^3$ was concluded in one study.

## REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

SILICA DIMETHYL SILYLATE

Silica dimethyl silylate (0, 500 mg/kg/d) was administered in feed to male (n = 2) and female (n = 10) Wistar rats for 6 months, during which the rats were mated twice, followed by a 3 week recovery period.[44] The offspring were observed through the 4 week lactation period then killed and necropsied. There were no mortalities attributable to treatment. There were no effects observed during treatment or at necropsy in the adults or the offspring. NOAEL was 500 mg/kg.
Silica dimethyl silylate (0, 497, 509 mg/kg/d) was administered to Wistar rats (n = 40/sex) in feed for 6 months, after which the rats were mated (1 male to 5 females).[45] The adult rats were killed and necropsied and the offspring were observed for external appearance and development. No abnormalities were observed in either generation. The NOAEL was 497 mg/kg/d for parental generation.

Silica dimethyl silylate (0, 100 mg/kg/d) was administered to Wistar rats (n = 20/sex) in feed for 24 months, after which the rats were mated (1 male to 5 females).[43] The offspring were adjusted to 5/sex in each litter and allowed to mature. After 7 months, they were mated and their litters were also adjusted to 5/sex. Both sets of offspring were killed and necropsied. There were no reproductive toxicity effects observed.

## GENOTOXICITY

### In Vitro

SILICA DIMETHYL SILYLATE

In an Ames test of a toluene extract of silica dimethyl silylate (15.8 - 5000 µg/plate) using *Salmonella typhimurium* (TA98, TA100, TA1537) and *Escherichia coli* (WP2urvA) with and without metabolic activation, no mutagenicity was observed.[46] Controls had the expected results.

An Ames test of a product (0 - 5000 µg/plate) containing silica dimethyl silylate (27%) was conducted using *S. typhilmurium* (TAI535, TA1537, TA98, TA100) and *E. coli* (WP2 trp, WP2 trp uvrA) with and without metabolic activation.[47] The concentration was calculated to be 1250 µg/plate dimethyl silicones and siloxanes and 100 µg/plate dimethyl silicones and siloxanes reaction products with silica. The test substance was not mutagenic.

An Ames test of silica dimethyl silylate (0 - 5000 µg/plate) was conducted using *S. typhimurium* (TA98, 100, TA1535, TA1538) with and without metabolic activation.[48] There was no evidence of mutagenicity. The controls had the expected results. An Ames test of silica dimethyl silylate (5 - 1580 µg/plate) was conducted using *S. typhlmurium* (TA98, 100, TA1537, TA1538) and *E. coli* (WP2 trp uvrA) with and without metabolic activation.[49] There was no evidence of mutagenicity. The controls had the expected results.

An in vitro mammalian chromosome aberration test of silica dimethyl silylate (63, 125, 250, 500 µg/ml) using Chinese hamster ovary (CHO) cells with and without metabolic activation was conducted. The frequency of effects without S9 were 0, 1%, 0, 0 at 63, 125, 250 and 500 µg/ml, respectively, and 3, 1, 1, 3 % with S9, respectively.[50] The author concluded that there was no evidence of genotoxicity. The controls had the expected results.

TRIMETHYLSILOXYSILICATE

An Ames test (0, 30, 80, 250, 700, 2000, 5000 µg/plate) using *S. typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP3uvrA) with and without metabolic activation was conducted.[32] There were no toxic effects and the revertant frequencies were similar to controls. Positive controls had the expected results. The authors concluded that trimethylsiloxysilicate was non-mutagentic in this assay.

In an Ames test, trimethylsiloxysilicate (156 - 500 µg/plate; MW - 3000-10,000) was not mutagenic to *S. typhimurium* (TA98 and TA100) with or without metabolic activation.[36] In another Ames test, trimethylsiloxysilicate (156 – 500 µg/plate; 3000 – 5000 in acetone) was not mutagenic to *S. typhimurium* (TA98 and TA100) with or without metabolic activation.
An Ames test of a mixture of trimethlsiloxysilicate (60%) and isododecane (40%; 156 - 5000 µg/plate) using *S. typhimurium* (TA98, TA100) was negative.[51]

### In Vivo

There were no in vivo genotoxicity studies discovered for any of the ingredients in this safety assessment.

## CARCINOGENICITY

Silica dimethyl silylate (100 mg/kg) was orally administered to Wistar rats (n = 20/sex) in feed daily for 24 months.[43] Rats were killed and necropsied at the end of the treatment period or after 3 weeks recovery. There were no carcinogenic effects observed. The nature and incidence of tumors were comparable with the historical control data.

## IRRITATION AND SENSITIZATION

### Irritation

***Dermal – Non-Human***
SILICA DIMETHYL SILYLATE

Silica dimethyl silylate (0.5 g moistened with tap water) was applied to the shaved skin of New Zealand white rabbits (n = 3; 1 male, 2 female) under occlusion for 4 h.[52] There was mild erythema in one rabbit at 1 h after removal. The irritation score was 0.2. Silica dimethyl silylate (0.5 g; 100%) was applied to the intact skin of New Zealand white rabbits (n = 3/sex) for 4 h under semiocclusion.[53] After removal, the skin was scored at 1, 24, 48, and 72 h. There were no signs of irritation at any observation period.

Silica dimethyl silylate (6% in aqueous methylhydroxethylcellulose-gel) was applied to the intact and abraded skin of New Zealand white rabbits (n = 3/sex) for 24 h under occlusion.[54] The skin was scored at removal, 48 h, and daily for 14 days. There were no signs of irritation at any observation period.

Silica dimethyl silylate (50% in olive oil) was applied to the intact and abraded skin of New Zealand white rabbits (n = 3/sex) for 24 h under occlusion.[54] After removal, the skin was scored at removal, 48 h, and daily for 14 days. There were no signs of irritation at any observation period.

A product (0.5 ml) containing Silica dimethyl silyate (27 wt.%) was tested for dermal irritation using male New Zealand white rabbits.[55] The test substance was administered to the clipped skin under semi-occlusion for 4 h then washed. There was no dermal irritation observed at 1, 24, 48, and 72 h.

TRIMETHYLSILOXYSILICATE

Trimethylsiloxysilicate (100%; 0.5 g) was administered to the intact skin of New Zealand White rabbits (n = 6) under occlusion for 4 h.[32] There were no signs of erythema or edema observed. The authors rated trimethylsiloxysilicate a dermal non-irritant.

Trimethylsiloxysilicate (2 g/kg) was administered to the shaved skin of New Zealand White rabbits (n = 10) under occlusion for 24 h.[32] The patch was then removed and the skin rinsed in corn oil. The rabbits were observed for 14 days. There were slight signs of grade 1 irritation in 4 rabbits which were resolved by day 2.

Trimethylsiloxysilicate (30% in olive oil; 0.1 mL; MW 3000-10,000) was not dermally irritating to white rabbits (n = 3) when applied to clipped skin for 4 consecutive days.[36]

TRIFLUOROPROPYLDIMETHYL/TRIMETHYLSILOXYSILICATE

Trifluoropropyldimethyl/trimethylsiloxysilicate (50%) was not a dermal irritant when administered to the clipped skin of Japanese white rabbits (n = 3).[37]

In a cumulative dermal irritation test using Japanese white rabbits (n = 3), trifluoropropyldimethyl/trimethylsiloxysilicate (50%) was not irritating to normal, clipped skin what administered 4 consecutive days.[37]

***Ocular – Non-Human***

SILICA DIMETHYL SILYLATE

Silica dimethyl silylate (100%; 0.1 g) administered into the eyes of New Zealand white rabbits (n = 3) caused only slight conjunctivae redness at 1 h after instillation.[56]

In an ocular irritation test using New Zealand white rabbits (n = 6), Silica dimethyl silyate (27 wt.%; 0.5 ml) was administered to the eye and examined at 1, 24, 48, and 72 h.[57] There was a diffuse crimson coloration of the conjunctivae and slight swelling of the eyelids observed in 1 rabbit. Slight redness of the conjunctivae alone was seen in the remaining 5 animals. The mean conjunctival redness was 0.6. Ocular reactions had resolved completely in all animals by 1, 3, or 7 days after instillation. All corneal and iridial scores for all animals at all observation times were zero. The authors concluded that the test substance was a non-irritant. Silica dimethyl silylate (0.1 – 0.2 g; 0.1 ml) was applied to one eye of New Zealand white rabbits (n = 3/sex).[39] Three of the treated eyes were not rinsed and 3 rinsed with saline after 20 – 30 sec. The eyes were scored at 1, 24, 48, and 72 h. There were no signs of irritation at any observation period.

Silica dimethyl silylate (0.1 – 0.2 g) was applied to one eye of New Zealand white rabbits (n = 8; sex not provided).[58] Five of the rabbits' eyes were not rinsed and 3 rinsed with saline after 20 – 30 sec. The eyes were scored at 1, 24, 48, and 72 h and 7 days. There were no signs of irritation at any observation period.

Silica dimethyl silylate (50%; 0.1 ml in olive oil) was applied to one eye of New Zealand white rabbits (n = 8; sex not provided).[58] Five of the rabbits' eyes were rinsed with saline after 5 min and 3 rinsed after 24 h. The eyes were scored at 1, 24, 48, and 72 h. Conjunctiva redness was scored at 1.0 at the first 3 observations and was resolved at 72 h. There were no other signs of irritation at any observation period.

Silica dimethyl silylate (0.1 ml; 0.1 – 0.2 g undiluted) was applied to one eye of New Zealand white rabbits (n = 5 males, 4 females). There was mild conjunctivae redness at 1 and 24 h which was resolved at 48 h.

An EpiOcular Human Cell Construct assay was conducted on a product containing silica dimethyl silylate (2%).[59] There was no irritation predicted.

TRIMETHYLSILOXYSILICATE

Trimethylsiloxysilicate (100%; 0.1 ml) was administered to the right eye of New Zealand White rabbits (n not provided).[32] The eyes were examined at 0, 1, 24, 48, and 72 h. There were no clinical signs or signs of irritation at any observation period. Trimethylsiloxysilicate (50% in olive oil; 0.1 mL; MW 3000-10,000) was not an ocular irritant to Japanese white rabbits (n = 3).[36]

Trimethylsiloxysilcate (50% in olive oil; 0.1 mL; MW 3000-5000) had a Draize score of 2 when administered to the eyes of Japanese white rabbits (n = 3).

A mixture of trimethylsiloxysilicate (60%) and isododecane (50% in olive oil) was reported to be practically non-irritating in rabbits (n = 3).[51]

TRIFLUOROPROPYLDIMETHYL/TRIMETHYLSILOXYSILICATE

Trifluoropropyldimethyl/trimethylsiloxysilicate (100%; 0.1 mL) had a Draize score of 0 in Japanese white rabbits (n = 3).[37]

***Dermal - Human***

Silica dimethyl silylate, trimethylsiloxysilylate, and trifluoropropyldimethyl/trimethylsilxoysilicate were not irritating up to 30%, 20%, and 50%, respectively, in multiple human patch tests and use tests of the ingredients and products containing the ingredients (Table 5).

***Ocular – Human***

An eyeliner containing silica dimethyl silylate (2%) and an eyeshadow containing trimethylsioxysilicate (20%) were not irritating in use tests (Table 5).[60,61]

**Sensitization**

***Non-Human***

TRIMETHYLSILOXYSILICATE

In a local lymph node assay (LLNA), trimethylsiloxysilicate (15%, 30%, 60% in acetone/olive oil) was dermally administered to the entire dorsal surface of each ear of mice (strain and n not provided) for 3 consecutive days.[32] The stimulation indexes were 1.0, 1.1, and 0.8 at 15%, 30%, and 60%, respectively. The authors concluded that trimethylsiloxysilicate had no reaction that was identified as sensitization.

Trimethylsiloxysilicate (50% in alcohol) was a weak sensitizer in a guinea pig maximization test (n = 5).[36]

TRIFLUOROPROPYLDIMETHYL/TRIMETHYLSILOXYSILICATE

Trifluoropropyldimethyl/trimethylsiloxysilicate (100%) was a weak sensitizer in a guinea pig maximization test (n = 5).[37]

***Human***

Silica dimethyl silylate, trimethylsiloxysilylate, and trifluoropropyldimethyl/trimethylsilxoysilicate were not sensitizing up to 30%, 20%, and 50%, respectively, in multiple human repeat insult patch tests (HRIPT) and use test of the ingredients and products containing the ingredients (Table 5).

## SUMMARY

The functions of silica silylate, silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/ trimethylsiloxysilicate in cosmetics include: antifoaming agents, anti-caking agents, bulking agents, binders, skin-conditioning agents-emollient, skin-conditioning agents-occlusive, slip modifiers, suspension agents-nonsurfactant, and viscosity increasing agents-nonaqueous. These grafted and co-condensed hybrid materials are amorphous and practically insoluble in most common solvents, much like un-modified silica.

Silica dimethyl silylate was reported to be used in 734 cosmetic products (593 leave-on and 142 rinse-off products) at 0.00003% - 10%; up to 10% in leave-on products; and up to 4% in rinse-off products. There were 245 used reported of silica silylate (244 in leave-on at 0.2% - 25% (highest in other hair preparations) and 1 rinse-off product (no concentrations of use were reported for rinse-off products). There were 633 uses reported of trimethylsiloxysilicate at 0.0001% – 30%; up to 30% in leave-on products; and up to 5% in rinse-off products. There were no uses reported of trifluoropropyldimethyl/trimetylsiloxysilicate but concentration of use was reported to be 2% – 20% in leave-on products.

Silica dimethyl silylate is used in perfumes. The product category may include products that are aerosolized or used as powders. Particles of silica dimethyl silylate average > 125 μm and none were < 90 μm, and only particles with an aerodynamic diameter of ≤ 10 μm are respirable.

Orally administered silica dimethyl silylate was eliminated from the body primarily in the feces in mice, monkeys, and humans. Inhaled silica dimethyl silylate collected in the lungs and lymph nodes of rats.

In acute studies, dermally administered silica dimethyl silylate and trimethylsiloxysilicate up to 2 g/kg were not toxic to rats. The oral $LD_{50}$ of silica dimethyl silylate was >7900 mg/kg for rats; trimethylsiloxysilicate had no effects at 5 g/kg. The oral $LD_{50}$ of trifluoropropyldimethyl/trimethylsiloxysilicate was > 2 g/kg in mice. There were no mortalities from the inhalation of silica dimethyl silylate up to 520 mg/m$^3$in rats. Intraperitoneally administered silica dimethyl silylate caused thickening of the liver and spleen capsules. The test substance was observed in the abdominal cavity.

The oral NOAEL for silica dimethyl silylate in rats was 500 mg/kg for 6 months and 100 mg/kg for 24 months. Rats that inhaled treated fumed silica dust for up to 4 weeks were observed to have crusty eyes, muzzle, and nose; closed eyes; irregular breathing; irritable disposition; lacrimation and salivation; scabs; and red and yellow/brown stained fur. The inhalation LOAEL was 31 mg/m$^3$for 2 weeks.

Aerosolized silica dimethyl silylate caused mortality at 209 mg/m$^3$ and respiratory distress at lower doses. There was a dose-dependent reduction in weight gain, reduction in feed consumption, increase in lung weight, decrease in relative liver weights, and decrease in absolute kidney weights. There was an increase in red blood cell counts, packed cell volume, and hemoglobin . Silica dimethyl silylate did not cause any developmental toxicity to rats up to 3.8 g/kg/d, rabbits up to 1600 mg/kg, hamsters up to 1600 mg/kg, or mice up to 1340 mg/kg. There were no reproductive effects in rats up to 509 mg/kg/d.
Silica dimethyl silylate was not genotoxic in several Ames tests and a mammalian chromosome aberration test. A product containing siloxanes and silicones, di-Me (dimethyl silicones and siloxanes) (18%) and dimethyl silicones and siloxane, reaction products with silica (2%)) was not genotoxic in an Ames test. Trimethylsiloxysilicate was not genotoxic in Ames tests. There were no in vivo genotoxicity studies discovered.

Orally administered silica dimethyl silylate at 100 mg/kg was not carcinogenic to rats.

Silica dimethyl silyate and trimethylsiloxysilicate were not dermally irritating to rabbits up to 100%.

Trifluoropropyldimethyl/trimethylsiloxysilicate was not dermally irritating to rabbits at 100%. In a human patch test, a mixture containing trimethylsiloxysilicate at 24% resulted in irritation in 2 out of 19 subjects. Silica dimethyl silylate at 100% was slightly or not irritating to the rabbit eye. Trimethylsioloxysilicate at 100% was practically or non-irritating to the rabbit eye.
Silica dimethyl silyate and trimethylsiloxysilicate were not dermally irritating to rabbits up to 100%. Trifluoropropyldimethyl/ trimethylsiloxysilicate was not dermally irritating to rabbits at 100%. Silica dimethyl silylate and trimethylsiloxysilylate, were not irritating or sensitizing up to 30% and 20%, respectively, in multiple human patch tests.. Trifluoropropyldimethyl/ trimethylsilxoysilicate was not irritating at 50% in multiple human patch tests. Silica dimethyl silylate was slightly or not irritating to the rabbit eye. Trimethylsioloxysilicate was practically or non-irritating to the rabbit eye. The results were negative in an LLNA of trimethylsiloxysilicate up to 60%. HRIPTs of products containing silica dimethyl silylate up to 7% were negative.

## DISCUSSION

The CIR Expert Panel noted gaps in the available safety data for some of the silylates and surface modified siloxysilicates in this safety assessment. Because these ingredients have similar structures and are used in cosmetics in similar ways, the available data can be used to support the safety of the entire group. These ingredients are stable amorphous solids, used mostly in formulations applied to the skin. These ingredients have virtually no water solubility and it appears that the only impurity would be alkanes (C7-10-iso) at a maximum of 0.35%, a residual solvent from the production process, which raises no safety concerns for dermal use.

The available safety test data demonstrated an absence of dermal irritation and sensitization at the reported concentrations of use. Silica dimethyl silylate did not cause reproductive or developmental toxicity in animal studies. Orally silica dimethyl silylate at 100 mg/kg was not carcinogenic. While there were no long-term studies that addressed systemic toxicity, these ingredients were not likely to pass through the stratum corneum of the skin because of their large size and their solubility properties.

Because these ingredients can be used in products that may be aerosolized, including sprays and powders, the Panel discussed the issue of potential inhalation toxicity. The data available from multiple inhalation studies, including acute and chronic exposure studies, indicate little potential for pulmonary overload or other respiratory effects at relevant doses. Although particles appear to have reached the lungs in these animal studies, the sizes of the particles used were either clearly within the respirable range (ie, ≤10 μm) or were not reported. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics.

The Panel considered other data available to characterize the potential for silylates and surface modified siloxysilicates to cause systemic toxicity, irritation, sensitization, or other effects. The Panel noted the lack of systemic toxicity at high doses in several

acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study. In addition, these ingredients are macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. Further, these ingredients are reportedly used at concentrations ≤10% in cosmetic products that may be aerosolized. The Panel noted that 95% - 99% of particles produced in cosmetic aerosols are not respirable. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information indicates that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

## CONCLUSION

The CIR Expert Panel concluded that silica silylate, silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/trimethylsiloxysilicate are safe in the present practices of use and concentration described in this safety assessment safe when formulated and delivered in the final product to be not irritating or sensitizing to the respiratory tract.

## TABLES AND FIGURES

**Table 1.** Definitions, functions, and structures of siloxysilicates and silylates assessment.[62]

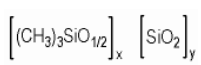
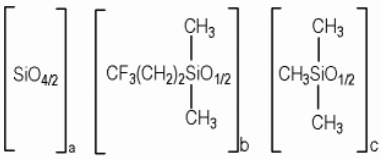
| Ingredient CAS No. | Definition | Function(s) | Other Names | Formula/structure |
|---|---|---|---|---|
| Silica Silylate<br>1015787-46-8<br>211811-62-0<br>68909-20-6<br><br>From trade name ingredients:<br>112153-70-5<br>112153-71-6<br>1123693-37-7<br>70536-25-3<br>371755-66-7 | Silica Silylate is a hydrophobic silica derivative where some of the hydroxyl groups on the surface of the fumed silica have been replaced by trimethylsiloxyl groups. | Antifoaming Agent; Bulking Agent; Skin-Conditioning Agent - Emollient; Suspending Agent - Nonsurfactant | Hydrophobic silica; a silylated silica | See Figure 1 |
| Silica Dimethyl Silylate<br>1158846-14-0<br>67762-90-7<br><br>From trade name ingredients:<br>60842-32-2<br>139351-18-1<br>106009-03-4<br>68611-44-9<br>63148-62-9 | Silica Dimethyl Silylate is a silica derivative in which the surface of the fumed silica has been modified by the addition of dimethyl silyl groups. | Anticaking Agent; Bulking Agent; Slip Modifier; Suspending Agent - Nonsurfactant; Viscosity Increasing Agent - Nonaqueous | Silica, [(dimethylsilyl)oxy]-modified; dichlorodimethylsilane-treated fumed silica; hydrophobic dichlorodimethylsilane-treated fumed; dichlorodimethyl-silane-treated silica; silane, dichlorodimethyl-, reaction products with silica; treated fumed silica dust | See Figure 1 |
| Trimethyl-siloxysilicate<br>56275-01-5<br>104133-09-7<br><br>From trade name ingredients:<br>68937-54-2 | Trimethylsiloxysilicate is a variable network of polysilicic acid units, which are endblocked with trimethylsilyl groups. | Antifoaming Agent; Skin-Conditioning Agent - Occlusive | Silicic acid, trimethylsilyl ester; hexamethyldisiloxane-tetraethyl orthosilicate copolymer; poly(trimethylsiloxy-silicate); tetraethoxysilane-hexamethyldisiloxane copolymer; trimethylsilyl silicate |  |
| Trifluoropropyld-imethyl/ trimethylsiloxysili-cate | Trifluoropropyldimethyl/ trimethylsiloxysilicate is a variable network of polysilicic acid units, which are endblocked with a mixture of trimethylsilyl groups and trifluoropropyl-dimethylsilyl groups. | Binder; Skin-Conditioning Agent - Emollient | |  |

**Table 2.** Physical and chemical properties of silica dimethyl silylate and trimethylsiloxysilicate.

| Property | Value | Reference |
|---|---|---|
| **Silica Silylate** | | |
| Physical Form | Free-flowing powder | [4] |
| Color | White | [4] |
| Density/Specific Gravity g/cm$^2$ | 0.04-0.1 | [4] |
| **Silica dimethyl silylate** | | |
| Physical Form | Fluffy powder | [44] |
| Color | White | [44] |
| Density/Specific Gravity g/cm$^2$ @ 20 $^o$C | 2.2 | [63] |
| Density/Specific Gravity g/cm$^2$ @ 20 $^o$C | 1.8-2.2 | [6] |
| Melting Point $^o$C | >520 | [64] |
| Water Solubility g/L @ $^o$C & pH | No | [64] |
| log $K_{ow}$ | Does not dissolve in either octanol or water | [64] |
| **Trimethylsiloxysilicate** | | |
| Physical Form | Solid powder | [7] |
| Color | White | [10] |
| Molecular Weight daltons | ~6500 | [7,9] |
| Density/Specific Gravity g/cm$^2$ @ 25 $^o$C | 0.52 | [65] |
| Bulk density g/cm$^3$ | 0.3 | [7] |
| Water Solubility g/L | Virtually insoluble | [7,9] |
| Thermal decomposition $^o$C | >200 | [7] |

**Table 3.** Current frequency and concentration of use according to duration and type of exposure provided in 2010.[18-20]

| Use type | Silica silylate | | Silica dimethyl silylate | | Trimethylsiloxysilicate | | Trifluoropropyldimethyl/ trimethylsiloxysilicate | |
|---|---|---|---|---|---|---|---|---|
| | # of Uses | Concentration (%) | # of Uses | Concentration (%) | # of Uses | Concentration (%) | # of Uses | Concentration (%) |
| **Totals/conc. range** | **245** | **0.2-25** | **734** | **0.00003-10** | **633** | **0.0001-30** | NR | **2-20** |
| *Duration of use* | | | | | | | | |
| Leave-on | 244 | 0.2-25 | 592 | 0.00003-10 | 611 | 0.0001-30 | NR | 2-20 |
| Rinse-off | 1 | NR | 142 | 0.0003-4 | 22 | 0.002-5 | NR | NR |
| Diluted for (bath) use | NR | NR | NR | NR | NR | NR | NR | NR |
| *Exposure Type* | | | | | | | | |
| Eye | 80 | 1-6 | 45 | 0.00003-3 | 255 | 0.4-30 | NR | 20 |
| Incidental ingestion | 96 | 2-24 | 281 | 1-10 | 30 | 2-30 | NR | NR |
| Incidental inhalation-sprays | 1 | NR | 35 | 0.002-3[1] | 17 | 0.005-10[2] | NR | 2[1] |
| Incidental inhalation-powders | 6 | 0.2-4 | 17 | 0.02-4 | 51 | 0.0001-19 | NR | NR |
| Dermal contact | 126 | 0.2-7 | 313 | 0.00003-6 | 501 | 0.0001-30 | NR | 2-20 |
| Deodorant (underarm) | NR | NR | 27 | 0.002-2 | NR | NR | NR | NR |
| Hair – non coloring | NR | 17-25 | 2 | NR | 13 | 5 | NR | NR |
| Hair - coloring | NR | NR | 130 | NR | 6 | 0.1 | NR | NR |
| Nail | 21 | 10 | 5 | 0.002-2 | 43 | 0.1 | NR | NR |
| Mucous Membrane | 97 | 2-24 | 285 | 0.0009-10 | 30 | 30 | NR | NR |
| Baby products | NR | NR | 1 | NR | NR | NR | NR | NR |

NR = not reported; Totals = rinse-off + leave-on product+diluted for bath uses.
[1] In a deodorant and/or a suntan product that may or may not be a spray.
[2] 0.4% in a body and hand skin care spray.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

**Table 4.** Inhalation studies of silica dimethyl silylate and silica silylate.

| Species (n) | Concentration(s); duration; particle size | Results | Reference |
|---|---|---|---|
| **Acute/single dose studies** | | | |
| **Silica dimethyl silylate** | | | |
| CRL: Cd (SD)BR rats (5/sex) | 0, 2280 mg/m$^3$/ 1 h; 0.15 µm | Clinical signs during and after treatment: irregular breathing. After treatment: poor coat quality and alopecia in females. | [66] |
| Cpb;WU Wistar rat (5/sex) | 0, 477 mg/m$^3$/ 4 h; 2.9 µm | No mortalities. Clinical signs: restless, half closed eyes. Body weights reduced first days, weight increased afterwards. | [67] |
| Wistar rats (5/sex) | 210, 540, 2100 mg/m$^3$; 4 h; 0.8-1 µm | No mortalities at the low dose group, 7 in the mid dose group, all the rats died in the high dose group. During exposure, clinical signs: closed eyes, labored breathing, respiratory distress, and hunched posture. Low dose group had few feces; mid dose group had lethargy, dyspnea, ptosis, piloerection, and few feces. High dose group had crusting/lacrimating eyes, opaque eyes, red-stained nose/mouth area, wet anogenital area, and an unkempt appearance. Necropsy: lungs were discolored at all concentrations and the mid and high dose groups had opaque eyes and white material in the nasal turbinates. | [68] |
| Crl:[WI] WU BR rats (n = 5/sex; high dose group 7/sex) | 520, 1120, 2790 mg/m$^3$; 4 h; 1.24 µm | None died in the low dose group; body weight gain was normal in the low dose group. All of the rats in the mid and high dose groups died. During exposure, the rats exhibited decreased, irregular breathing at all doses. After exposure, the low dose group exhibited increased breathing rates, labored breathing, and blepharospasm, all of which resolved in 4 days. At necropsy, the lungs in the low dose group were filled with foam. The mid dose group had hemorrhage and reduced elasticity in the lungs, soiled fur, and white powder in the nasal cavity. The high dose group had petechia on the lungs, blocking lumps of white particles and slime in the nose and and hemorrhage in the nasopharynx. Histopathology revealed erythrocytes and edema in alveoli, epithelial lining interrupted or flattened, and scarce goblets cells. The lumina of the nasopharynx, larynx, and brochi/bronchioli contained large quantities of pale-eosinophilic material mixed with nucleated cells and erythrocytes. The material filled the entire lumen in the smaller bronchioli. | [69] |
| Wistar rats (n = 5/sex) | 0, 477 mg/m$^3$; 4 h; particle size <5% (56%), ≥ 7.7 µm (44%) | $LC_{50}$ = > 477 | [67] |
| **Multiple dose Studies** | | | |
| **Silica Silylate** | | | |
| Rats (strain not provided; n = not provided) | 0, 10, 50, 150 mg/m$^3$ for up to 12 months; killed and necropsied at 2 weeks, 1, 3, 6, 12 months or after 2 months recovery | Mortality was dose related: 8% (control), 12% (10 mg/m$^3$), 26% (50 mg/m$^3$) and 33% (150 mg/m$^3$). In the surviving rats, 10 mg/m$^3$ had no effect, and 50 mg/m$^3$ and 150 mg/m$^3$ produced collections of foamy macrophages within the alveoli. | [70] |
| Cynomolgus monkeys (n = not provided) | 0, 10, 50, 150 mg/m$^3$ for up to 12 months; killed and necropsied at 2 weeks, 1, 3, 6, 12 months or after 2 months recovery | In monkeys, 10 mg/m3 had no effect, and 50 mg/m3 and 150 mg/m3 produced interstitial fibrosis, which did not resolve or progress during the recovery period | [70] |
| Wistar rats (n = 10/sex) | 0, 31, 87, 209 mg/m$^3$ for 6 h/d, 5 d/wk, 2 weeks | Signs of respiratory distress in all test groups. Body weight gain and food consumption reduced at 87 and 209 mg/m$^3$. No change in hematological parameters. Changed liver and kidney weights at 87 and 209 mg/m$^3$; not associated with histopathological changes. Concentration-dependent increase in absolute/relative lung weights. Lungs of several animals in all groups pale, spotted, swollen and spongy, and occasional small hemorrhages. Lungs of animals in all test groups showed increased cellularity, accumulation of alveolar macrophages, alveolar edema and early granulomata. NOAEL < 31 mg/m$^3$. | [71] |
| Wistar rats (n = 70/sex) | 34.7 mg/m$^3$ for 6 h/d, 5 d/wk, 13 weeks; 52 weeks recovery | Lung collagen content increased immediately after exposure, and did not return to control levels during 52 wk recovery. Granuloma-like lesions, alveolar macrophage accumulation, cellular debris, and increased septal cellularity occurred at varying times post exposure | [72,73] |
| Wistar rats (n = 40/sex) | 0, 31, 87, 209 mg/m$^3$; for 6 h/d, 5 d/wk, 2 weeks (high dose started at 420 mg/m$^3$ and reduced over 4 d); particle size could not be determined due to electrostatic charges | 4 males and 2 females died within 2 days in high-dose group. Rats in this group had severe respiratory distress and apathy. After reduction to 209 mg/m$^3$, clinical signs: slight to moderate respiratory distress and poor general health. Mid dose group: Dyspnea. Dose-dependent reduction in weight gain, reduction in feed consumption, increase in lung weight, decrease in relative liver weights, and decrease in absolute kidney weights. Increase in red blood cell counts, packed cell volume and hemoglobin in the mid-dose males and high-dose males and females. Lungs had focal bronchiolar mucus proliferation, intraluminal mucus deposition, granulomata, focal increased septal cellularity, and accumulation of alveolar macrophages. In rats that died, perivascular edema, alveolar edema, and hemorrhages along with slight | [74] |

| | | | |
|---|---|---|---|
| | | bronchiolar necrosis. There were no remarkable findings in the nasal cavity. The LOAEL was 31 mg/m$^3$ due to histopathic findings in the lungs. | |
| Wistar Cpb:WU rats (n = 10/sex) | 0, 35 mg/m$^3$ (calculated 34.74 mg/m$^3$); 6 h/d, 5 d/wk, 13 weeks with 13, 26, 39 and 52 weeks recovery; particle size not provided | An additional group of 50 rats were treated and allowed post recovery times of 12, 26, 39, and 52 weeks. 3 rats died for unrelated reasons during treatment.<br>Decreased body weights in males weeks 6 – 9. At 13 weeks, males had increased red blood cells, hemoglobin content, packed cell volumes and prothrombine time. At the end of treatment and 13 weeks recovery, females had increased neutrophils and decreased lymphocytes. Females had decreased urinary volume with associated increased urinary density.<br>Increased lung weights (absolute and relative) in males and females until week 39 post-exposure and at week 13 of exposure. Increased absolute thymus weights in males. At week 13, males and females had lesions of the lungs (including spotted, irregular or gray surface and spongy tissue) and enlarged mediastinal lymph nodes.<br>At week 13 of exposure, lungs had granuloma-like lesions, accumulations of alveolar macrophages, alveolar spaces filled with granular material, debris and polymorphonuclear leucocytes, increased septal cellularity, alveolar bronchiolization and interstitial fibrosis. Mediastinal lymph nodes characterised by accumulation of macrophages. Findings in the nose comprised slight necrosis or atrophy of the olfactory epithelium and were resolved at 13 weeks. Changes in the lungs and mediastinal lymph nodes decreased in incidence and severity at 13 weeks post exposure or had completely disappeared at 52 weeks post exposure. Nose [sic] was recovered at week 13 post exposure. No effects on male and female gonads. Collagen content of the lungs increased in males and females at week 13 of exposure and, at 13 and 39 weeks post exposure. Silicon levels in the lungs as well as in the mediastinal lymph nodes increased in males and females at week 13. There was slight necrosis/atrophy of the olfactory epithelium. | [72] |
| Female Sprague-Dawley rats (n = 80) | 50 mg/m$^3$; 5 h/d, twice/wk, 8 or 12 months with 0 – 5 months recovery; <7 µm | 8 and 12 Month post exposure: Interstitial white dust deposits and slightly enlarged lymph nodes. Lung had many dust cells in alveoli, locally perivascular and peribronchiolar dust cell deposits with slight to moderate formation of fibrous tissue. Lymph nodes increased in number of granular phagocytes and local fibrosis.<br>Post recovery period: Interstitial grey-white dust deposits, more at 5 months; moderately enlarged grey-black lymph nodes after 1 month, smaller after 3 and 5 months. Lungs had slight epithelial desquamation up to 1 month; locally perivascular and peribronchiolar dust cell deposits with slight to moderate formation of fibrous tissue; thickening of part of the alveolar wall. Lymph nodes had increased number of granular phagocytes and local fibrosis. Signs of recovery from 1- 5 months. | [38] |
| Rats (n = 340) | 100 mg/m$^3$; 5 h/d, 5 d/wk for 1 yr, 3 or 6 months recovery; particle size not provided | All treated rats had small grey-white dust foci under the lung surface, particularly in the upper lung lobes. Mediastinal lymph nodes were slightly to moderately enlarged after a period of 3 months exposure. After 9 months of exposure these lymph nodes also had a grey-black appearance. In rats found dead, adhesion of the pleura, inflamatory cell infiltrations and lung abscesses. After 3 or 6 month post exposure period a time-dependent reduction of the number of grey-white dust-foci was observed in the lungs; mediastinal lymph nodes were reduced in size (compared to during the exposure period) and had a grey/black and soft appearance.<br>At 3, 6 and 12 months of exposure increasing incidences of desquamous alveolar cells (with and without dust content), foci of dust cells (in bronchioli, peribrochiolar and perivascular) with increasing (in time) number of dust granulas and cell detritus in the alveolar space (12 months) in the lungs. Mediastinal lymph nodes had increasing number of dust cells containing higher numbers of dust granulomas (3-12 months exposure). A reticulin network developed with increased exposure times in lungs. No signs of proliferation, fibrosis, or necrosis in the lungs or mediastinal lymph nodes.<br>At 3 or 6 month post exposure period, lungs had groups of alveoli containing accumulations of dust cells, but no desquamous alveolar cells. Peribronchiolar and perivascular small nodules were noted, without proliferation, necrosis or fibrosis. Number and size of the dust cell foci were reduced. Mediastinal lymph nodes contained large amounts of dust cells after 3 and 6 months. Fine reticulin network was visible with no connective tissue. | [29] |
| Female rats (n = 235; control n = 12) | 0, 80 mg/m$^3$; 4 h/d 1 yr; particle size not provided: Positive control 45 g/m$^3$ type of silica not clear | 60 rats in the treatment group died during treatment due to bronchiopneumonia, broncho-ectasia, and abscess in the lungs but were not considered substance-specific. At 3 months, the rats had dust cell granulomata in the lungs and alveolar spaces filled with dust cells and desquamous alveolar cells. Mediastinal lymph nodes were enlarged and filled with dust cells. In the control group, 41 of 120 rats died spontaneously. At 1 year, small grey-white foci under the pleura and moderately enlarged mediastinal lymph nodes were observed. Dust accumulation did not cause fibrotic responses during the 3, 5, and 8 month recovery period and the dust amount decreased over time. There were no indications of silicosis. | [75] |

**Table 5**. Human irritation and sensitization studies of silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/ trimethlsiloxysilicate and products containing these ingredients.

| Ingredient | Concentration | Study | n | Results | Reference |
|---|---|---|---|---|---|
| Silica dimethyl silylate | 7.5%, 15%, 30% in squalane | HRIPT | 45 | No irritation or sensitization | [76] |
| Silica dimethyl silylate | 24% (mixed with isododecane) in petrolatum | Single patch test | 19 | Irritation in 2 subjects | [36] |
| Trimethylsiloxysilicate (MW 3000-10,000) | 20% in olive oil | Single patch test | 20 | No irritation | [36] |
| Trimethylsiloxysilicate (MW 3000-5000) | 20% in petrolatum | Single patch test | 19 | ± response in 2 subjects | [36] |
| Trifluoropropyldimethyl/ trimethylsiloxysilicate (MW 3000-10,000) | 50% with cyclomethicone 45% and hydrogenated polysobutene 5% | Single patch test | 19 | ± response in 2 subjects | [37] |
| **Product** | | | | | |
| Antiperspirant; silica dimethyl silylate | 1.4%; 0.2 g | HRIPT | 99 | No irritation or sensitization | [77] |
| Antiperspirant; silica dimethyl silylate | 1.4%; 0.2 g | HRIPT | 99 | No irritation or sensitization | [77] |
| Antiperspirant; silica dimethyl silylate | 1.4%; 0.2 g | HRIPT | 102 | No irritation or sensitization | [78] |
| Eyeliner; silica dimethyl silylate | 2%; 0.2 g | HRIPT | 107 | No irritation or sensitization | [79] |
| Lipstick; silica dimethyl silylate | 7%; 0.2 g | HRIPT | 100 | No irritation or sensitization | [80] |
| Lipstick basecoat (HVS494-155); trimethylsiloxysilicate | 24.7% | Occlusive patch test | 10 | Slight irritation (0.5) | [81] |
| Eye shadow; trimethylsiloxysilicate | 20% | Occlusive patch test | 50 | No irritation | [82] |
| Lipstick; trimethylsiloxysilicate | 30% | Occlusive patch test | 50 | No irritation | [83] |
| Lipstick; trimethylsiloxysilicate | 30% | Occlusive patch test | 50 | No irritation | [84] |
| "Eye area product"; trimethylsiloxysilicate | 5% | Occlusive patch test | 50 | No irritation | [85] |
| "Eye area product"; trimethylsiloxysilicate | 5% | Occlusive patch test | 50 | No irritation | [86] |
| "Eye area product"; trimethylsiloxysilicate | 5% | Occlusive patch test | 50 | No irritation | [87] |
| "Eye area product"; trimethylsiloxysilicate | 5% | Occlusive patch test | 50 | No irritation | [88] |
| Lipstick (HVF105-062[sic] & HVF 105-063); trimethylsiloxysilicate | 30.47% & 30.51% | Single patch test | 13 | No irritation or sensitization | [89] |
| Liquid lipcolor basecoat combined with lipcolor topcoat; trimethylsiloxysilicate | 12.335% (24.67% in product) | HRIPT | 106 | No irritation or sensitization | [90] |
| Liquid lipcolor basecoat combined with lipcolor topcoat; trimethylsiloxysilicate | 12.335% (24.67% in product) | HRIPT | 106 | No irritation or sensitization | [91] |
| Eyeliner; trimethylsiloxysilicate | 20% | HRIPT | 108 | No irritation or sensitization | [92] |
| Eye shadow; trimethylsiloxysilicate | 14.36% | HRIPT | 108 | No irritation or sensitization | [93] |
| Suntan product; trimethylsiloxysilicate | 10% | HRIPT | 103 | No irritation or sensitization | [60] |
| Blush stick; trimethylsiloxysilicate | 5.5 | HRIPT | 600 | No irritation or sensitization | [94] |
| Lipstick; trimethylsiloxysilicate | 24.67% | Used daily for 4 weeks by sensitive skin subjects | 29 f | Minimal irritation; no sensitization (5 subjects with mild, very slight irritation/dryness | [95,96] |
| Lipstick; trimethylsiloxysilicate | 24.67% | Used daily for 8 weeks (2 different colors, each applied for 4 weeks) | 57 | Minimal irritation; no sensitization (5 subjects with mild, very slight irritation/dryness | [97] |
| Eyeliner; silica dimethyl silylate | 2% | Used for 13 or 14 consecutive days | 31 f | No irritation or sensitization | [98] |
| Liquid lipstick; trimethylsiloxysilicate | 30.51% | Used daily for 2 weeks | 26 f | Mild to moderate subjective irritation reactions in ~ 1/3 of the subjects | [96] |
| Eye shadow; | 20% | Used once daily for 28 days | 10 | No eye or eyelid irritation | [61] |

**Table 5**. Human irritation and sensitization studies of silica dimethyl silylate, trimethylsiloxysilicate, and trifluoropropyldimethyl/ trimethlsiloxysilicate and products containing these ingredients.

| Ingredient | Concentration | Study | n | Results | Reference |
|---|---|---|---|---|---|
| trimethylsiloxysilicate | | | | | |
| Eyeliner; trimethylsiloxysilicate | 5% | Used once daily for 28 days | 10 | No eye or eyelid irritation | [99] |
| Eye shadow; trimethylsiloxysilicate | 5% | Used once daily for 28 days | 10 | No eye or eyelid irritation | [99] |
| Product not provided; trimethylsiloxysilicate | 5% | Used once around eye region daily for 28 days | 10 | No eye or eyelid irritation | [100] |
| Product not provided; trimethylsiloxysilicate | 5% | Used once around eye region daily for 28 days | 10 | No eye or eyelid irritation | [101] |

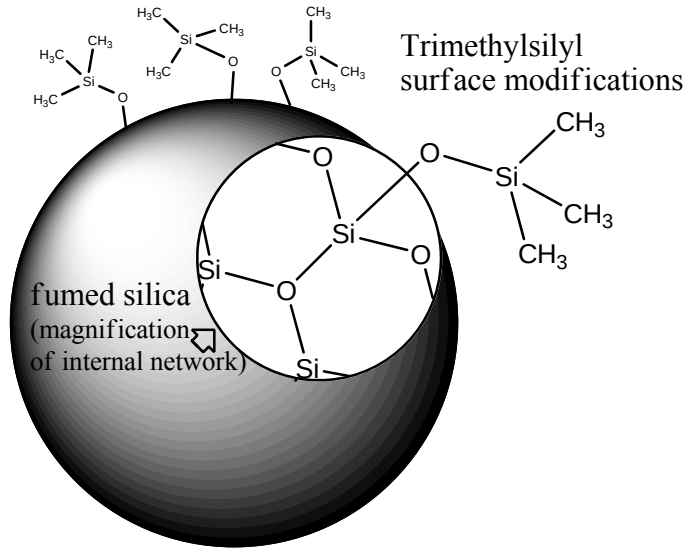



**Figure 1.** Trimethylsilyl surface modifications.

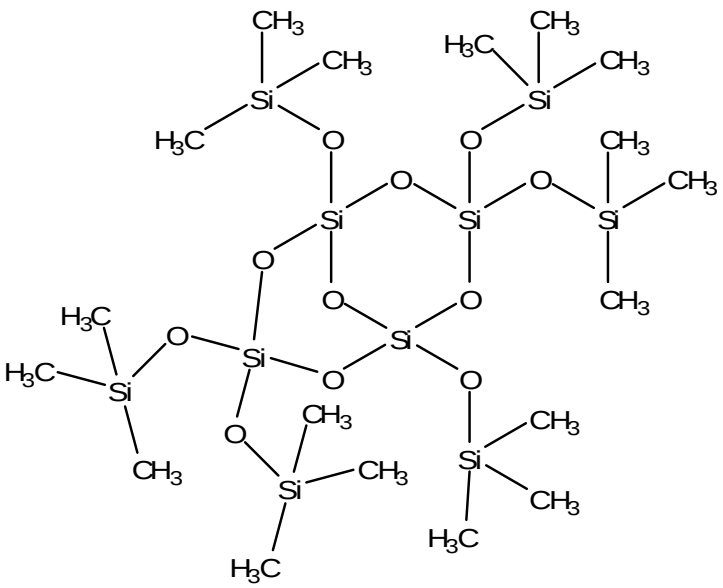


**Figure 2.** Co-condensed silica.

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