Safety Assessment of Alkoxyl Alkyl Silanes as Used in Cosmetics

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ABSTRACT

This is a safety assessment of alkoxyl alkyl silanes as used in cosmetics. The functions of these ingredients include: binder, skin-conditioning agent – miscellaneous, skin-conditioning agent – emollient, and surface modifier. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed relevant data related to these ingredients. The Panel concluded that Bis-Stearoxydimethylsilane, Stearoxytrimethylsilane, Triethoxycaprylylsilane, and Trimethoxycaprylylsilane are safe as cosmetic ingredients in the practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a review of the scientific literature and unpublished data relevant for assessing the safety of the alkoxyl alkyl silanes as used in cosmetics. The ingredients in this report are structurally-related silanes bearing both alkyl and alkoxyl groups. The 4 ingredients in this report are:

- Bis-Stearoxydimethylsilane
- Stearoxytrimethylsilane
- Triethoxycaprylylsilane
- Trimethoxycaprylylsilane

According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), the functions of these ingredients include: binder, skin-conditioning agent – miscellaneous, skin-conditioning agent – emollient, and surface modifier (Table 1).[1]

The Panel reviewed other siloxane ingredients, such as Methicone and other related Methicone-containing ingredients, and concluded that those ingredients were safe as used in cosmetic products.[2] The Panel also reviewed cyclic siloxanes, the cyclomethicones (e.g., Cyclotetrasiloxane, Cyclopentasiloxane and Cyclohexasiloxane), and concluded that they were safe as used in cosmetic products.[3]

Trimethoxycaprylylsilane is reported to function as a surface modifier; therefore toxicity studies of metal particles coated with alkoxyl alkyl silanes are included in this safety assessment.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[4] In this safety assessment report, ECHA is cited as the reference for summaries of information from industry obtained from the ECHA website.

CHEMISTRY

Definition and Structure

The ingredients in this report are structurally-related silanes bearing both alkyl and alkoxy groups (Figure 1).

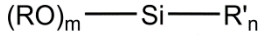


Figure 1. Alkoxyl Alkyl Silanes, where m+n=4 and R & R' are methyl or alkyl groups

Physical and Chemical Properties

Triethoxycaprylylsilane and Trimethoxycaprylylsilane are liquids that work well as dispersants for substances such as titanium dioxide. Triethoxycaprylylsilane and Trimethoxycaprylylsilane are clear and colorless (Table 2).[4,5]

Method of Manufacture

The alkoxyl alkyl silanes can be synthesized via hydrosilation of the appropriate alkoxy silane with an olefin (e.g., Triethoxycaprylylsilane may be synthesized via hydrosilation of 1-octene with triethoxysilane and a platinum catalyst).[6] Alternatively, these ingredients may be synthesized via silation of appropriate alcohols with a disilazane (e.g., Stearoxytrimethylsilane may be synthesized via silation of octadecanol with hexamethyldisilazane and an organocatalyst).[7] At the completion of the reaction, water is added and the organic materials are extracted with ethyl acetate.

Impurities

A product mixture containing Bis-Stearoxydimethylsilane (approximately 75%), stearyl alcohol (approximately 16%), and dimethicone (approximately 9%), may contain <0.1% cyclotetrasiloxane as a manufacturing impurity.[8] Analysis of three batches of this mixture showed that Al, As, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Hg, Mn, Mo, Ni, Pb, Sb, Sn, Sr, Tl, V, W, Zn, and Zr were not present (detection level < 2 ppm); trace levels (<0.1%) of cyclotetrasiloxanes, cyclopentasiloxane, and cyclohexasiloxane were present.

Triethoxycaprylylsilane is reported to be 95%-100% pure.[5] Impurities are reported to include ethanol (0.2%), octane (<1.5%), siloxanes (<2%), and branched octyltriethoxysilanes (<2%).

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. The data received from the FDA are collected from manufacturers through the FDA's Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Council in response to a survey of the maximum reported use concentrations by category.

According to 2016 VCRP survey data, Triethoxycaprylylsilane is reported to be used in 417 formulations, 413 leave-on formulations and 4 rinse-off formulations (Table 3).[9] Stearoxytrimethylsilane and Trimethoxycaprylylsilane are reported to be used in 10 and 4 formulations, respectively.

The results of the concentration of use survey conducted by the Council in 2015 indicate that Triethoxycaprylylsilane has the highest reported maximum concentration of use; it is used at up to 2.6% in suntan products.[10] The other three ingredients are reported to be used at 0.77% or lower.

No uses were reported in the VCRP for Bis-Stearoxydimethylsilane, but concentration of use data were received from industry; it was reported to be used in a foundation in the Council survey. Therefore, it can be assumed that there is at least one use for this ingredient.

Three of the alkoxyl alkyl silanes are in products that are used around the eyes (e.g., Triethoxycaprylylsilane in eye shadow up to 2.5%), and Triethoxycaprylylsilane is used in products that could possibly be ingested and/or have exposure to the mucous membranes (e.g., in lipstick up to 1%).

Additionally, Triethoxycaprylylsilane is used in cosmetic sprays and could possibly be inhaled; it is reported to be used at up to 0.021% in body and hand sprays and up to 0.011% in perfumes. In practice, 95%-99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles <10 µm compared with pump sprays.[11,12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[13,14] Triethoxycaprylylsilane is used in face powders at up to 2%. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[15-17]

None of the alkoxyl alkyl silanes named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.[18]

According to Annex VI to European Regulations (EC) No 1223/2009 Triethoxycaprylylsilane is listed as a permitted zinc oxide (nano) coating for UV filters.[19] Zinc oxide (nano) is not to be used in applications that may lead to exposure of the end-user's lungs by inhalation. Zinc oxide is only to be used under certain conditions, which include "…uncoated, or coated with [T]riethoxycaprylylsilane, dimethicone, dimethoxydiphenylsilanetri-ethoxycaprylylsilane cross- polymer, or octyl triethoxy silane."

TOXICOKINETIC STUDIES

Dermal Penetration

Bis-Stearoxydimethylsilane

A product mixture (3 mg/mL in ethanol/water) containing Bis-Stearoxydimethylsilane (approximately 75%) was placed in a donor chamber. The test was conducted using porcine ear skin.[8,20] Samples of receptor fluid were taken at 0, 0.5, 1, 2, 4, 6, 8, and 24 h and analyzed by atomic absorption spectroscopy. None of the product was detected in the receptor chamber. It was concluded that the test item did not penetrate through porcine skin.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Human

Triethoxycaprylylsilane

No toxicokinetics data were discovered; however, in humans, hydrolysis of Triethoxycaprylylsilane is expected to produce three moles of ethanol for each mole of octylsilanetriol.[5] Triethoxycaprylylsilane undergoes rapid hydrolysis with a half-life of 0.3-0.6 h at a pH of 7.0 and 25˚C and 1.2-1.9 h at pH 4.0.[5] Survival of Triethoxycaprylylsilane is expected to be transient depending on the test system, and observed intrinsic toxicity is likely due to a mixture of the parent molecule and the hydrolysis products ethanol and octylsilanetriol, and to a lesser degree any polymerization products. Based on the chemical structure of Triethoxycaprylylsilane, the hydrolysis products are expected at a ratio of 3 moles ethanol to 1 mole octylsilanetriol.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Triethoxycaprylylsilane

New Zealand White rabbits (n=5/sex/dose) were dermally exposed to Triethoxycaprylylsilane (2000, 4000 or 8000 mg/kg) under occlusion for 24 h.[5] The study protocol was in accordance with the Environmental Protection Agency's (EPA) Toxic Substances Control Act (TSCA) Health Effects Test Guideline.[40 CFR 798.1100] The rabbits were observed for 14 days following exposure. One female and three male rabbits died in the 8000 mg/kg group; one male rabbit died in the 4000 mg/kg group. Signs of toxicity were transient, involved the central nervous system, and included limb paresis or paralysis. Other clinical signs included labored breathing, iritis, slight wetness of the perinasal fur, and weight loss (some with emaciation). Necropsy of the rabbits that died revealed hemorrhaged intestines and a small amount of blood in the urine. Gross pathologic examination of all survivors revealed dark or bright red lungs. One rabbit exhibited intestines partially filled with gas, an enlarged spleen, and a raised tan nodule on one kidney. There were no treatment-related microscopic lesions in selected tissues (including spinal cord, sciatic nerve, kidneys, and urinary bladder). The acute dermal LD_{50} in male rabbits was 6730 mg/kg and in female rabbits > 8000 mg/kg.

Trimethoxycaprylylsilane

When Trimethoxycaprylylsilane (100%; 0.5 mL) was applied to the shaved dorsal skin of white Russian rabbits (n=3) under occlusion for 4 h, no systemic effects were detected.[4] No further information was provided.

Oral

Bis-Stearoxydimethylsilane

When a product mixture (2000 mg/kg) containing Bis-Stearoxydimethylsilane (concentration approximately 75%, dosage approximately 1500 mg/kg), stearyl alcohol, and dimethicone was orally administered to rats (n=5/sex), none of the rats died, there were no clinical signs of toxicity, and the necropsies were unremarkable.[8,21] There were no effects on body weight changes during the 14-day observation period.

Triethoxycaprylylsilane

A single dose of Triethoxycaprylylsilane (7280, 10,300 and 14,600 mg/kg in a 0.25% aqueous methyl cellulose solution) was administered by gavage to Sprague-Dawley rats (n=5/sex), and the rats were observed for 14 days.[5] The study protocol was in accordance with EPA TSCA Health Effects Test Guideline.[40 CFR 798.1175] The predominant signs of toxicity included effects on the central nervous system (sluggishness, aggressive behavior, and unsteady gait with limb paresis or paralysis, loss of righting reflex, and prostration). Other clinical signs included an unkempt and/or moribund appearance, emaciation, a red crust on the perinasal and periocular fur, and a moderate amount of blood in the urine. All deaths occurred within 4-9 days after dosing (total deaths not specified); three moribund female rats in the 14,600 mg/kg group were killed early for humane reasons. Necropsy of the rats that died during treatment or observation period revealed discolored lungs, livers, stomachs and intestines, small stomachs, hemorrhaged or gas-filled intestines, bladders distended with red liquid or urine (males); a large amount of blood was present in the urine of three males. The rats that survived the observation period had no gross lesions at necropsy. Selected tissues (brain, spinal cord, sciatic nerve, lungs, kidneys, and urinary bladder) from eight male and seven female rats were examined microscopically; the only lesions that were considered to be treatment-related were tubular dilation of the kidneys, renal mineralization and hemorrhages of the urinary bladder. The LD_{50} was 12,200 mg/kg for male rats, 11,500 mg/kg for female rats, and 11,800 mg/kg for the combined sexes.

Triethoxycaprylylsilane (5110 mg/kg in peanut oil) was administered as a single dose by gavage to Bor: WISW (SPFCpb) rats (n=5/sex) and the rats were observed for 14 days.[5] The study protocol was in accordance with the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 401. The predominant clinical signs of toxicity were effects on the central nervous system (incoordination, stilted gait, labored breathing, sunken sides and vocalization on handling). Other signs of toxicity included hypokinesia, diarrhea, piloerection, red encrusted snout, and body weight reduction. One female died on day 7 after dosing; at necropsy, the gastrointestinal tract was severely autolytic. At necropsy no abnormalities were detected in the animals that survived until the end of the study. The LD_{50} was >5110 mg/kg for male and female rats.

Trimethoxycaprylylsilane

The reported oral LD_{50} for Trimethoxycaprylylsilane in Wistar rats (n=10/sex) was >3500 mg/kg for both males and females.[4] After a dosage of 3236 mg/kg, there were coordination disturbances, piloerection, chromodacryorrhea, increased salivation, and red nasal discharge. At 4752 mg/kg, there was additional decreased muscle tone, loss of righting reflexes, and increased diuresis. Other clinical signs included tremors, vocalization on handling, lacrimation, opacity of the cornea, and green discolored urine. The development of toxic effects was not always immediate; coordination disturbances were observed 2 h after administration of the test material, and the other clinical signs occurred between days 2 and 5. All clinical signs resolved by day 21 of the observation period.

Inhalation

Triethoxycaprylylsilane

In a study conducted in a manner similar to OECD TG 403, Crl:CD (R) BR, VAF (R) PLUS, Sprague-Dawley rats (n=5/sex) were exposed to a saturated vapor concentration of Triethoxycaprylylsilane in air (approximately 248 mg/m^3) in a whole-body inhalation chamber for 4 h and then observed for 14 days.[5] There were no deaths during the exposure or the observation period. Hyperactivity during the exposure period was observed in one rat. No exposure-related effects were noted on body weights and no abnormal gross lesions were noted at necropsy. The LC_{50} was greater than the saturated vapor concentration.

Trimethoxycaprylylsilane

Wistar rats (n=5/sex) were exposed to aerosolized Trimethoxycaprylylsilane in a whole-body chamber (duration not specified); because the concentration of the test material did not reach the desired levels (actual concentrations achieved not specified and no further information was provided), a nose-only apparatus was used to expose the rats.[4] It is not clear if the same or new rats were used when the authors switched methods of exposure. The rats were exposed for 4 h in the nose-only apparatus and observed for 14 days thereafter. The mean actual concentrations of exposure in the nose-only apparatus were 0.9, 2.36, 2.53, and 6.2 g/m^3 (corresponding nominal concentrations: 3.5, 9.8, 15.4, and 27.6 g/m^3, respectively).

None of the rats died in the 0.9 g/m^3 group, one male and three female rats died in the 2.36 g/m^3 group, no males and four females died in the 2.53 g/m^3 group, and one male and all five females died in the 6.2 g/m^3 group.

During exposure to 0.9 g/m^3 in the nose-only apparatus, the rats had a hunched appearance, piloerection, and mostly closed eyes. Breathing patterns were superficial and irregular during the first hour of exposure; breathing patterns became more regular concomitant with a decreased breathing frequency (1-2 breaths/sec vs 3-4 breaths/sec normally). Directly after exposure, breathing frequency was irregular in rats exposed to 0.9 g/m^3. No abnormalities were observed 4 days after exposure to 0.9 g/m^3. However, exposure to 0.9 g/m^3 resulted in reduced body weight gain in male rats measured 14 days after exposure, and reduced body weight or body weight gain in female rats 7 and 14 days after exposure.

Piloerection was observed during the first 4 days of observation in one female rat exposed to 2.36 g/m^3. Superficial breathing patterns and wet heads were observed in rats exposed to 2.36 or 2.53 g/m^3, and labored breathing was observed in four female rats exposed to 2.53 g/m^3. Rats in the 2.36 g/m^3 group showed drowsiness shortly after the end of exposure. Body weight gain of the surviving rats exposed to 2.36 or 2.54 g/m^3 was generally not affected. No abnormalities were observed after 4 days in rats exposed to 2.53 g/m^3.

Exposure to 6.2 g/m^3 in the nose-only apparatus resulted in a very low, deep or superficial, irregular breathing frequency (<1 breath/sec) 30 min after the start of exposure. In general, breathing patterns became more stable thereafter (1-2 breaths/sec). The rats exhibited wet heads 2 h after the start of the exposure. Directly after exposure, breathing frequency was labored in rats exposed to 6.2 g/m^3. The rats with labored breathing were lethargic. The first 4 days of the observation period revealed piloerection, wet noses, drowsiness, and tightly closed eyes in surviving rats exposed to 6.2 g/m^3. Piloerection remained until day 7 post exposure. Dyspnea was observed in one male 14 days after exposure; its limbs were blue, the rat was skinny and showed piloerection and signs of ataxia. All four surviving rats exposed to 6.2 g/m^3 showed severe body weight reduction 7 days after exposure; body weight gain was observed 14 days after exposure in 3 of these rats.

At necropsy, red discolored lungs were observed in rats exposed to 2.36 g/m^3. Rats exposed to 2.53 g/m^3 had rusty-brown discolored lungs. Dark-red discolored, and sometimes swollen or darkly spotted, and/or edematous lungs were found in the rats that died, or were killed in extremis after exposure to 6.2 g/m^3. Furthermore, grey-white spots were observed on the lung lobes of three female rats. In the other rats in the 6.2 g/m^3 group that were killed in extremis, no other abnormalities were observed. In all surviving rats necropsied at the end of the 14-day observation period, no abnormalities were found, except for spotted lungs in one male exposed to 6.2 g/m^3. The LC_{50} for Trimethoxycaprylylsilane was 7.5 and 1.9 g/m^3 for male and female rats, respectively. The combined LC_{50} was 3.9 g/m^3.[4]

Triethoxycaprylylsilane - Coated Particles

In a pulmonary toxicity study, Triethoxycaprylylsilane-coated titanium dioxide particles (2 and 10 mg/kg) were instilled into the lungs of male Crl:CD (SD)IGS BR rats (n=6/group/recovery time) with and without Tween 80 (1%).[22] The Triethoxycaprylylsilane-coated titanium dioxide particles were 230 nm (assumed diameter; mean or median not reported), with a particle size range of 0.1–0.9 µm, and a surface area of 8.2 m^2/g; these particles were hydrophobic. Saline was the control substance. After saline instillation (2 from each group) and at 24 h, 1 week, 1 month, and 3 months (4 from each group), the rats were then killed, their lungs were lavaged with warm phosphate-buffered saline and examined. The numbers of cells recovered by broncho-alveolar lavage from the lungs of any of the Triethoxycaprylylsilane-coated titanium dioxide particles-exposed groups were not different from saline-instilled controls at any post-exposure time point. Histopathological analyses of a lung tissue section of rats in the high dose groups at 1 month post-exposure showed normal pulmonary architecture and, other than a few particle-laden macrophages, were not very different from a saline-instilled lung section at 1 month post-exposure. The authors concluded that the Triethoxycaprylylsilane-coated titanium dioxide particles did not cause pulmonary toxicity.

Zinc oxide particles coated with Triethoxycaprylylsilane (1, 4, 8, 16, 32, 64, or 128 µg) suspended in water with 2% mouse serum were intratracheally instilled into the lungs of C57BL/6N mice (n=3).[23] The particles were 130 nm in diameter; when analyzed in suspension, the median diameter was 208±74 nm and mean diameter was 225±32 nm, indicating

agglomeration and an asymmetrical particle-size distribution. The mice were killed and necropsied 24 h after instillation. Acute pulmonary inflammation was observed (marked by polymorphonuclear neutrophil influx) with cell damage (marked by increased lactate dehydrogenase and total protein) in broncho-alveolar lavage fluid (BALF) in the 64 and 128 µg groups. Systemic inflammation was indicated by increased blood neutrophils and decreased blood lymphocytes in the lung tissue. These signs were not observed in the 1-32 µg groups.

Short-Term Toxicity Studies

Oral

Bis-Stearoxydimethylsilane

In a 28-day oral gavage study conducted in accordance with OECD TG 407, a product mixture (50, 200, 1000 mg/kg) containing Bis-Stearoxydimethylsilane (approximately 75%) was reported to have a no-observed-adverse-effect level (NOAEL) of 1000 mg/kg/d (approximately 750 mg/kg/d Bis-Stearoxydimethylsilane) in SPF-bred Wistar rats.[8,24,25] None of the rats died and there were no clinical signs during the test period. There were no adverse effects observed in the grip strength test and locomotor activity test during week 4 of the test period. Feed consumption and body weight changes were similar to the control group (vehicle only). Hematology and clinical biochemistry parameters of blood collected at the end of treatment were similar in the test and control groups. Macroscopic and microscopic findings at necropsy were unremarkable; organ weights were similar in the control and treatment groups.

Triethoxycaprylylsilane

In a combined repeated-dose/reproductive/developmental toxicity screening test conducted in accordance with OECD TG 422, Triethoxycaprylylsilane (0, 100, 300 or 1000 mg/kg/d in dried, de-acidified peanut oil) was administered 7 days a week by gavage to Sprague-Dawley rats (n=10/sex).[5] There was a group of females evaluated for repeated-dose toxicity and another group evaluated for reproductive toxicity. The same males were used in both the toxicity and reproductive phases of the study. Males and females of the repeated-dose toxicity study were treated for 28 and 29 days, respectively. Females of the reproductive-toxicity group were treated with the same dose rates for up to 45 days (i.e., prior to mating through post-partum day 4). Animals were observed twice daily for mortality, morbidity, and moribundity. Clinical examinations were performed daily following dosing. Functional observational battery (FOB) and motor activity evaluations were performed on males and females of the repeated-dose toxicity group. Detailed physical examinations and body weight measurements were performed weekly. Individual feed consumption was recorded weekly, except during the cohabitation period. Blood samples for hematology and serum chemistry evaluations were collected at the scheduled necropsy. Complete necropsies were performed, and selected organs were weighed. Microscopic examination was performed on protocol-specified tissues from the control and high-dose males, and females of the repeated-dose toxicity and reproductive-toxicity groups. Based on clinical and histopathology findings in the high dose group, various target tissues of the males and females of the repeated-dose toxicity and reproductive-toxicity groups were examined at the mid- and low-dose groups. [See results specific to reproduction in the Developmental and Reproductive Toxicity section.]

Clinical signs included an increase in soiling of the head (around the nose, chin, and muzzle) in the mid- and high-dose males and females of the repeated-dose toxicity groups, and in the females of the high-dose reproductive-toxicity group. Clinical observations consistent with neuromuscular toxicity (decreased activity, dragging of the hind limbs, and/or uncoordinated gait) occurred only in the high-dose reproductive toxicity group, and were not observed in the males or females of the repeated-dose toxicity group. Due to the severity of these clinical signs, three females of the high-dose reproductive-toxicity group were killed prior to scheduled necropsy. There were no changes observed during FOB and motor activity tests conducted with males and females of the repeated-dose toxicity group (no clinical signs before termination), most likely due to the shorter duration of exposure compared to the females of the reproductive-toxicity group (29 days for females of the repeated-dose toxicity group vs up to 45 days for females of the reproductive-toxicity group). Treatment-related decreases in group mean body weights and/or body weights gains were observed in all rats in the high-dose groups with associated decreases in feed consumption in the females of the repeated-dose and reproductive-toxicity groups. There were no treatment related clinical pathology findings.

There was an increase in mean absolute and relative liver weights of males and females in the high-dose toxicity group. Histopathological findings were identified in the liver as dose-related increases in the incidence of centrilobular hypertrophy in the mid- and high-dose groups in the repeated-dose toxicity and reproductive-toxicity studies, which was associated with an increase in mean absolute and relative liver weights; these liver effects were not considered adverse by the authors because these changes are consistent with common adaptive changes that occur in the liver upon xenobiotic administration. Histopathological findings were identified in the bladder as diffuse epithelial hyperplasia in all rats in the high-dose groups in the repeated-dose toxicity study. Other unspecified histopathological findings were also identified in the kidneys, adrenal glands, thymus, spleen, brain, spinal cord, peripheral nerves, and skeletal muscles in the high-dose groups. In the brain, 40% and 80% of the high-dose groups in the repeated-toxicity study and females in the reproductive-toxicity study, respectively, exhibited white matter degeneration. Degeneration of the spinal cord occurred in 50% and 90% of the females of the high-dose group in the repeated-dose toxicity study and reproductive-toxicity groups, respectively. The peripheral nerves (sciatic and tibial) also showed minimal to severe degeneration and demyelination in the high-dose group in the repeated-toxicity study and reproductive-toxicity groups, with less incidence and severity occurring in the repeated-dose

toxicity females. Based on the bladder epithelial hyperplasia in males and the neuromuscular findings in the females of the repeated-dose toxicity and reproductive groups at 1000 mg/kg/d, the NOAEL for systemic toxicity was 300 mg/kg/d.[5]

Fischer 344 rats (n=5/sex, 10/sex in high-dose and control group) were administered Triethoxycaprylylsilane (200, 2000, and 10,000 ppm) in the diet for 28 days.[5] The study protocol was similar to that of OECD TG 407. Mean test substance consumption values for males were 12.2, 114.4, and 592.2 mg/kg/d for the 200, 2000, and 10,000 ppm target concentrations, respectively. Mean test substance consumption for females was 13.4, 122.6, and 639.6 mg/kg/d for the 200, 2000, and 10,000 ppm target concentrations, respectively. Following termination of dosing, 5 rats/sex from the high-dose and control groups were allowed a 2-week recovery period. Clinical signs, feed consumption, body and organ weights, hematology, clinical chemistry evaluations, gross pathology and histopathology evaluations were monitored; no changes indicating an adverse effect were observed. The NOAEL was determined to be >10,000 ppm (the highest dose tested), corresponding to dose rates of approximately 592.2 and 639.6 mg/kg/d for male and female rats, respectively.

Inhalation

Triethoxycaprylylsilane - Coated Particles

In an inhalation toxicity study, male Wistar rats (n=17/group/time point) were exposed to Triethoxycaprylylsilane-coated zinc oxide nanoparticles (0, 0.5, 2.5, and 12.5 mg/m^3; 22,126, 87,044, 233,360 particles/cm^3, respectively) in a head/nose only apparatus for 6 h/day for 5 days in accordance with OECD TG 412.[26] During exposure, the 12.5 mg/m^3 exposure was measured at 219,031 particles/cm^3; particle size and surface area were not specified. Twelve rats in each group were killed and necropsied on either day 4 or 25; nine of these rats were examined histopathologically and organ burdens were determined in three rats (results not reported). On study days 7 and 28, the lungs of the remaining five rats in each group were lavaged, and the BALF was analyzed for markers indicative of injury of the broncho-alveolar region. On exposure days, clinical examination was performed before, during and after exposure.

The inhalation of zinc oxide nanoparticles coated with Triethoxycaprylylsilane for five days resulted in local inflammation in the lungs of the rats. Examination showed activation of the draining lymph nodes. Minimal to moderate necrosis of the olfactory epithelium was observed. The effects occurred in a concentration-dependent manner and were reversed by the end of the recovery period, except for a multifocal increase in alveolar macrophages that was still present. At the lowest concentration of 0.5 mg/m^3, increased levels of a few mediators in the BALF and in serum were determined. Also, of the six rats examined, minimal (grade 1) multifocal necrosis of the olfactory epithelium was noted in the nasal cavity in one rat treated at the lowest dose. Therefore, a no-observed-adverse-effect-concentration (NOAEC) could not be established. The lowest concentration of 0.5 mg/m^3 was considered to be the low-observed-adverse-effect-concentration (LOAEC).[26]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART)

Triethoxycaprylylsilane

As stated previously, Triethoxycaprylylsilane (0, 100, 300 or 1000 mg/kg/d in dried, de-acidified peanut oil) was administered 7 days a week by gavage to 10 rats/sex/group for up to 45 consecutive days in a combined repeated-dose/reproductive/developmental toxicity screening test.[5] The study was in accordance with OECD TG 422. Females were divided into a repeated-toxicity group and a reproductive-toxicity group. The same males were used for both the repeated-dose toxicity and reproductive-toxicity phases of the study. Males were treated for 28 days. Reproductive-toxicity group females were treated for up to 45 days (14 days prior to mating, during mating, gestation, and up to and including postpartum day 4). Mating was initiated after 2 weeks of dosing. Females in the reproductive-toxicity group cohabitated with males of the same treatment group until positive evidence of mating occurred. A maximum of 14 days were allowed for mating. Reproductive parameters evaluated included evidence of mating, pregnancy, duration of gestation, mean number of corpora lutea and mean number of uterine implantation sites, mean mating and fertility indices and evaluation of loss of offspring (pre-implantation and post-natal loss). [See results specific to toxicity in the Short-Term Toxicity Studies section.]

Changes in reproductive parameters were observed in the high-dose group and were associated with marked maternal toxicity. Mating and fertility were unaffected by treatment. The mean duration of gestation was increased (5.6%) compared to the control group. Of the seven dams that successfully initiated parturition, four exhibited dystocia (difficult/prolonged labor). The authors concluded that it was not possible to determine with confidence if 1000 mg/kg/d represents the NOAEL. Therefore, the reproductive toxicity NOAEL was considered to be >300 mg/kg/d.

To evaluate the developmental toxicity of Triethoxycaprylylsilane, dams and pups were killed on postpartum day 4 and examined for external gross lesions. Developmental parameters evaluated included total litter size, mean litter size, mean live litter size, mean litter weight, mean ratio of live births/litter size, sex ratio, pup viability, pup body weight, and body weight gain. Changes in developmental parameters were observed in the high-dose group and were associated with marked maternal toxicity; the total litter sizes in this group were unaffected by treatment but the mean number of live male and female pups/dam at first litter check on post-natal day (PND) 0 was decreased (39.3%) compared to controls. PND 0 mean litter weights, average pup body weights and body weight gains were similar to controls. By PND 4, several dams in the high-dose group had been killed due to the severity of various clinical signs and/or difficulty during labor. Only 4 dams survived to PND 4. Of these litters, the total viable pups on PND 4 were decreased compared to controls, resulting in a 25.2% decrease in percent viability of pups/dam on PND 4 compared to controls. This decrease was due to a single dam with a 14.3% post-natal loss of offspring. The remaining dams had no post-natal loss of pups between Days 0-4. PND 4 mean litter weights, average pup body weights and body weight gains in the high-dose group were also decreased compared to

controls. External gross lesions were not observed for treated dams or pups. The authors concluded that it was not possible to determine with confidence if 1000 mg/kg/d represents the NOAEL. Therefore, they considered the developmental toxicity NOAEL to be >300 mg/kg/d.[5]

GENOTOXICITY STUDIES

In Vitro

In vitro genotoxicity studies are summarized in Table 4.

In multiple genotoxicity assays, Bis-Stearoxydimethylsilane (up to 5000 µg/plate), Trimethoxycaprylylsilane (up to 5000 µg/plate), and Triethoxycaprylylsilane (up to 10,000 µg/plate) were negative for genotoxicity. Trimethoxycaprylylsilane was not cytotoxic.[4,5,8,24,27]

In Vivo

Triethoxycaprylylsilane - Coated Particles

A mouse micronucleus assay was conducted in accordance with OECD TG 474 with intraperitoneally injected Triethoxycaprylylsilane-coated zinc oxide nanoparticles (0, 15, 30, 60 mg/kg; 10 mL/kg) using male NMRI mice (n=5/dose/time).[26] Bone marrow cells were harvested for evaluation of micronuclei at 24 h post-dose (vehicle, positive controls, and low-, mid-, and high-dose) and 48 h post-dose (vehicle and high-dose only). There were no statistically significant or biologically relevant differences in the number of erythrocytes containing micronuclei either between the vehicle control groups and the three dose groups, or between the two intervals (24 and 48 h). The number of normochromatic or polychromatic erythrocytes containing small micronuclei or large micronuclei did not deviate from the vehicle control values at either of the intervals and was within the historical vehicle control data range. The controls had the expected results.

CARCINOGENICITY STUDIES

Carcinogenicity data were not found in the published literature and no unpublished data were provided.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Bis-Stearoxydimethylsilane

A product mixture containing Bis-Stearoxydimethylsilane (approximately 75%) was reported to be non-irritating in rabbits.[8] No further information was provided.

Triethoxycaprylylsilane

Triethoxycaprylylsilane (100%; 0.5 mL) was applied under occlusion for 4 h to the intact skin of New Zealand White rabbits (n=3/sex).[5] The study protocol followed EPA TSCA Health Effects Test Guideline. [40 CFR 798.4470] The rabbits were restrained for the 4-h contact period; when the coverings were removed, excess test substance was removed. Moderate erythema (grade 2) and moderate edema (grades 2-3) were observed in all rabbits at the 1-h observation time; this was resolved by day 7. At day 7, desquamation was observed on two animals. The Primary Irritation Index (PII) was 3.041 (3=primary skin irritant; 4=corrosive to the skin). The substance was considered to be moderately irritating to the skin.

Triethoxycaprylylsilane (100%; 0.5 mL) was applied to the skin of Russian white rabbits (n=2 male, 1 female) for 4 h under occlusion in accordance with OECD TG 404.[5] The coverings were removed and the test substance was not washed off. Moderate erythema (grades 2-3) and moderate-to-severe edema (grades 3-4) were observed in all three rabbits at 1 h. Desquamation was observed in all animals beginning on day 7. All skin effects had completely resolved by day 10. The Primary Dermal Irritation Index (PDII) was 5.1 on a scale of 0 to 8. The substance was considered to be highly irritating to the skin.

In a toxicological study described previously, New Zealand White rabbits (n=5/sex) were dermally exposed to Triethoxycaprylylsilane (2000, 4000 or 8000 mg/kg) under occlusion for 24 h.[5] The study protocol followed EPA TSCA Health Effects Test Guideline. [40 CFR 798.1100] Dermal reactions included erythema, edema, necrosis, fissuring, desquamation and alopecia; it was not specified which dose level(s) caused these reactions.

Trimethoxycaprylylsilane

Trimethoxycaprylylsilane (assumed 100%; 0.5 mL) was administered to the shaved dorsal skin of white Russian rabbits (n=3) under occlusion for 4 h.[4] The test site was observed at 1, 24, and 72 h, then daily for 14 days. Moderate to severe erythema was observed in all three rabbits immediately after removal of the patches, which resolved by day 10 of observation. Slight edema in one rabbit and moderate edema in the other two rabbits was observed immediately after the end of exposure, which was resolved by day 9. All rabbits showed eschar formation from the middle of the first observation week, which had not completely peeled off in two rabbits until the end of the observation period. The mean PDII was 4.9 on a scale of 0 to 8; the mean value for erythema/eschar was 2.42, and the mean value for edema was 2.5. Trimethoxycaprylylsilane was considered irritating to rabbit skin.

Sensitization

Animal

Bis-Stearoxydimethylsilane

In a Magnusson/Kligman assay conducted according to OECD TG 406 using guinea pigs (n=20, control=10) of a product mixture containing Bis-Stearoxydimethylsilane (75%), the test group was intradermally injected with the test substance (10%, 7.5% Bis-Stearoxydimethylsilane; with and without Freund's complete adjuvant).[8,24,28] One week later, the product mixture was dermally administered at 75% (in Alembicol D, 52.50% Bis-Stearoxydimethylsilane). Two weeks later, the guinea pigs were challenged with the product mixture at 50% (37.5% Bis-Stearoxydimethylsilane). There was no sensitization response observed.

OCULAR IRRITATION STUDIES

Animal

Bis-Stearoxydimethylsilane

A product mixture containing Bis-Stearoxydimethylsilane (approximately 75%) was reported to be non-irritating in the eyes of rabbits.[8] No further information was provided.

Triethoxycaprylylsilane

A single instillation of Triethoxycaprylylsilane (assumed 100%; 0.1 mL) was made into one eye of each New Zealand White rabbit (n=3/sex) and the eyes were not rinsed.[5] The study protocol was in accordance with the EPA TSCA Health Effects Test Guideline.[40 CFR 798.4500] The untreated eyes served as controls. Irritation was scored according to the Draize method at 1, 24, 48 and 72 h after administration. Transient iritis (grade 1) was apparent in 4 treated eyes at 1 h, but had resolved at 24 h. Minor to moderate conjunctival irritation characterized by redness and swelling (grades 1-2) with a moderate amount of ocular discharge (grades 1-2) was observed in all treated eyes. All of the rabbits had a normal ocular appearance by day 7. The maximum average score (MAS) was 12.33 (in a scale of 0 to 110) at 1 h; the scores at 72 h and day 7 were <0. Triethoxycaprylylsilane was considered slightly irritating.

In an acute eye irritation/corrosion study conducted in accordance with OECD TG 405, a single instillation of Triethoxycaprylylsilane (0.1 mL) was applied to the conjunctiva of one eye of albino Russian white rabbits (n=1 male, 2 female).[5] The untreated eyes served as controls. The eyes were not rinsed. Diffuse redness of the conjunctiva (grade 2) seen in all three rabbits resolved within 48 h. Slight swelling (grade 1) was observed in all three rabbits at 1 h; discharge was also noted in one rabbit at this time point. No effects on the cornea or iris were observed. The irritation index was 2.0 (on a scale of 0 to 110). Triethoxycaprylylsilane was considered slightly irritating.

Trimethoxycaprylylsilane

In a Draize test using white Russian albino rabbits (n=1 male, 2 females), Trimethoxycaprylylsilane (0.1 mL) was instilled into one eye of each rabbit.[4] Eyes were not rinsed and were observed for 3 days. There were no effects observed on the corneas and irises. The conjunctiva reacted with hyperemia (grade 1) in one rabbit and a diffuse crimson or beefy discoloration (grade 2 or 3) was observed in two rabbits. In addition, slight swelling (grade 1) or swelling with partial eversion of lids (grade 2) was observed. Swelling had completely disappeared at 24 h and redness was not observed 48 or 96 h after instillation. Discharge with moistening around the eye was recorded for two rabbits only at the 1-h observation time. The mean irritation score was 4 out of a possible 80. It was concluded that Trimethoxycaprylylsilane was not irritating to the eyes of rabbits.

SUMMARY

This is a review of the available scientific literature and unpublished data relevant to assessing the safety of the alkoxyl alkyl silanes as used in cosmetics. The ingredients in this report are structurally-related silanes and bear both alkyl and alkoxyl groups. The functions of these ingredients include skin-conditioning agent – miscellaneous, skin-conditioning agent – emollient, binder, and surface modifier.

According to 2016 VCRP survey data, Triethoxycaprylylsilane is reported to be used in 417 formulations, 413 which are leave-on formulations and 4 that are rinse-off formulations. Stearoxytrimethylsilane and Trimethoxycaprylylsilane are reported to be used in 10 and 4 formulations, respectively. Bis-Stearoxydimethylsilane had no reported uses in the VCRP.

The 2015 Council survey reports that Triethoxycaprylylsilane has the highest reported maximum concentration of use; it is used at up to 2.6% in suntan products. The other three ingredients are reported to be used at 0.77% or lower.

A product mixture containing Bis-Stearoxydimethylsilane (approximately 75%) did not penetrate porcine skin in an *in vitro* assay.

The acute dermal LD_{50} of Triethoxycaprylylsilane was 6730 mg/kg in male rabbits and > 8000 mg/kg in female rabbits. When Trimethoxycaprylylsilane was administered to the skin of rabbits under occlusion for 4 h, there were no systemic effects observed.

When a product mixture containing Bis-Stearoxydimethylsilane (approximately 1500 mg/kg) was orally administered to rats, none of the rats died, there were no clinical signs of toxicity, and the necropsies were unremarkable. For Triethoxycaprylylsilane, the LD_{50} was 12,200 mg/kg for male rats, 11,500 mg/kg for female rats, and 11,800 mg/kg for the combined sexes. In another assay, the LD_{50} value was >5110 mg/kg for male and female rats. The reported oral LD_{50} for Trimethoxycaprylylsilane in rats was >3500 mg/kg for both males and females; after a dose of 3236 mg/kg, there were coordination disturbances, piloerection, chromodacryorrhea, increased salivation, and red nasal discharge.

There were no deaths during exposure or the observation period when rats were exposed to a saturated vapor of approximately 248 mg/m^3 of Triethoxycaprylylsilane in a whole body inhalation chamber for 4 h.

The inhalation LC_{50} for Trimethoxycaprylylsilane following a 4 h exposure was 7.5 and 1.9 g/m^3 for male and female rats, respectively; the combined LC_{50} was 3.9 g/m^3. Clinical signs included superficial and irregular breathing during the first hour of exposure, wet heads, lethargy, piloerection, tightly closed eyes. Body weight gains were reduced during the observation period. The lungs of the rats that died or were killed in extremis were discolored and spotted.

Triethoxycaprylylsilane-coated titanium oxide particles at 10 mg/kg did not cause pulmonary toxicity when instilled into the lungs of rats. Zinc oxide particles coated with Triethoxycaprylylsilane caused acute pulmonary inflammation with cell damage in BALF at 64 and 128 µg in mice but not at 1-32 µg.

In a 28-day oral study, a product mixture containing Bis-Stearoxydimethylsilane at approximately 75% was reported to have a NOAEL of 1000 mg/kg/d (approximately 750 mg/kg/d Bis-Stearoxydimethylsilane) in rats.

In a repeated-dose/reproductive/developmental toxicity screening test, the NOAEL for systemic toxicity was 300 mg/kg/d Triethoxycaprylylsilane when administered for 28-29 days. Clinical signs at 300 and 1000 mg/kg/d included an increase in soiling around the nose, chin, and muzzle. Neuromuscular toxicity was observed at 1000 mg/kg/d. Treatment-related decreases in group mean body weights and/or body weights gains were observed in all rats in the high-dose groups with associated decreases in feed consumption in the toxicity group females and reproductive group females. There were no treatment related clinical pathology findings. The NOAEL was >10,000 ppm (the highest dose tested), corresponding to dosages of approximately 592.2 and 639.6 mg/kg/d for male and female rats, respectively, when Triethoxycaprylylsilane was administered in the diet for 28 days.

The inhalation of zinc oxide nanoparticles coated with Triethoxycaprylylsilane for five days resulted in local inflammation in the lungs of the rats. A NOAEC could not be established; the lowest concentration of 0.5 mg/m^3 was considered to be the LOAEC.

The reproductive and developmental toxicity NOAELs were >300 mg/kg/d for orally administered Triethoxycaprylylsilane in female rats; Triethoxycaprylylsilane was administered from 14 days prior to mating through 4 days postpartum. Reproductive effects only occurred in the 1000 mg/kg/d group in association with marked maternal toxicity.

A product mixture containing Bis-Stearoxydimethylsilane (approximately 75%) was reported to not be mutagenic at doses up to 5000 µg/plate in an Ames assay. In two separate assays, Triethoxycaprylylsilane was negative for mutagenicity in bacterial reverse mutation assays with *Salmonella typhimurium* and *Escherichia coli*, with and without metabolic activation at up to 10,000 µg/plate. In an *in vitro* chromosome aberration assay, Triethoxycaprylylsilane was cytotoxic to Chinese hamster ovary (CHO) cells with metabolic activation at 50 µg/mL and without metabolic activation at 20 µg/mL. In another *in vitro* chromosome aberration assay, Triethoxycaprylylsilane was negative for the induction of chromosome aberrations and was not clastogenic up to 1570 µg/mL. In Ames tests, Trimethoxycaprylylsilane was not mutagenic to *S. typhimurium* up to 5000 µg/plate.

A mouse micronucleus assay of Triethoxycaprylylsilane-coated zinc oxide nanoparticles was negative at up to 60 mg/kg.

A product mixture containing Bis-Stearoxydimethylsilane (approximately 75%) was reported to be non-irritating in rabbits. The PII was 3.041 when Triethoxycaprylylsilane (assumed 100%) was administered to rabbits; the substance was considered as moderately irritating to the skin. In another assay (assumed 100%), the PDII was 5.1 and Triethoxycaprylylsilane was considered to be highly irritating to rabbit skin. When rabbits were dermally exposed to Triethoxycaprylylsilane at 2000-8000 mg/kg under occlusion for 24 h, dermal reactions included erythema, edema, necrosis, fissuring, desquamation and alopecia; it was not specified which dose level(s) caused these reactions. Trimethoxycaprylylsilane was considered irritating to rabbit skin at 100%.

A product mixture containing 75% Bis-Stearoxydimethylsilane was reported to be non-sensitizing in a Magnusson Kligman assay using guinea pigs.

A product mixture containing Bis-Stearoxydimethylsilane at approximately 75% was reported to be non-irritating in the eyes of rabbits. After a single instillation of Triethoxycaprylylsilane, the MAS was 12.33 at 1 h; the scores at 72 h and day 7 were <0; Triethoxycaprylylsilane was considered slightly irritating. In an acute eye irritation/corrosion study, the irritation index was 2.0 for Triethoxycaprylylsilane and the test substance was considered slightly irritating. In a Draize test, using rabbits, there were no effects observed on the corneas and irises and Trimethoxycaprylylsilane was considered to be non-irritating.

DISCUSSION

The Panel considered dermal, oral, and inhalation toxicity studies, and DART animal studies, with acute to short-term exposures at concentrations much greater than levels (up to 2.6%) reported to be used in cosmetics. Genotoxicity

studies were negative in both *in vitro* and *in vivo* studies. A product containing 75% Bis-Stearoxydimethylsilane was not sensitizing in a Magnusson Kligman assay. While these studies were conducted on animals, the Panel agreed with applying the results of these studies to humans. The Panel also noted that any irritation noted was at concentrations well above the reported concentrations of use.

The Panel was satisfied that the inhalation and genotoxicity studies on metal particles coated with Triethoxycaprylylsilane were sufficient to show that application as surface modifiers would not cause toxicity when used in cosmetics.

The Panel noted gaps in the available safety data for the alkoxyl alkyl silanes in this safety assessment. The available sensitization data on Bis-Stearoxydimethylsilane are sufficient to cover the other three ingredients in this group. The available overall data for Bis-Stearoxydimethylsilane, Triethoxycaprylylsilane, and Trimethoxycaprylylsilane are sufficient to cover the lack of data for Stearoxytrimethylsilane. Similarity between structural activity relationships can be extrapolated and concentrations of use in cosmetics can be used to support the safety of each member of this group.

The Panel also expressed concern about heavy metals that may be present. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

There was no evidence presented that the starting material hexamethyldisilazane persists in the finished product. The addition of water at the end of the manufacturing process will consume any residual hexamethyldisilazane. Industry should use cGMPs when producing and using these ingredients to ensure that residual impurities are minimized.

The Panel discussed the issue of incidental inhalation exposure from body and hand sprays and perfumes. Triethoxycaprylylsilane is used in face powders at up to 2%. The limited data available from inhalation studies, including acute and short-term exposure data, suggest little potential for respiratory effects at relevant doses. In one study of Triethoxycaprylylsilane-coated titanium dioxide particles, the particles were reported to have a particle size range of 0.1-0.9 µm. The Panel noted the results of high-dosage intratracheal installation studies in animals showing that respirable Triethoxycaprylylsilane-coated titanium dioxide particles caused no effects at the lower dosages tested. In another study, Triethoxycaprylylsilane-coated zinc oxide particles had a reported diameter of 0.13 µm; the median diameter was reported to be 0.208±0.074 µm and the mean diameter was 0.225±0.032 µm, which indicated agglomeration. The Panel considers the sizes of a substantial majority of the coated particles are larger than those in the respirable range and/or undergo aggregation and agglomeration to form larger particles in formulation that would be larger than those in the respirable range. The Panel noted that 95%-99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that Bis-Stearoxydimethylsilane, Stearoxytrimethylsilane, Triethoxycaprylylsilane, and Trimethoxycaprylylsilane are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Definitions, CAS Nos., idealized structures, and functions of the alkoxyl alkyl silane ingredients in this safety assessment.[1, CIR Staff]

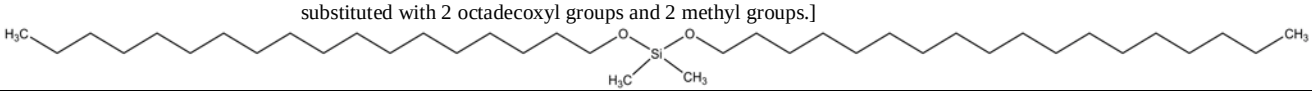
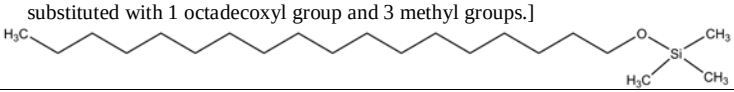
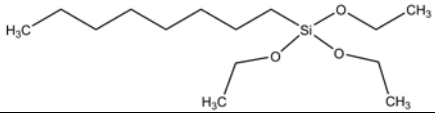
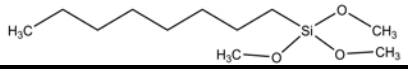
Ingredient CAS No.	Definition & Structures	Function(s)
Bis-Stearoxydimethylsilane 29043-70-7	Bis-Stearoxydimethylsilane is the silicon compound that conforms to the formula. [Bis-Stearoxydimethylsilane is an organo-silicon compound, Si-substituted with 2 octadecoxyl groups and 2 methyl groups.] 	Skin-conditioning agent - miscellaneous
Stearoxytrimethylsilane 18748-98-6	Stearoxytrimethylsilane is the organo-silicon compound that conforms to the formula. [Stearoxytrimethylsilane is an organo-silicon compound, Si-substituted with 1 octadecoxyl group and 3 methyl groups.] 	Skin-conditioning agent - emollient
Triethoxycaprylylsilane 2943-75-1	Triethoxycaprylylsilane is the siloxane ether that conforms to the formula. [Triethoxycaprylylsilane is an organo-silicon compound, Si-substituted with 3 ethoxyl groups and 1 octyl group.] 	Binder
Trimethoxycaprylylsilane 3069-40-7	Trimethoxycaprylylsilane is the siloxane ether that conforms to the formula. [Trimethoxycaprylylsilane is an organo-silicon compound, Si-substituted with 3 methoxyl groups and 1 octyl group.] 	Binder; surface modifier

Table 2. Chemical and physical properties of alkoxyl alkyl silane ingredients.

Property	Value	Reference
Bis-Stearoxydimethylsilane		
Physical Form	Solid	[24]
Color	White	[24]
Odor	Odorless	[24]
Molecular Weight g/mol	597.13	[29]
Density/Specific Gravity @ 50°C	0.84	[24]
Melting Point °C	35	[24]
Stearoxytrimethylsilane		
Molecular Weight g/mol	342.68[a]	
Density/Specific Gravity	0.8±0.1 est.[b]	[30]
Vapor pressure mmHg@ 25 °C	0.0±0.9 est[b]	[30]
Boiling Point °C	387.1±10.0 est[b]	[30]
logP	10.65 est[b]	[30]
Triethoxycaprylylsilane		
Physical Form	Liquid	[5]
Color	Clear/colorless	[5]
Molecular Weight g/mol	276.49[a]	
Density/Specific Gravity g/cm^3 @ 23°C	0.876	[5]
Vapor pressure mmHg@ 25°C	0.1±0.4 est[c]	[31]
Melting Point °C	-46	[5]
	-40	[31]
Boiling Point °C	257	[5]
	265	[31]
Water Solubility g/L @ 22.8°C	<0.13	[5]
log K_{ow} @ 23°C	~3.7[b]	[5]
logP	5.45 est[c]	[31]
Trimethoxycaprylylsilane		
Physical Form	Liquid	[4]
Color	Clear/colorless	[4]
Molecular Weight g/mol	231.1	[32]
Density @ 20°C	0.91	[4]
Viscosity kg/(s m)@ °C	0.10	[4]
Vapor pressure mmHg@ 20°C	157.5	[4]
Boiling Point °C	227	[4]
	246	[4]
Water Solubility g/L @ 20°C	0.0133	[4]
log P_{ow}	3.9±0.2	[4]

[a] Estimated from molecular formula

[b] The water solubility and log K_{ow} values may not be accurate because the chemical is hydrolytically unstable.

[c] Estimated by ACD/Labs Percepta Platform - PhysChem Module

est.=estimated

Table 3. Frequency of use according to duration and exposure of alkoxyl alkyl silanes.[9,10]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Triethoxycaprylylsilane		Bis-Stearoxydimethylsilane		Stearoxytrimethylsilane		Trimethoxycaprylylsilane	
Total/range	**417**	**0.000001-2.6**	**NR**	**0.38**	**10**	**0.1-0.55**	**4**	**0.1-0.77**
Duration of use								
Leave-on	413	0.000001-2.6	NR	0.38	10	0.1-0.55	4	0.1-0.77
Rinse-off	4	0.0005-0.087	NR	NR	NR	0.55	NR	NR
Diluted for (bath) use	NR	0.001-0.048	NR	NR	NR	NR	NR	NR
Exposure type[a]								
Eye area	120	0.005-2.5	NR	NR	1	0.36	1	0.1-0.14
Incidental ingestion	15	0.0024-1	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	9; 36[b]; 14[c]	0.011-0.021; 0.004-0.8[b]	NR	NR	7[b]; 1[c]	NR	1[b]	NR
Incidental inhalation-powders	40; 14[c]	0.006-2; 0.000001-2.4[d]	NR	NR	1[c]	0.55[d]	NR	0.6[d]
Dermal contact	386	0.000001-2.6	NR	0.38	10	0.1-0.55	4	0.1-0.77
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	4	0.8	NR	NR	NR	0.55	NR	NR
Hair-coloring	5	NR	NR	NR	NR	NR	NR	NR
Nail	2	0.18-0.15	NR	NR	NR	NR	NR	NR
Mucous Membrane	19	0.001-1	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

NR=Not Reported; Totals=Rinse-off + Leave-on + Diluted for Bath Product Uses.

[a] Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[b] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[c] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[d] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 4. *In vitro* genotoxicity studies of alkoxyl alkyl silanes.

Ingredient; Concentration	Assay	Results	Reference
Bis-Stearoxydimethylsilane (approximately 75%) with stearyl alcohol and dimethicone; 33.3-5000.0 µg/plate	Ames assay, OECD TG 471; *S. typhimurium* (TA98, TA100, TA1535, and TA1537) with and without metabolic activation. No controls were specified. The experiment was conducted twice.	Negative. No toxic effects were observed.	8,24,27
Triethoxycaprylylsilane; up to 10,000 µg/plate	Ames assay, OECD TG 471; *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2 uvrA) with and without metabolic activation. No controls were specified. The experiment was conducted twice.	Negative. Cytotoxic concentration in both studies was >5000 µg/plate.	5
Triethoxycaprylylsilane (16-50 µg/mL with metabolic activation, 6.4-35.4 µg/mL without metabolic activation)	Chromosome aberration assay (similar to OECD TG 473). The cells were exposed for 6, 24 and 48 h in the absence of metabolic activation and for 6 h in the presence of metabolic activation.	There were no increases in structural or numerical chromosome aberrations. Cytotoxic to CHO cells with metabolic activation at 50 µg/mL and without metabolic activation 20 µg/mL and higher. The controls had the expected results.	5
Triethoxycaprylylsilane ; 0.016-157 µg/mL in ethanol	Chromosome aberration assay, OECD TG 473, using CHO cells.	Negative with and without metabolic activation. The controls had the expected results.	4
Trimethoxycaprylylsilane; up to 10 mg/plate	Bacterial reverse mutation assay, OECD TG 471; with *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2 uvrA)	Negative with and without metabolic activation. Not cytotoxic. The controls had the expected results.	4
Trimethoxycaprylylsilane; up to10 mg/plate	Bacterial reverse mutation assay, OECD TG 471; with *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2 uvrA)	Negative with and without metabolic activation. Not cytotoxic. The controls had the expected results.	4
Trimethoxycaprylylsilane; 33.3-5000 µg/plate	Ames test; *S. typhimurium* (strains TA98, TA100, TA1535, and TA1537)	Negative with and without metabolic activation. Not cytotoxic. The controls had the expected results.	4

CHO=Chinese hamster ovary

OECD TG=Organisation for Economic Co-operation and Development Test Guideline

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