Safety Assessment of Linear Phenyl-Substituted Methicones as Used in Cosmetics

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ABBREVIATIONS

AICIS	Australian Industrial Chemicals Introduction Scheme
CAS	Chemical Abstracts Service
CII	cumulative irritation index
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
cSt	centistokes
DNCB	2,4-dinitrochlorobenzene
DPM	disintegrations per minute
ECHA	European Chemicals Agency
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
GHS	Globally Harmonized System
HRIPT	human repeat insult patch test
INC	Ingredient Nomenclature Committee
LC	lethal concentration
LD	lethal dose
LLNA	local lymph node assay
MED	minimal erythema dose
MII	mean irritation index
MMTS	maximum mean total score
MW	molecular weight
NOAEL	no-observed-adverse-effect-level
N/A	not applicable
NR	not reported/none reported
NS	not specified
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
PII	primary irritation index
SEHSC	Silicones, Environmental, Health, and Safety Center
SI	stimulation index
SIOPT	single insult occlusive patch test
SLS	sodium lauryl sulfate
SPF	sun protection factor
TG	test guideline
US	United States
UV	ultraviolet
UVA/UVB	ultraviolet radiation A (long-wavelength)/ ultraviolet radiation B (mid-wavelength)
VCRP	Voluntary Cosmetic Registration Program
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 7 linear phenyl-substituted methicones as used in cosmetic formulations; Phenyl Trimethicone has been previously reviewed by the Panel. These ingredients are reported to function in cosmetics mostly as anti-foaming agents and skin and/or hair conditioning agents. The Panel reviewed the relevant data to determine the safety of these ingredients and concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

INTRODUCTION

This assessment reviews the safety of the following 7 linear phenyl-substituted methicones as used in cosmetic formulations:

Diphenyl Dimethicone
Diphenylsiloxy Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone
Phenyl Dimethicone
Phenyl Methicone
Phenyl Trimethicone
Trimethylsiloxyphenyl Dimethicone

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of the ingredients included in this assessment are reported to function in cosmetics as anti-foaming agents and skin and/or hair conditioning agents (Table 1).[1]

The rationale for this grouping of ingredients stems from the fact that these ingredients are structurally-related as linear phenyl-substituted methicones (i.e. polymers of methicone and dimethicone). In 2022, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a final amended report on 30 dimethicone, methicone, and methicone-substituted polymers, with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled when applied using airbrush devices.[2]

In 1986, the Panel published a final report on the safety of Phenyl Trimethicone, with the conclusion that Phenyl Trimethicone is safe as a cosmetic ingredient in the practices of use and concentration described in the safety assessment.[3] The Panel reaffirmed this conclusion, as published in 2006.[4] Excerpts of data from the original 1986 safety assessment of Phenyl Trimethicone are included throughout the text of this document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or Summary section.) For complete and detailed information, the original report can be accessed on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; the search was last conducted July 2023. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA)[5,6] and Australian Industrial Chemicals Introduction Scheme (AICIS)[7] websites. Please note that these sources provide summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when these sources are cited.

CHEMISTRY

Definition and Structure

The definitions and structures of the linear phenyl-substituted methicones included in this review are provided in Table 1. The ingredients in this group are all linear phenyl-substituted methicones (siloxane polymers). Generically, ingredients are organic derivatives of silica, SiO_2, with organic groups replacing some of the oxygens in the polymeric silica molecule.[3] These polymers comprise an alternating framework of silicon with other molecules. The interspersed molecules are covalently bonded to the silicon through a carbon-silicon linkage. For example, Diphenylsiloxy Phenyl Trimethicone (CAS No. 352230-22-9) is a linear siloxane polymer that conforms to the idealized structure depicted in Figure 1.

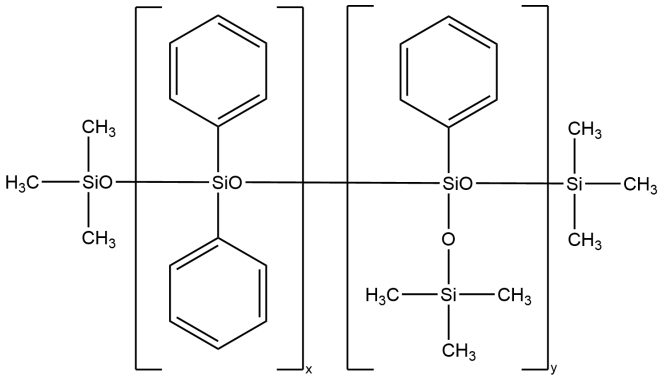


Figure 1. Diphenylsiloxy Phenyl Trimethicone (x and y are undefined)

It should be noted that the Panel was informed that the CAS No. 70131-69-0 was previously incorrectly assigned to polyphenylsilsesquioxane *and* Phenyl Trimethicone in the CAS and in the *Dictionary*, potentially leading to continued misidentification. The Ingredient Nomenclature Committee (INC) has since removed this CAS No. from the *Dictionary* monograph on Phenyl Trimethicone.[8] Accordingly, data related to polyphenylsilsesquioxane, a non-linear, caged structure, is not being considered in this report. Please note that the use of this CAS No. for both polyphenylsilsesquioxane and Phenyl Trimethicone is still erroneously promulgated in the CAS file and elsewhere.

Chemical Properties

Phenyl Trimethicone is a water white, almost odorless, fluid silicone polymer.[3] Physicochemical properties of Phenyl Trimethicone include a boiling point of 265 °C (at 760 mm Hg), specific gravity of 0.970 (at 25 °C), kinematic viscosity between 5 and 30 centistokes [cSt], a refractive index of 1.459, and a total acid number of 0.25 (maximum). The ultraviolet spectrum for Phenyl Trimethicone indicates weak absorbance centered at approximately 327 nm.

According to one supplier, a sample of Diphenyl Dimethicone had a number average molecular weight (MW) of 1711 g/mol, a weight average MW of 3105 g/mol, and a polydisperity index of 1.816.[9] Another supplier described the number average MW of Diphenyl Dimethicone to be > 1000 g/mol and the number average MW of Diphenylsiloxy Phenyl Trimethicone to be 500 - 1000 g/mol.[10] A sample of Phenyl Trimethicone was described by a supplier as having a number average MW of 725 g/mol, a weight average MW of 920 g/mol, and a polydisperity index of 1.27.[11] Another sample of Phenyl Trimethicone was deemed to contain greater than 70% material < 1000 g/mol when measured by conventional gel permeation chromatography against polystyrene standards.[12] A sample of Trimethylsiloxyphenyl Dimethicone was described as having a number average MW of 3279 g/mol and a weight average MW of 20,569 g/mol.[13] Additionally, 97.5% of this sample was deemed to comprise a MW > 1000 g/mol, while 0.05% was deemed to comprise a MW ≤ 500 g/mol.

Method of Manufacture

In one industrial process, silica is first converted to tetraethoxysilane, and the ethoxy groups are replaced with the desired chemical group by the Grignard reaction. The resulting organosilanes are hydrolyzable to organo-substituted silicic acids, called "silanols," which rapidly condense with each other to produce the silicon-oxygen-silicon framework of the silicone polymers. In these silicone structures, the organic radicals are firmly bonded to the silicon through a carbon-silicon linkage. Each silicon atom is linked to neighboring silicon atoms through an oxygen atom.

Diphenyl Dimethicone

A supplier described the manufacture of Diphenyl Dimethicone as a five-step process, involving hydrolysis, polymerization, neutralization, distillation, and filtration.[9] The hydrolysis reaction produces diphenyl dimethyl silicone hydrolysate, which along with dimethylcyclosiloxane and methyl-ended siloxane, is added to the reactor and mixed with a base catalyst for synthesis. Upon neutralization, the reaction is terminated, and the unreacted polymer is removed via distillation, prior to filtration and packaging. The general manufacturing process of Diphenyl Dimethicone is described by another supplier as the hydrolysis of a mixture of dichlorodiphenylsilane, dichlorodimethylsilane, and chlorotrimethylsilane, followed by catalyst polymerization.[14]

Diphenylsiloxy Phenyl Trimethicone

The general manufacturing process of Diphenylsiloxy Phenyl Trimethicone is described by a supplier as the hydrolysis of a mixture of trichlorophenylsilane, dichlorodiphenylsilane, and chloromethylsilane followed by catalyst polymerization.[15]

Phenyl Trimethicone

A supplier described the manufacture of Phenyl Trimethicone as a three-step process, involving hydrolysis, distillation, and filtration.[11] The hydrolysis reaction produces phenyl trimethicone hydrolysate, which is then distilled to remove low

molecular weight impurities and filtered prior to packaging. In another method of manufacture provided by a supplier, silanes first undergo hydrolysis to produce Phenyl Trimethicone.[12] The resulting hydrolysis product is then stripped, filtered, and tested for quality prior to packaging.

Impurities

Diphenyl Dimethicone; Diphenylsiloxy Phenyl Trimethicone

According to a supplier, a sample of Diphenyl Dimethicone and a sample of Diphenylsiloxy Phenyl Trimethicone each contained < 0.1% of cyclotetrasiloxane, < 0.1% cyclopentasiloxane, and < 0.1% cyclohexasiloxane.[10]

Phenyl Trimethicone

A sample of Phenyl Trimethicone was described by a supplier as comprising ≤ 50 ppm methanol and ≤ 1 ppm benzene.[12]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP survey data, Phenyl Trimethicone has the greatest reported frequency of use; it is reported to be used in 705 formulations, 659 of which are leave-on products (Table 2).[16] Results from a concentration of use survey conducted by the Council in 2021 (and reported in 2022) indicate that Phenyl Trimethicone has the highest reported maximum concentration of use, at 59.5% in non-coloring shampoos; it also has the highest reported maximum concentration of use in leave-on formulations, at up to 24.8% (in other makeup preparations).[17] Both frequency and maximum reported concentration of use have increased since Phenyl Trimethicone was last considered.[4] As noted in the chemistry section of this report, CAS No. 70131-69-0 was erroneously associated with both polyphenylsilsesquioxane and Phenyl Trimethicone in the *Dictionary* (now corrected to be only associated with polyphenylsilsesquioxane therein). Therefore, the frequency and concentrations of use reported for Phenyl Trimethicone in this assessment may be inflated due to the possible erroneous inclusion of reporting of polyphenylsilsesquioxane under Phenyl Trimethicone.

Diphenylsiloxy Phenyl Trimethicone is reported to be used in 275 formulations, and Diphenyl Dimethicone is reported to be used in 150 formulations (Table 3).[16] All other ingredients are used in less than 37 formulations. Use concentration data were reported for Diphenylsiloxy Phenyl/Propyl Trimethicone in makeup bases at 5.3%, but no uses were received in the VCRP; however, it should be presumed there is at least one use in this category.[18]

Several of the ingredients are reported to be used in products applied near the eye (e.g., Diphenylsiloxy Phenyl Trimethicone is used at up to 19.9% in eyeliners), and in products that can result in incidental ingestion (e.g., Diphenyl Dimethicone is used at up to 24.1% in lipsticks). Phenyl Trimethicone is reported to be used in baby products at up to 6.5%. Additionally, some of these ingredients are used in formulations that could possibly be inhaled; for example, according to the Council survey, Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol hair sprays, at up to 15.6% in face powders, and at up to 2.2% in aerosol deodorants.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The linear phenyl-substituted methicone ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[19]

Non-Cosmetic

Phenyl Methicone and Phenyl Trimethicone are both approved as indirect food additives and are used as adhesives in the components of articles intended for use in the packaging, transporting, or holding of food [21CFR § 175.105]. Additionally, Phenyl Trimethicone is an approved indirect food additive used as a polymeric coating for food-contact surfaces of articles

intended for use in food processing, manufacture, and packaging [21CFR § 175.300]; furthermore, Phenyl Trimethicone is required to contain no more than 2%, by weight, of cyclosiloxanes, having up to and including 4 siloxy units, for this use.

TOXICOKINETIC STUDIES

Dermal Absorption

The dermal absorption of Phenyl Trimethicone was evaluated in 5 male subjects.[3] During a 25-d pretest period, baseline analysis of 24-h silicon urine levels was conducted. Phenyl Trimethicone (50 mg/kg) was applied once daily over the entire back surface of the 5 subjects for 10 d; the test material remained on the skin for 20 h, before the excess was removed by washing. Blood and urine silicon concentrations obtained on day 1, 3, 6, 8, and 10 of treatment did not show any significant increases in blood or urinary silicon concentrations.

Diphenylsiloxy Phenyl Trimethicone

Based on its physicochemical properties, Diphenylsiloxy Phenyl Trimethicone has an estimated dermal absorption value of 10%.[7] (However, this is possibly for the monomer (< 1000 g/mol).)

Absorption, Distribution, Metabolism, and Excretion (ADME)

Phenyl Trimethicone

Seven rats were fed Phenyl Trimethicone (4% in the diet; between 944 - 1071 mg), with olive oil and rat cake powder (16% and 80% of the diet, respectively) for 8 d.[20] Tissues, feces, and urine were examined for silicon presence. No silicon was found in the lipids of the gastrointestinal tract, feces, liver, kidney, or fat depots of control animals which were only fed rat cake powder and olive oil. For animals treated with Phenyl Trimethicone, almost all of the siloxane was recovered as silicon in the feces or gastrointestinal tract, indicating no siloxane absorption (mean % siloxane fluid recovery of 96.0 ± 1.0).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

An acute, 24-h, dermal application of Phenyl Trimethicone was considered non-toxic to 10 albino rats when administered at 2000 mg/kg via an occlusive sleeve.[3] In 3 separate experiments, no deaths occurred in groups of 10 male albino mice which received a single oral dose of 10 ml/kg of a cosmetic product, containing 10% Phenyl Trimethicone. Single doses of Phenyl Trimethicone, ranging from 10,200 - 34,600 mg/kg were orally administered to groups of 8 male and 8 female Sprague-Dawley rats, and the animals were observed for 14 d before necropsy. One rat in the 34,600 mg/kg group died; others at the highest dose exhibited hypoactivity, muscular weakness, diarrhea, diuresis, ruffled fur, and weight loss. No significant gross lesions were found in the tissues and organs; the test material was deemed non-toxic. No mortality, body weight changes, behavioral changes, or gross pathological changes occurred in 540 male rats administered an oral dose of 3.3 mg/kg Phenyl Trimethicone for 7 d. An acute, oral, 5 ml/kg dose of a product containing 5% Phenyl Trimethicone resulted in leg weakness, transient vasodilation of the ears, and hypoactivity in 5 male and 5 female Sprague-Dawley rats; these effects resolved within 6 h post-treatment and no deaths occurred.

The acute dermal, oral, and inhalation toxicity studies summarized below are described in Table 4.

The acute dermal LD_{50} of Diphenylsiloxy Phenyl Trimethicone, when applied under semi-occlusion to male and female Wistar rats, was determined to be > 2000 mg/kg.[6,7] In an acute dermal toxicity study, the LD_{50} value was determined to be > 2000 mg/kg bw when Trimethylsiloxyphenyl Dimethicone was applied for 24 h under occlusive conditions to male and female Sprague Dawley rats.[21]

The acute oral LD_{50} of Diphenyl Dimethicone, administered via a stomach tube at doses of 8190; 16,380; 32,770; or 65,540 mg/kg in rats, was determined to be > 65,540 mg/kg bw.[22] One rat from each of the 3 highest dose groups died 3 or more days after dosing, each exhibiting diffuse pulmonary and hepatic hemorrhage; no other gross abnormalities were found upon necropsy. A single dose of 5000 mg/kg bw Diphenyl Dimethicone was administered to male and female albino rats in an acute oral toxicity study; the LD_{50} was determined to be > 5000 mg/kg.[23] In other acute oral toxicity studies, the LD_{50} value for Diphenylsiloxy Phenyl Trimethicone was > 2000 mg/kg in female Wistar Han rats,[6,7] and the LD_{50} values for Phenyl Trimethicone were ≥ 2000 mg/kg in female Wistar rats and > 5000 mg/kg in male and female rats.[5] The acute oral LD_{50} value for a test material comprising 78 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11 was determined to be > 5000 mg/kg in male and female Wistar-derived albino rats.[24] An LD_{50} of > 2000 mg/kg bw was determined in an acute oral toxicity study evaluating Trimethylsiloxyphenyl Dimethicone, administered via gavage, in corn oil, to CD rats.[13]

In an acute inhalation toxicity study of Diphenyl Dimethicone, groups of 5 male and 5 female albino rats were exposed to the undiluted, vaporized test article (whole body) at concentrations of 5, 10, 23, 24, 42, 90, 101, 168, or 214 mg/l for 1 h.[22] One animal from the 42 mg/l and one from the 101 mg/l group died during the exposure period. All dosage groups, except the 5 mg/l group, had animals that died within 24 h of dosing. Severe and diffuse pulmonary hemorrhages accounted for most of the deaths and pulmonary consolidation was found in surviving animals. The LC_{50} was determined to be 18 mg/l.

Short-Term and Subchronic Toxicity Studies

Dermal

No adverse effects were observed in 4 rabbits which received daily dermal applications of 50 ml/kg Phenyl Trimethicone for 20 d.[3] Groups of 10 New Zealand albino rabbits were dermally treated with 2, 6, or 20 mg/kg Phenyl Trimethicone, in polypropylene glycol (control), for 20 d. Local skin reactions were characterized by slight desquamation at the application site of both test and control animals. No toxic effects were noted in body weight, hematological values, blood chemistry, urine analysis, and gross or microscopic pathological findings of the test or control groups. Ten male New Zealand rabbits were dosed for 28 d with 200 mg/kg Phenyl Trimethicone to evaluate dermal toxicity. No significant adverse effects were noted with reference to body weight, mortality, behavioral reactions, testicular histology, and spermatogenic activity. The dermal toxicity of a skin moisturizer containing 2.5% Phenyl Trimethicone was evaluated for 90 d in groups of 10 New Zealand white rabbits.[3] Two treatment groups were administered 5.5 or 8.4 mg/cm^2 per 8.4% body surface area of the test article, and compared to a control group. Erythema, slight edema, and slight desquamation were observed in both groups throughout the experiment. These effects appeared slightly more severe at the 8.4 mg/cm^2 dose during the first month of exposure; no differences between dose groups were observed by the second month. Signs of dermal irritation were nearly maximal in the first week and increased gradually in severity during the last month of exposure. No treatment-related effects in hematology, clinical chemistry, organ weights, or histopathology were observed.

Oral

Details of the short-term and subchronic toxicity studies summarized below are provided in Table 5.

Groups of 10 male and 10 female Sprague-Dawley rats were dosed with 0, 5, 20, or 80 mg/kg/d of a mixture containing 15% Diphenyl Dimethicone (in a vehicle solution of 10% polyethylene glycol 660 hydroxystearate, in purified water), via gavage, for 90 d.[25] No deaths related to treatment with the test article occurred and no changes were observed in body weight and food consumption. Higher absolute and relative liver weights in animals given 80 mg/kg were considered to be treatment-related and were correlated with slight hepatocellular hypertrophy seen in 8 males and 10 females in the 80 mg/kg group; both effects were considered toxicologically significant. Liver enlargement was noted in 3 males from the 80 mg/kg group, which was attributed to treatment with the test article. The no-observed-adverse-effect-level (NOAEL) for the test item containing 15% Diphenyl Dimethicone was determined to be 20 mg/kg/d. In a short-term oral toxicity study, performed in accordance to the Organisation for Economic Development (OECD) test guideline (TG) 407, groups of Wistar Han rats (5/sex) were given 0, 200, 600, or 1000 mg/kg bw Diphenylsiloxy Phenyl Trimethicone, in corn oil, via gavage, for 28 d.[6,7] A statistically significant reduction in body weight gain was observed in male rats (18 - 19%) in the 1000 mg/kg group and in female rats (48%) from the 600 and 1000 mg/kg groups. In the liver, hepatocellular hypertrophy was seen in all test animals, and changes in hepatic fatty tissue deposition were seen in males from the high dose group and all the test females. Compared to controls, relative liver weights increased in the low-, mid-, and high-dose groups for both males and females. Additionally, increased incidence of bile duct production was seen in males from the mid-dose group and in females from the low- and mid-dose groups. Treatment-related microscopic liver changes were observed in all test animals, and minimal hypertrophic changes in the follicular epithelium of the thyroid gland were observed in 2 males from the low-dose group, 1 male from the mid-dose group, and 4 males from the high-dose group. The NOAEL was determined to be > 1000 mg/kg. In a short-term oral toxicity study, CD rats (5/sex) were administered 0, 20, 150, or 1000 mg/kg/d Trimethylsiloxyphenyl Dimethicone in corn oil, via gavage, for 4 wk.[26] No deaths or significant changes related to the test material were observed; the NOAEL was determined to be 1000 mg/kg/d.

Inhalation

Five male and 5 female rats were exposed (whole body) to an aerosol containing 3% Phenyl Trimethicone, twice daily, 5 d/wk, for 4 wk.[3] A single exposure consisted of a 30-s burst, followed by a 15-min exposure to the test material within a 350 l inhalation chamber. The animals exposed to the Phenyl Trimethicone aerosol gained slightly less weight than the controls; no other toxic effects were observed.

One cat, 2 guinea pigs, 2 rabbits, and 4 rats were exposed, whole-body, to a mist of Phenyl Methicone at the rate of 67.4 mg/min (at a concentration of 0.52 mg/l) for 7 h/d for 10 d.[27] No deaths occurred and moderate degenerative changes in the livers of cats and guinea pigs were considered only circumstantially associated with siloxane exposure.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Dermal

Phenyl Trimethicone was tested in several dermal developmental and reproductive toxicity studies.[3] In one study using 3 groups of 26 rats and 3 groups of 15 rabbits, 50 or 500 mg/kg Phenyl Trimethicone was applied topically to 2 groups of each species on days 6 - 16 or 6 - 18 of gestation, respectively. Untreated animals served as controls. Rats were killed on day 20 and rabbits were killed on day 30. Fetuses were removed by cesarean section, and one half were examined microscopically, while the other half were examined for skeletal abnormalities. In the rats, the mean number of implantation sites and mean number of live fetuses derived from control and test group dams were comparable; however, 10 fetuses from the low-dose group and 3 fetuses from the high-dose group had incompletely developed sternebrae. A greater number of rat fetuses derived

from the test groups had bipartite sternebrae and lack of closure of the coronal suture, compared to controls. Of the rabbits tested, one dam died in the control group and two animals died from the low-dose group. The control rabbit group had a greater mean number of implantation sites than the test groups, although the mean number of live fetuses from all 3 groups was comparable. None of the fetuses delivered from dead dams in the control (8), low-dose (9), or high-dose (2) groups were abnormal, besides showing signs of immaturity. All live pups had fully developed sternebrae and normal ribs with no abnormalities in the soft tissues; the delayed ossification found in both test groups of rats was therefore considered a species variation. Two separate studies evaluated the teratogenicity of Phenyl Trimethicone, in groups of 10 or 15 rabbits; 200 mg/kg of the test material was applied on days 6 - 18 of gestation in both studies. Rabbits in the first study received either 200 mg/kg corn oil, Phenyl Trimethicone in corn oil, or were untreated. A slight but significant increase in the number of resorption sites and decreased viability of the Phenyl Trimethicone-treated fetuses was observed. Rabbits in the second study received either 200 mg/kg Phenyl Trimethicone (undiluted), sesame oil, or were untreated. No deaths, unusual reactions, or adverse effects on maternal body weight, or the viability and external/internal development of the fetuses was observed. Consequently, Phenyl Trimethicone was not considered teratogenic in either study.

Oral

Phenyl Trimethicone was assayed for effects upon uterine weights in groups of 6 immature female Wistar rats which were bilaterally ovariectomized 3 d prior to treatment.[3] On the fourth day, groups of 6 rats received 0.01, 0.1, 1, or 10 mg/kg Phenyl Trimethicone in sesame oil, via gavage; animals received a daily dose for 3 d and were necropsied after the final dose. Controls received the oil vehicle. No toxic effects or changes in uterine weights were observed in treated animals.

Details of the oral developmental and reproductive toxicity studies summarized below are provided in Table 6.

The effect of maternal (and paternal) consumption of Diphenylsiloxy Phenyl Trimethicone upon reproductive and developmental toxicity was evaluated in accordance with OECD TG 422.[6] Groups of Sprague-Dawley rats (10/sex/group) were administered 0, 100, 500, or 1000 mg/kg bw/d Diphenylsiloxy Phenyl Trimethicone, in corn oil, via gavage; both males and females were treated with the test substance 2 wk prior to, and during, mating. No statistically significant changes in body weight, food consumption, or organ weights were observed or treatment-related effects were apparent for reproductive endpoints in the parents (including testis weight, epididymis weight, mean gestation length, mean number of corpora lutea, mean number of implantation sites, mean mating and fertility indices) nor were there effects observed in the offspring for gross pathology, mean litter size, mean litter weight, or mean ration live births/litter size. Thus, under the conditions of this study, the NOAEL for reproductive (male and female) and developmental toxicity was determined to be ≥ 1000 mg/kg bw/d. Groups of 20 male Wistar rats were given Phenyl Trimethicone, in oil (oil identity not specified), via gavage, at doses of 0, 100, 300, or 1000 mg/kg bw, 5 d/wk, for 4 wk.[5] The main purpose of this study was to observe if testicle weight reduction occurred with repeated doses of the test article. No visible changes, body weight fluctuations, or deaths occurred during the course of the study, and no effects on testicle weight or histology were observed. The NOAEL for effects on body weight, testicle weight, and histology was determined to be > 1000 mg/kg.

GENOTOXICITY STUDIES

Phenyl Trimethicone was not mutagenic in an Ames test using Salmonella strains, both with and without metabolic activation.[3] (Test concentrations were not stated.)

Details of the genotoxicity studies summarized below are provided in Table 7.

Diphenylsiloxy Phenyl Trimethicone, dissolved in ethanol, was not genotoxic when tested at concentrations up to 5000 µg/plate in an Ames test performed, in accordance with OECD TG 471, using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2, with or without metabolic activation.[6,7] In a mammalian chromosomal aberration study performed in accordance with OECD TG 473, the genotoxic potential of Diphenylsiloxy Phenyl Trimethicone (in ethanol) was tested in the Chinese hamster lung (V79) cell line, with and without metabolic activation.[6,7] Cell lines were treated with 0.025 - 0.3 µl/ml of the test article for 4 h, 0.006 - 0.2 µl/ml for 18 h, or 0.013 - 0.1 µl/ml for 28 h, without metabolic activation; cells treated with metabolic activation were treated with either 0.003 - 0.2 µl/ml or 0.040 - 5 µl/ml of the test substance for 4 h. Cell numbers below 50% of the controls or poor metaphase quality were observed in cells treated with ≥ 0.15 µl/ml of the test substance in the absence of metabolic activation for 18 h. No statistically significant increase in the frequency of cells with chromosome aberrations was induced in either the absence or presence of metabolic activation. The test article was considered non-clastogenic to Chinese hamster lung cell lines. Trimethylsiloxyphenyl Dimethicone, dissolved in 10% Tween 80 solution, was not genotoxic in an Ames test when tested in *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 strains at up to 100 µl/plate, with and without metabolic activation.[28]

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

An undiluted, 24-h dose of 0.5 ml Phenyl Trimethicone was non-irritating to the skin of 6 albino rabbits.[3] A foundation cream containing 5% Phenyl Trimethicone was applied at 0.5 ml to 6 rabbits, for 14 d; slight erythema, slight edema, and desquamation were observed. The cream had a primary irritation index of 1.9 (max = 8) and was considered mildly irritating. Three separate products, each containing 10% Phenyl Trimethicone, were found to be slightly irritating to groups of 6 male New Zealand white rabbits when tested at 0.5 ml in single insult occlusive patch tests. Phenyl Trimethicone (tested at 5% in propylene glycol during induction, and at 10 and 20% in petrolatum during challenge) was not irritating or sensitizing to 10 female guinea pigs in a maximization test.[3]

In clinical testing, the cumulative irritation score of a moisturizer containing 2.5% Phenyl Trimethicone was found to be 13 (max = 630) in 9 subjects.[3] The product was classified as a mild material (essentially no experimental irritation). Undiluted Phenyl Trimethicone was not found to be irritating or sensitizing in a human repeated insult patch test (HRIPT) of 50 subjects.[3] In an HRIPT using groups of 8 subjects, the highest total irritancy score of 17 cosmetic products, each containing 10% Phenyl Trimethicone, was 5 (max = 256) and the highest individual score was 1 (max = 8); overall, the products were considered minimally irritating. No irritation or sensitization was observed in 2 separate modified Draize-Shelanski HRIPTs of a cosmetic foundation containing 5% Phenyl Trimethicone (189 subjects) and a moisturizer containing 2.5% Phenyl Trimethicone (239 subjects).

Details of the dermal irritation and sensitization studies summarized below are provided in Table 8.

Diphenyl Dimethicone (100% pure and applied neat) was not irritating when applied to New Zealand white rabbit skin (0.5 ml) in a primary dermal irritation test, under occlusive conditions.[29] In another primary skin irritation test, performed in accordance OECD TG 404, a semi-occlusive application of 0.5 ml 100 % pure Diphenylsiloxy Phenyl Trimethicone was not irritating when applied neat to the skin of 3 New Zealand white rabbits.[30] In a similar study, Diphenylsiloxy Phenyl Trimethicone was deemed slightly irritating (or non-irritating, in another description) to 1 male and 2 female New Zealand white rabbits; very slight to well-defined erythema was noted in all animals 1 h after patch removal and mean erythema/eschar scores were 0.33 for animal 1 and 2, and 0.67 for animal 3.[6,7] Very slight erythema persisted in all animals until the 24 h reading and in 1 animal at the 48-h reading; all effects were reversible within 72 h. A single occlusive application of a mixture comprising 72 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11 (0.5 ml) was not irritating to 6 New Zealand white rabbit skin in an acute skin irritation test.[31] A semi-occlusive application of Trimethylsiloxyphenyl Dimethicone was not irritating to New Zealand white rabbit skin (0.5 ml) in a primary skin irritation test, performed in accordance with OECD TG 404.[32] Several 24-h single insult occlusive patch tests (SIOPTs) were performed using: a lip color formulation containing 9.06% Diphenyl Dimethicone (20 subjects), an ampoule formulation containing 0.5 % Diphenylsiloxy Phenyl Trimethicone (20 subjects), an eye primer formulation containing 10% Phenyl Trimethicone (21 subjects), and a shine gloss formulation containing 5% Trimethylsiloxyphenyl Dimethicone (18 subjects); the test substances were deemed non-irritating.[33-36] A SPF cream containing 3.2363% Phenyl Trimethicone and a serum formulation containing 2% Trimethylsiloxyphenyl Dimethicone did not cause irritation in a 14-d cumulative irritation test of 25 subjects and in a 15-d cumulative irritation test of 28 subjects, respectively.[37,38]

The sensitization potential of a product containing 15% Diphenyl Dimethicone (tested at concentrations of 2.5, 5, 10, 25, or 50%, in acetone: olive oil (4:1 v/v)) was evaluated using groups of 4 female CBA mice in a local lymph node assay (LLNA).[39] Two of 4 of the animals in the 10% group died on day 3 and 1 of the animals in the 50% group died on day 6; these deaths were not attributed to the test article. No positive lymphoproliferative responses were noted at any of the concentrations and the test article was deemed non-sensitizing. Diphenyl Dimethicone (100%) was not sensitizing in a Buehler test using 6 male and 6 female Hartley albino guinea pigs.[29] Groups of 4 female mice were tested with Diphenylsiloxy Phenyl Trimethicone (tested at concentrations 25, 50, or 100% w/w in acetone: olive oil (4:1 v/v)) in two separate LLNAs.[6,7,30] All mice in the 100% group exhibited slight ear swelling on both ear lobes on day 2 and 3, and similar results were seen for all mice in the 50% group on day 3; these results persisted throughout the observation period; the test materials were not considered sensitizing. The sensitizing potential of Trimethylsiloxyphenyl Dimethicone was evaluated in a guinea pig maximization test, in accordance with OECD TG 406.[40] Groups of 10 Dunkin Hartley guinea pigs received intradermal injections of the test article as supplied, at 50% in isotonic solution, at 50% in Freund's complete adjuvant (FCA) combined with isotonic solution. Since a subsequent 48-h, occlusive application of the undiluted test article did not cause irritation, 0.5 ml of 10% sodium lauryl sulfate (SLS), in paraffin oil, was applied to the skin on day 8, followed by a 48-h, occlusive application of the test article, applied neat, on day 9. On day 22, a 24-h occlusive challenge application was made, and challenge sites were scored 24 and 48 h after patch removal; the test article was deemed to be non-sensitizing.

A modified Marzulli-Maibach human repeated insult patch test (HRIPT) of a formulation containing 2% Diphenyl Dimethicone was completed in 111 subjects; the test material was neither irritating nor sensitizing.[41] An ampoule containing 0.5% Diphenylsiloxy Phenyl Trimethicone and a lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone were not irritating or sensitizing in 2 separate occlusive HRIPTs performed in 112 and 109 subjects, respectively.[42,43] A formulation containing 0.2% Phenyl Methicone was neither irritating or sensitizing in a Marzulli-Maibach HRIPT performed in 107 subjects.[44] A product containing 20% Phenyl Trimethicone was neither irritating or sensitizing in an occlusive HRIPT performed in 53 subjects.[45] A concealer formulation containing 26.18% Phenyl Trimethicone was not sensitizing to 26

subjects in a maximization assay.[46] Similarly, a semi-occlusive HRIPT of a product containing 28.67% Phenyl Trimethicone was performed in 203 subjects; the test material was not sensitizing.[47] HRIPTs performed using a cream formulation containing 3% Trimethylsiloxyphenyl Dimethicone (103 subjects), a product containing 38% Trimethylsiloxyphenyl Dimethicone (205 subjects), and 100% pure Trimethylsiloxyphenyl Dimethicone (51 subjects) yielded negative results.[48-50]

Photosensitization/Photoallergy

Phenyl Trimethicone

The photosensitization potential of a lotion containing 7.5% Phenyl Trimethicone, and 2 other products, was assessed in a photocontact allergenicity assay of 27 subjects.[51] During the pre-testing phase, the minimal erythema dose (MED) of each subject was determined by exposing one side of the midback to a series of radiation exposures from a xenon arc solar simulator (290 - 400 nm; long-wave ultraviolet light (UVA) = 75 mW/cm^2). During the induction phase the following procedure was performed twice a wk, over 3 wk (total of 6 exposures): 24-h occlusive patch applications of 40 mg of the test materials were wiped dry, exposed to 2 MED doses, left open for 48 h, and exposed to a subsequent 24-h occlusive application, made to the same test site. After a 10 - 14 d rest period, during the challenge phase, the test materials were applied as done during the induction phase, in duplicate, to previously untreated sites; one set of patches were wiped dry and irradiated with 0.5 MED of solar simulated radiation plus 4 J/cm^2 of UVA. The second set of patches were not radiated and served as control treated sites. All test sites were examined for reactions at 48 and 72 h following UV exposure. No reactions were observed at either timepoint. The test material was not considered to be a potential photosensitizer.

Trimethylsiloxyphenyl Dimethicone

The photo-allergic potential of a serum containing 2% Trimethylsiloxyphenyl Dimethicone was assessed in a similar manner to the study described above in 26 subjects (minor differences: 40 µl patch applications, UVA/mid-wavelength ultraviolet light (UVB) during induction, one additional blank control was irradiated during challenge).[52] No reactions were observed, and the repeated dermal application of the test material was not contraindicated with sunlight exposure.

OCULAR IRRITATION STUDIES

Phenyl Trimethicone, tested undiluted (in 6 rabbits) and at 10% in 3 cosmetic products (in groups of 6 rabbits), was not considered irritating to rabbit eyes in several Draize tests.[3] Slight conjunctivitis occurred from instilling 0.10 ml of a foundation cream, containing 5% Phenyl Trimethicone in 6 albino rabbit eyes; no evidence of corneal dullness or iritis was observed.

Details of the ocular irritation studies summarized below are provided in Table 9.

Groups of 3 albino rabbits had Diphenyl Dimethicone instilled, undiluted (0.1 ml) into one eye.[22] In the first group, eyes remained unwashed, while eyes were washed after 2 s or 4 s after exposure in a second and third group; eyes were observed for irritation for up to 7 d. A maximum score of 8 (out of 110), which indicated slight irritation was observed within 4 h for 1 animal in the second group. By day 3 all eyes appeared normal, regardless of rinsing status; the test article was considered slightly and transiently irritating to the eyes of rabbits. According to the Globally Harmonized System (GHS) classification, Diphenylsiloxy Phenyl Trimethicone was not irritating to 1 male and 2 female New Zealand white rabbit eyes in an acute, 72-h ocular irritation study, performed in accordance with OECD TG 405.[6,7] When evaluated using Kay and Calandra criteria (same test), the test article was deemed slightly irritating; mild ocular changes, including reddening of the conjunctivae and sclerae, discharge, and chemosis were observed 1 h after instillation, but resolved within 24 h. Directly instilled Phenyl Methicone (unspecified amount) was determined to be non-irritating to rabbit eyes (number and strain not specified) in a 48-h ocular irritation test; slight irritation observed 4 and 8 h after exposure subsequently subsided.[27] A mixture of 78 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11 produced a maximum mean total score (MMTS) of 0 when tested for ocular irritancy potential in 6 New Zealand white rabbits; the test article was deemed non-irritating.[53] In another acute ocular irritation study, Trimethylsiloxyphenyl Dimethicone was slightly irritating to male New Zealand white rabbit eyes, when instilled as supplied without rinsing.[54] Eyes were examined for up to 72 h after instillation. The mean values for opacity to the cornea, congestion to the iris, and chemosis and enanthema to the conjunctiva were 0, 0.5, 0.5, and 1.39, respectively.

EXPOSURE ASSESSMENT

In an Australian exposure assessment, total daily systemic exposure to Diphenylsiloxy Phenyl Trimethicone, from concurrent use of cosmetic products applied via various routes, was calculated using concentration of 30% in all cosmetic products, except in aerosol products (in which a maximum concentration of 3% was used).[7] Dermal exposure use patterns were assumed to be similar to those in Europe, and were calculated using 10% dermal absorption; exposure from aerosol products was calculated assuming an adult inhalation rate of 20 m^3/d, in a two-zone approach. Based on these daily systemic exposure calculations, assuming maximum aggregate exposures from simultaneous use of all possible cosmetic products, the combined internal dose of Diphenylsiloxy Phenyl Trimethicone was estimated to be 7.68 mg/kg bw/d.

SUMMARY

According to the *Dictionary*, the 7 linear phenyl-substituted methicone ingredients reviewed in this safety assessment are reported to function in cosmetics as antifoaming agents and skin and/or hair conditioning agents. This group of linear phenyl-substituted methicones are either siloxane polymers or compounds of silicone molecules attached to phenyl or propyl groups. Data from the 2023 VCRP and Council survey indicate that Phenyl Trimethicone has the highest reported use in 659 leave-on products, as well as the highest reported concentration of use, at up to 59.5% in non-coloring shampoos. Phenyl Trimethicone is also reported to be used in leave-on formulations at up to 24.8%.

Based on its physicochemical properties, Diphenylsiloxy Phenyl Trimethicone is estimated to have a dermal absorption value of 10%. Phenyl Trimethicone fed to rats at 4% in the diet for 8 d was mostly recovered as silicon (mean % recovery: 96 ± 1.0) in the feces or gastrointestinal tract, indicating no siloxane absorption.

In an acute dermal toxicity study, the LD_{50} of Diphenylsiloxy Phenyl Trimethicone, when applied under semi-occlusion to Wistar rats, was determined to be > 2000 mg/kg. The acute dermal LD_{50} value for Trimethylsiloxyphenyl Dimethicone was determined to be > 2000 mg/kg bw when applied to Sprague Dawley rat skin under occlusive conditions. The acute oral toxicity of Diphenyl Dimethicone was evaluated in rats administered a single oral dose of 8190; 16,380; 32,770; or 65,540 mg/kg Diphenyl Dimethicone, via gavage. One rat from each of the 3 highest dose groups died 3 or more days after dosing, each exhibited diffuse pulmonary and hepatic hemorrhage; the acute oral LD_{50} was determined to be > 65,500 mg/kg. In another acute oral toxicity study, male and female albino rats received a single dose of 5000 mg/kg bw Diphenyl Dimethicone; the LD_{50} value was determined to be > 5000 mg/kg. The oral LD_{50} value for Diphenylsiloxy Phenyl Trimethicone in female Wistar Han rats was determined to be > 2000 mg/kg. The acute oral LD_{50} values for Phenyl Trimethicone were determined to be > 2000 mg/kg in female Wistar rats and > 5000 mg/kg in male and female rats. The acute oral LD_{50} value for a test material comprising 78 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11 was determined to > 5000 mg/kg in male and female Wistar-derived albino rats. An LD_{50} of > 2000 mg/kg bw was determined in an acute oral toxicity study evaluating Trimethylsiloxyphenyl Dimethicone in CD rats.

In an acute inhalation study, albino rats were exposed (whole-body) to undiluted, vaporized Diphenyl Dimethicone at concentrations of 5, 10, 23, 24, 42, 90, 101, 168, or 214 mg/l for 1 h. Animals from every dosage group, except the 5 mg/l group, died within 24 h of exposure. Severe and diffuse pulmonary hemorrhages accounted for most of the deaths and pulmonary consolidation was found in surviving animals; the LC_{50} was determined to be 18 mg/l.

Groups of 10 male and 10 female Sprague Dawley rats were orally dosed with 0, 5, 20, or 80 mg/kg/d of a mixture containing 15% Diphenyl Dimethicone, via gavage, for 90 d. Higher absolute and relative liver weights, liver enlargement, and slight hepatocellular hypertrophy in animals from the 80 mg/kg group were considered to be treatment-related and toxicologically significant. The NOAEL for the test article was determined to be 20 mg/kg/d. No treatment related changes or deaths occurred during a short-term oral toxicity study in which Wistar Han rats were dosed with 0, 200, 600, or 1000 mg/kg Diphenylsiloxy Phenyl Trimethicone in corn oil, via gavage, for 28 d. Statistically significant reductions in the body weight gain of male rats (18 - 19%) in the 1000 mg/kg group and females (48%) in the 600 and 1000 mg/kg groups were observed, when compared to controls. Treatment-related microscopic liver changes were observed in all test animals, and minimal hypertrophic changes in the follicular epithelium of the thyroid gland were observed in 2 males from the low-dose group, 1 male from the mid-dose group, and 4 males from the high dose group. The NOAEL was determined to be > 1000 mg/kg. No deaths or significant changes related to the test material were observed in a short-term oral toxicity study in which CD rats received 0, 20, 150, or 1000 mg/kg/d Trimethylsiloxyphenyl Dimethicone, in corn oil, via gavage, for 4 wk. The NOAEL was determined to be 1000 mg/kg/d. In an inhalation study, no mortality occurred in 1 cat, 2 guinea pigs, 2 rabbits, and 4 rats exposed, whole body, to a mist of Phenyl Methicone (67.4 mg/min) contained in a chamber, at a concentration of 0.52 mg/l, for 7 h/d, over 10 d. In the absence of control data, moderate degenerative changes in the livers of the cats and guinea pigs were considered only circumstantially associated with siloxane exposure.

Groups of Sprague-Dawley rats (10/sex/group) received 0, 100, 500, or 1000 mg/kg bw/d Diphenylsiloxy Phenyl Trimethicone, in corn oil, via gavage 2 wk prior to mating, and until 4 d postpartum, in a reproductive and developmental toxicity study. No treatment-related effects on reproductive endpoints in the parents, including testis weight, epididymis weight, mean gestation length, mean number of corpora lutea, mean number of implantation sites, mean mating and fertility indices, nor changes in gross pathology, mean litter size, mean litter weight, or mean ratio live births/litter size of the pups were observed. The NOAEL for reproductive (male and female) and developmental toxicity was determined to by ≥ 1000 mg/kg bw/d. In a 4-wk study of the effects of Phenyl Trimethicone on testicular histology and weight, male Wistar rats were dosed with up to 1000 mg/kg Phenyl Trimethicone 5d/wk, via gavage. No visible changes, body weight fluctuations, deaths, or changes in testicle histology or weight were observed. The NOAEL for effects on body weight, testicle weight, and histology was determined to be > 1000 mg/kg.

In an Ames test, Diphenylsiloxy Phenyl Trimethicone was tested at concentrations up to 5000 µg/plate, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2. No increase in revertant colonies was observed in the presence or absence of metabolic activation. The genotoxic potential of Diphenylsiloxy Phenyl Trimethicone, tested at up to 5 µl/ml for 4, 18, or 28 h, with and without metabolic activation, was evaluated in a mammalian chromosomal aberration test,

using the Chinese hamster lung cell line. Cell numbers below 50% of the controls or poor metaphase quality were observed in cells treated in the absence of metabolic activation with ≥ 0.15 µl/ml of the test substance for 18 h. No statistically significant increase in the frequency of cells with chromosome aberrations was induced in either the absence or presence of metabolic activation. Trimethylsiloxyphenyl Dimethicone was not genotoxic when tested at up to 100 µl/plate with and without metabolic activation in an Ames test using *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538.

Diphenyl Dimethicone (100% pure and applied neat) was not irritating when applied occlusively to New Zealand white rabbit skin in a primary dermal irritation test. In another primary dermal irritation test, a semi-occlusive application of Diphenylsiloxy Phenyl Trimethicone was considered not irritating to New Zealand white rabbit skin. Diphenylsiloxy Phenyl Trimethicone was not irritating and slightly irritating or non-irritating, in 2 separate, 4-h, semi occlusive patch tests made to New Zealand white rabbit skin, when tested neat. In the second test, very slight erythema persisted in all animals until 24 h after patch removal, and in 1 animal at the 48-h reading; all effects were reversible within 72 h. Trimethylsiloxyphenyl Dimethicone and a mixture of 72 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11 were not irritating to New Zealand white rabbit skin in 2 separate acute dermal irritation tests. A lip color formulation containing 9.06% Diphenyl Dimethicone, an ampoule formulation containing 0.5% Diphenylsiloxy Phenyl Trimethicone, an eye primer formulation containing 10% Phenyl Trimethicone, and a shine gloss formulation containing 5% Trimethylsiloxyphenyl Dimethicone were deemed non-irritating in separate 24-hr single insult occlusive patch tests. A SPF cream formulation containing 3.2363% Phenyl Trimethicone and a serum formulation containing 2% Trimethylsiloxyphenyl Dimethicone were not irritating in a 14-d cumulative irritation test and 15-d cumulative irritation test, respectively.

A product containing 15% Diphenyl Dimethicone (tested at concentrations of 2.5, 5, 10, 25, or 50% in acetone:olive oil (4:1 v/v)) was not sensitizing in a LLNA in groups of 4 female CBA mice; 2 of the animals from the 10% group died on day 3 and 1 of the animals in the 50% group died on day 6, but these deaths were not attributed to the test article. Diphenyl Dimethicone (100%) was not sensitizing in a Buehler test using male and female Hartley albino guinea pigs. In two LLNAs using female mice, the topical application of 25, 50, or 100 % w/w Diphenylsiloxy Phenyl Trimethicone in acetone and olive oil (4:1 v/v) was not considered sensitizing. Trimethylsiloxyphenyl Dimethicone, tested at 50% in FCA during intradermal injection (both applied neat during challenge), was not irritating or sensitizing in a guinea pig maximization test. A formulation containing 2% Diphenyl Dimethicone was neither irritating nor sensitizing in a Marzulli-Maibach HRIPT completed in 111 subjects. Similarly, an ampoule formulation containing 0.5% Diphenylsiloxy Phenyl Trimethicone and a lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone were neither irritating or sensitizing in 2 separate occlusive HRIPTs performed in 112 and 109 subjects, respectively. A formulation containing 0.2% Phenyl Methicone was neither irritating or sensitizing in a Marzulli-Maibach HRIPT performed in 107 subjects. An occlusive HRIPT of a product containing 20% Phenyl Trimethicone (53 subjects), a maximization assay of a concealer formulation containing 26.18% Phenyl Trimethicone (26 subjects), a semi-occlusive HRIPT of a product containing 28.67% Phenyl Trimethicone (203 subjects), and 3 separate HRIPTs of a cream formulation containing 3% Trimethylsiloxyphenyl Dimethicone (103 subjects), a product containing 38% Trimethylsiloxyphenyl Dimethicone (205 subjects), and 100% pure Trimethylsiloxyphenyl Dimethicone (51 subjects) all yielded negative results.

A lotion containing 7.5% Phenyl Trimethicone was not considered to be a potential photosensitizer in a photocontact allergenicity assay of 27 subjects. The repeated dermal application of a serum containing 2% Trimethylsiloxyphenyl Dimethicone was not contraindicated with sunlight exposure in a test of photoallergic potential in 26 subjects.

The ocular irritation potential of Diphenyl Dimethicone was tested in albino rabbit eyes; the maximal irritation score (8 of out of 110) was observed within 4 h in 1 animal from the group with eyes washed after 2 s; any signs of irritation resolved by the second or third day. Under these conditions, the test article was considered slightly, and transiently irritating to rabbit eyes. In an acute ocular irritation study, rabbit eyes were treated with undiluted Diphenylsiloxy Phenyl Trimethicone for 72 h; the test article was deemed slightly irritating to rabbit eyes based on Kay and Calandra criteria, but was not deemed irritating according to the Globally Harmonized System of classification. Phenyl Methicone was slightly irritating at 4 and 8 h after being instilled in rabbit eyes; subsequently, the irritation subsided. A mixture of 78 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11 produced an MMTS of 0 when tested for acute irritancy in the eyes of New Zealand white rabbits; the test article was deemed a non-irritant. In another acute ocular irritation study, Trimethylsiloxyphenyl Dimethicone was deemed slightly irritating to male New Zealand white rabbit eyes; the mean values for opacity to the cornea, congestion to the iris, and chemosis and enanthema to the conjunctiva were 0, 0.5, 0.5, and 1.39, respectively.

Total daily systemic exposure to Diphenylsiloxy Phenyl Trimethicone was evaluated in an Australian exposure assessment. The simultaneous use of cosmetic products applied via varied routes of exposure was estimated to be 7.68 mg/kg bw/d, assuming 30% concentration in all cosmetic products, with the exception of aerosols (in which a maximum concentration of 3% was used).

DISCUSSION

This assessment reviews the safety of 7 linear phenyl-substituted methicones as used in cosmetic formulations. The Panel only considered toxicological safety data on these 7 linear phenyl-substituted methicones and concluded that these ingredients

are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

The Panel concluded that some data submitted under the name Phenyl Trimethicone were erroneously assigned to this ingredient (i.e., the test article was the unrelated chemical polysilsesquioxane) and are not applicable to this safety assessment. Furthermore, the Panel considered that it is possible that the reported frequency and maximum concentrations of use reported for Phenyl Trimethicone might be inflated due to the erroneous assignment of use data for polysilsesquioxane to Phenyl Trimethicone; however, the Panel emphasized that they do not expect that these potentially misreported use levels could exceed those of actual use levels. Accordingly, the determination of safety made by the Panel is limited to the linear phenyl-substituted methicones being assessed in this report, and, neither applies to polyphenylsilsesquioxane nor is it based thereon.

The Panel considered toxicological data for these linear phenyl-substituted methicones as mostly comprehensive, with multiple routes and durations of exposure, with the exception that the available inhalation toxicity data for these ingredients are inadequate, based upon the reported concentrations of use. Negative studies for genotoxicity and developmental and reproductive toxicity were considered robust. Furthermore, no evidence of dermal irritation or sensitization were found for these ingredients. Transient signs of irritation were observed in a 15-d cumulative irritation study, in which a serum containing 2% Trimethylsiloxyphenyl Dimethicone, was tested using 28 subjects. The Panel discussed that there was no further evidence of these ingredients causing irritation or sensitization, even when tested at higher concentrations. Thus, the Panel reasoned that these results may not be attributable to the ingredient alone and were possibly influenced by the formulation and product type as well.

The Panel also considered the available method of manufacturing and impurities data for some ingredients as inferable to the remaining ingredients in this group. Namely, the Panel considered data for Diphenyl Dimethicone and Phenyl Trimethicone as inferable to Phenyl Dimethicone and Phenyl Methicone, while data on Diphenylsiloxy Phenyl Trimethicone was considered suitable inference for Diphenylsiloxy Phenyl/Propyl Trimethicone and Trimethylsiloxyphenyl Dimethicone.

Furthermore, the Panel agreed that data on short-term intermittent-exposure inhalation toxicity and on the particle size distribution and concentrations of use for these ingredients in products which may be incidentally inhaled were inadequate. Consequently, the remaining data needs are:

- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in products that could be incidentally inhaled (i.e., Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation toxicity study described in the original report on Phenyl Trimethicone (i.e., a 4-wk study in which rats were exposed twice daily to a 30-s burst of an aerosol containing 3% Phenyl Trimethicone, followed by a 15-min chamber exposure).

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Therefore, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 7 linear phenyl-substituted methicone ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

Diphenyl Dimethicone
Diphenylsiloxy Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone
Phenyl Dimethicone
Phenyl Methicone
Phenyl Trimethicone
Trimethylsiloxyphenyl Dimethicone

TABLES

Table 1. Definitions, idealized structures, and reported functions[1, CIR Staff]

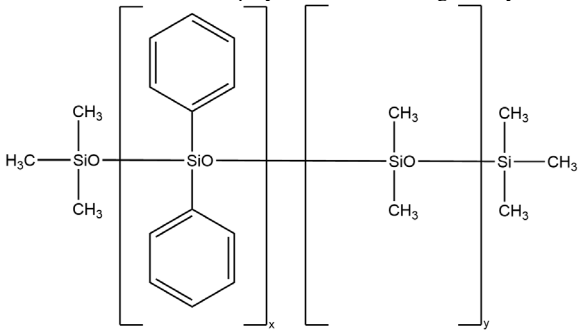
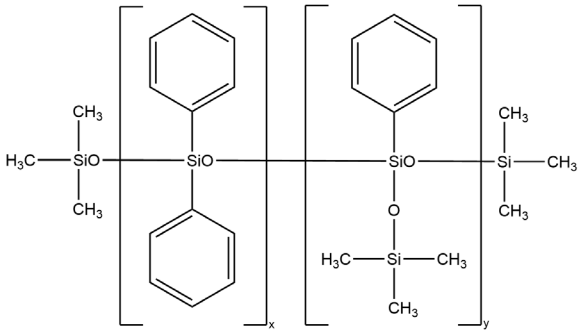
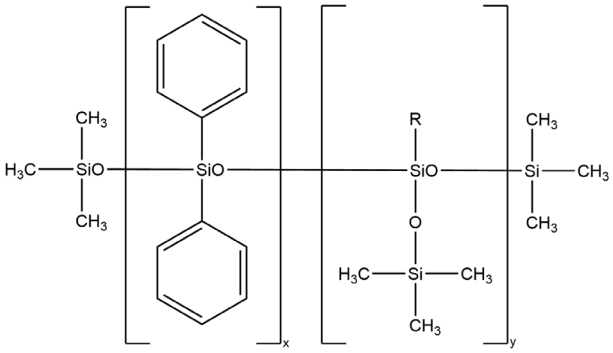
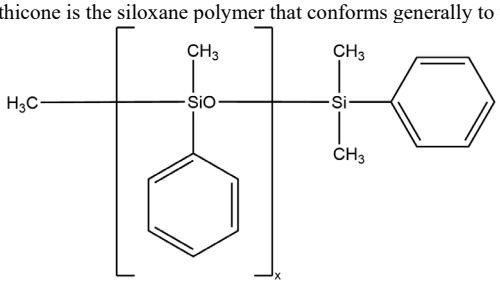
Ingredient/CAS No.	Definition	Function(s)
Diphenyl Dimethicone 68083-14-7	Diphenyl Dimethicone is a siloxane polymer that conforms generally to the structure: 	Antifoaming agents; Skin-conditioning agents - occlusive
Diphenylsiloxy Phenyl Trimethicone 352230-22-9	Diphenylsiloxy Phenyl Trimethicone is the silicone compound that conforms to the structure: 	Antifoaming agents; Hair conditioning agents; Skin-conditioning agents-miscellaneous
Diphenylsiloxy Phenyl/Propyl Trimethicone	Diphenylsiloxy Phenyl/Propyl Trimethicone is the silicone compound that conforms to the structure:  wherein R represents either a phenyl or propyl group.	Hair conditioning agents; Skin conditioning agents - emollient
Phenyl Dimethicone 9005-12-3	Phenyl Dimethicone is the siloxane polymer that conforms generally to the structure: 	Antifoaming agents; Skin-conditioning agents - occlusive

Table 1. Definitions, idealized structures, and reported functions[1, CIR Staff]

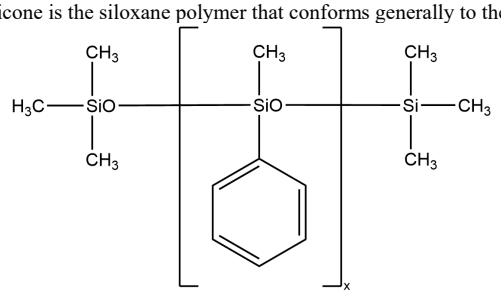
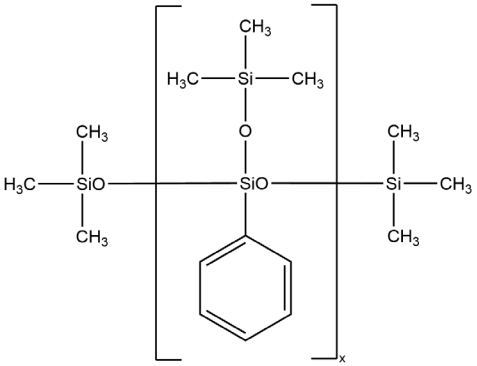
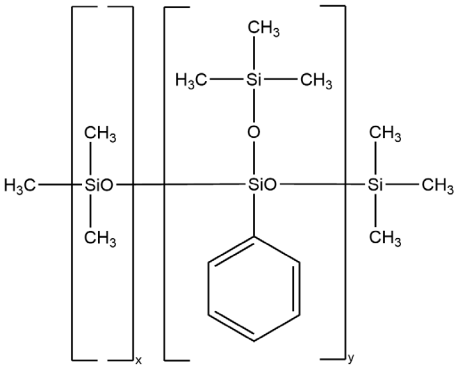
Ingredient/CAS No.	Definition	Function(s)
Phenyl Methicone 31230-04-3 63148-58-3	Phenyl Methicone is the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agents - emollient
Phenyl Trimethicone 195868-36-1 2116-84-9 73559-47-4	Phenyl Trimethicone is the siloxane polymer that conforms generally to the structure: 	Antifoaming agents; Hair conditioning agents; Skin-conditioning agents - occlusive
Trimethylsiloxyphenyl Dimethicone 73138-88-2	Trimethylsiloxyphenyl Dimethicone is the siloxane polymer that conforms generally to the structure: 	Hair conditioning agents

Table 2. Frequency (2023/2002) and concentration (2022/2004) of use according to duration and exposure for Phenyl Trimethicone

	# of Uses		*Max Conc of Use (%)*	
	2023[16]*	**2002[4]**	**2022[17]***	**2004[4]**
Totals**	**705**	**279**	**0.1 – 59.5**	**0.0075-36**
summarized by likely duration and exposure***				
Duration of Use				
Leave-On	659	*264*	*0.1 – 24.8*	*0.0075 - 36*
Rinse-Off	46	*14*	*0.75 – 59.5*	*0.3 - 4*
Diluted for (Bath) Use	NR	*1*	*NR*	*NR*
Exposure Type				
Eye Area	102	83	0.75 - 17	0.008 - 15
Incidental Ingestion	96	34	1 - 13.8	0.08 - 36
Incidental Inhalation-Spray	57; 121[a]; 55[b]	24; 56[a]; 7[b]	0.1 -7.5; 6[a]	0.1 – 18; 0.2 – 11[a]; 0.2 -18[b]
Incidental Inhalation-Powder	31; 55[b]; 3[c]	10; 7[b]	1.2 – 15.6; 1.7 – 13[c]	0.1 – 8; 0.2 - 18[b]
Dermal Contact	426	175	0.1 – 24.8	0.0075 - 22
Deodorant (underarm)	1[a]	1[a]	spray: 2.2; not spray: 1.8 – 10.2	NR
Hair - Non-Coloring	174	69	0.5 – 59.5	0.1 - 18
Hair-Coloring	9	NR	NR	NR
Nail	NR	NR	3	0.5
Mucous Membrane	97	36	1 – 13.8	0.08 - 36
Baby Products	3	NR	6.5	NR
as reported by product category				
Baby Products				
Baby Lotions/Oils/Powders/Creams	3	NR	NR	NR
Other Baby Products	NR	NR	6.5	NR
Bath Preparations (diluted for use)				
Bath Oils, Tablets, and Salts	NR	1	NR	NR
Eye Makeup Preparations				
Eyebrow Pencil	2	NR	8.8	NR
Eyeliner	10	1	3.4 - 16.5	2 - 6
Eye Shadow	70	77	2.4 - 17	4 - 13
Eye Lotion	1	NR	NR	0.008 - 1
Mascara	NR	1	NR	0.1 - 0.4
Other Eye Makeup Preparations	19	4	0.75	6 - 15
Fragrance Preparations				
Cologne and Toilet Water	NR	NR	NR	0.5
Perfumes	1	1	3	NR
Powders (dusting/talcum, excl aftershave talc)	NR	1	NR	NR
Other Fragrance Preparation	2	NR	0.5	0.5
Hair Preparations (non-coloring)				
Hair Conditioner	32	8	0.75 - 3	0.3 - 2
Hair Spray (aerosol fixatives)	48	23	0.5 - 7.5	0.1 - 18
Hair Straighteners	5	NR	NR	NR
Shampoos (non-coloring)	2	NR	59.5	1
Tonics, Dressings, and Other Hair Grooming Aids	57	31	0.51 - 9 (not spray); 2 (pump spray); 7 (aerosol)	5 - 11
Other Hair Preparations	30	7	3	0.5 - 2
Hair Coloring Preparations				
Hair Tints	4	NR	NR	NR
Hair Rinses (coloring)				
Hair Color Sprays (aerosol)	5	NR	NR	NR
Makeup Preparations				
Blushers (all types)	22	1	5.2	2 - 15
Face Powders	31	9	1.2 - 15.6	0.1 - 18
Foundations	67	17	7 - 12	2 - 22
Leg and Body Paints	NR	NR	NR	2
Lipstick	96	34	1 - 13.8	0.08 - 36
Makeup Bases	22	8	NR	NR
Rouges	4	2	2 - 4.8	NR
Makeup Fixatives	2	NR	NR	NR
Other Makeup Preparations	34	13	12.1 - 24.8	0.0075 - 22
Manicuring Preparations (Nail)				
Nail Creams and Lotions	NR	NR	NR	0.5
Nail Polish and Enamel	NR	NR	3	NR
Other Manicuring Preparations				
Personal Cleanliness Products				
Deodorants (underarm)	1	1	1.8 - 10.2 (not spray); 2.2 (aerosol)	NR
Feminine Deodorants	1	NR	NR	NR
Shaving Preparations				
Aftershave Lotion	NR	1	NR	0.5 - 2

Table 2. Frequency (2023/2002) and concentration (2022/2004) of use according to duration and exposure for Phenyl Trimethicone

	# of Uses		*Max Conc of Use (%)*	
	2023[16]*	**2002[4]**	**2022[17]***	**2004[4]**
Beard Softeners	1		NR	
Preshave Lotions (all types)	NR	1	2.5	2
Other Shaving Preparations	NR	NR	NR	0.5
Skin Care Preparations				
Cleansing	1	4	NR	2 - 4
Face and Neck (exc shave)	39	3	3.4 - 13 (not spray)	4 - 6
Body and Hand (exc shave)	15	4	1.7 (not spray)	0.2 - 18
Moisturizing	56	15	0.8 - 22.7 (not spray)	0.8-3
Night	2	NR	NR	2
Paste Masks (mud packs)	2	NR	NR	NR
Skin Fresheners	6	NR	NR	NR
Other Skin Care Preparations	11	NR	0.5 - 4.9	2
Suntan Preparations				
Suntan Gels, Creams, and Liquids	1	2	0.1 (aerosol); 0.5 (pump spray)	0.5 - 9
Indoor Tanning Preparations	NR	8	NR	0.2 - 5
Other Suntan Preparations	NR	NR	6	2

NR – not reported

*It is possible that the reported frequency and concentrations of use may be inflated because CAS No. 70131-69-0 is erroneously assigned to both polyphenylsilsesquioxane *and* Phenyl Trimethicone. However, actual use ranges are not expected to exceed the maximum levels reported herein.

**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.

***likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

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

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

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

Table 3. Frequency (2023)[16] and concentration (2021)[18] of use according to likely duration and exposure and by product category

	# of Uses	**Max Conc of Use (%)**	**# of Uses**	**Max Conc of Use (%)**	**# of Uses**	**Max Conc of Use (%)**
	Diphenyl Dimethicone		**Diphenylsiloxy Phenyl Trimethicone**		**Diphenylsiloxy Phenyl/Propyl Trimethicone**	
Totals*	**150**	**0.1 – 24.1**	**275**	**0.3 – 19.9**	**NR**	**5.3**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*148*	*0.1 – 24.1*	*268*	*0.3 – 19.9*	NR	*5.3*
Rinse-Off	*2*	*NR*	*7*	*1 – 8.8*	NR	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	12	NR	44	4.4 – 19.9	NR	NR
Incidental Ingestion	84	1.9 - 24.1	62	9.4 – 15.2	NR	NR
Incidental Inhalation-Spray	1; 15[a]; 2[b]	0.1 - 1	40[a]; 16[b]	0.3 – 5; 3.5[a]	NR	NR
Incidental Inhalation-Powder	2[b]	0.42[c]	13; 16[b]	5.7; 0.4 – 0.5[c]	NR	NR
Dermal Contact	64	0.42 – 1.3	213	0.4 – 19.9	NR	5.3
Deodorant (underarm)	NR	NR	NR	spray: 0.5 not spray: 0.5	NR	NR
Hair - Non-Coloring	2	0.9 - 1	NR	1.2 – 3.5	NR	NR
Hair-Coloring	NR	0.1	NR	0.3 – 8.8	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	84	1.9 – 24.1	62	9.4 – 15.2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts						
Eye Makeup Preparations						
Eyebrow Pencil			NR	4.4		
Eyeliner			1	19.9		
Eye Shadow	12	NR	30	15		
Eye Lotion			5	NR		
Mascara						
Other Eye Makeup Preparations			8	NR		
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes						
Powders (dusting/talcum, excl aftershave talc)						
Other Fragrance Preparation						

Table 3. Frequency (2023)[16] and concentration (2021)[18] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Hair Preparations (non-coloring)						
Hair Conditioner	1	NR	NR	1.2		
Hair Spray (aerosol fixatives)	1	0.9 - 1				
Hair Straighteners						
Shampoos (non-coloring)						
Tonics, Dressings, and Other Hair Grooming Aids			NR	3.5		
Other Hair Preparations						
Hair Coloring Preparations						
Hair Tints			NR	8.8		
Hair Rinses (coloring)			NR	1		
Hair Color Sprays (aerosol)	NR	0.1	NR	0.3		
Makeup Preparations						
Blushers (all types)	2	NR	19	4.7		
Face Powders			13	5.7		
Foundations	1	0.6 - 1.3	29	3.3 - 7.5		
Leg and Body Paints						
Lipstick	84	1.9 - 24.1	62	9.4 - 15.2		
Makeup Bases	NR	NR	1	NR	NR	5.3
Rouges	26	NR	11	NR		
Makeup Fixatives			1	NR		
Other Makeup Preparations	1	NR	30	NR		
Manicuring Preparations (Nail)						
Nail Creams and Lotions						
Nail Polish and Enamel						
Other Manicuring Preparations						
Personal Cleanliness Products						
Deodorants (underarm)			NR	0.5 (aerosol) 0.5 (not spray)		
Feminine Deodorants						
Shaving Preparations						
Aftershave Lotion						
Beard Softeners						
Preshave Lotions (all types)						
Other Shaving Preparations						
Skin Care Preparations						
Cleansing	1	NR	5			
Face and Neck (exc shave)	1	0.42 (not spray)	11	0.4 - 0.5 (not spray)		
Body and Hand (exc shave)	1	NR	5	5 (spray)		
Moisturizing	13	NR	36	1.7 (not spray)		
Night			4	NR		
Paste Masks (mud packs)			2	NR		
Skin Fresheners	2	NR				
Other Skin Care Preparations	4	NR	2	2 - 9		
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Indoor Tanning Preparations						
Other Suntan Preparations						
	Phenyl Dimethicone		**Phenyl Methicone**		**Trimethylsiloxyphenyl Dimethicone**	
Totals*	**3**	**0.0096 – 19.5**	**15**	**0.28**	**37**	**0.2 - 23**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*3*	*0.0096 – 19.5*	15	*0.28*	*36*	*0.2 - 23*
Rinse-Off	*NR*	*NR*	NR	*NR*	*1*	*0.5*
Diluted for (Bath) Use	*NR*	*NR*	NR	*NR*	*NR*	*NR*
Exposure Type*						
Eye Area	NR	2.1	1	NR	6	14
Incidental Ingestion	NR	19.5	NR	NR	17	18 - 23
Incidental Inhalation-Spray	2[a]	NR	4[a]; 2[b]	NR	1[b]	5[a]
Incidental Inhalation-Powder	NR	NR	2[b]	0.28[c]	1[b]	3.5
Dermal Contact	1	2.1	12	0.28	19	3.5 - 20
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	NR	NR	1	0.5 - 5
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.0096	3	NR	NR	0.2
Mucous Membrane	NR	19.5	NR	NR	17	18 – 23
Baby Products	NR	NR	NR	NR	NR	NR

Table 3. Frequency (2023)[16] and concentration (2021)[18] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts						
Eye Makeup Preparations						
Eyebrow Pencil					1	
Eyeliner					1	NR
Eye Shadow	NR	2.1			3	14
Eye Lotion			1	NR		
Mascara						
Other Eye Makeup Preparations					1	NR
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes						
Powders (dusting/talcum, excl aftershave talc)						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioner					1	0.5
Hair Spray (aerosol fixatives)						
Hair Straighteners						
Shampoos (non-coloring)						
Tonics, Dressings, and Other Hair Grooming Aids	2	NR			NR	5
Other Hair Preparations					NR	5
Hair Coloring Preparations						
Hair Tints						
Hair Rinses (coloring)						
Hair Color Sprays (aerosol)						
Makeup Preparations						
Blushers (all types)						
Face Powders					NR	3.5
Foundations			3	NR	1	NR
Leg and Body Paints						
Lipstick	NR	19.5			17	18 - 23
Makeup Bases	1	NR				
Rouges						
Makeup Fixatives						
Other Makeup Preparations			2	NR	11	NR
Manicuring Preparations (Nail)						
Nail Creams and Lotions						
Nail Polish and Enamel	NR	0.0096	2	NR	NR	0.2
Other Manicuring Preparations			1	NR		
Personal Cleanliness Products						
Deodorants (underarm)						
Feminine Deodorants						
Shaving Preparations						
Aftershave Lotion						
Beard Softeners						
Preshave Lotions (all types)						
Other Shaving Preparations						
Skin Care Preparations						
Cleansing						
Face and Neck (exc shave)			2	0.28 (not spray)	1	NR
Body and Hand (exc shave)						
Moisturizing			2	NR	NR	20 (not spray)
Night			2	NR		
Paste Masks (mud packs)						
Skin Fresheners						
Other Skin Care Preparations						
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Indoor Tanning Preparations						
Other Suntan Preparations						

NR – not reported
*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.
**likely duration and exposure are derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Diphenylsiloxy Phenyl Trimethicone	Wistar Han rats	5/sex	none	OECD TG 402. Semi-occlusive application of 2000 mg/kg bw for 24 h.	LD_{50} >2000 mg/kg. Slight crust formation in 1 female rat on the fourteenth and fifteenth day of observation. There were no signs of systemic or clinical toxicity.	6,7
Trimethylsiloxyphenyl Dimethicone	Sprague-Dawley rats	5/sex	none	OECD TG 402. Occlusive application of 2000 mg/kg bw for 24 h.	LD_{50} > 2000 mg/kg bw. No mortality nor pathological clinical signs were noted.	21
ORAL						
Diphenyl Dimethicone	Rats (strain not specified)	3/sex	none	Rats were administered 8190, 16,380, 32,770, or 65,540 mg/kg bw of the test article, intragastrically. Animals were observed for 14 d before necropsy.	LD_{50} > 65,550 mg/kg bw, computed via the Miller and Taint method. Abdominal pain was observed after administration, followed by excessive laxation and urinary incontinence. One rat/group from the three highest dose groups died (3 or more days after dosing) and diffuse pulmonary hemorrhage and petechial hepatic hemorrhage was observed. No gross abnormalities were found at necropsy.	22
Diphenyl Dimethicone	Albino rats	5/sex	none	Animals were given 5000 mg/kg bw of the test article, via gavage. Animals were observed for 14 d prior to necropsy.	LD_{50} > 5000 mg/kg	23
Diphenylsiloxy Phenyl Trimethicone	Female Wistar Han rats	3/group	corn oil	OECD TG 423. The animals were given 2000 mg/kg bw of the test article, via gavage.	LD_{50} > 2000 mg/kg. Slightly ruffled fur was observed in 1 male and 1 female for up to 3 h after administration. No mortality or other abnormalities occurred.	6,7
Phenyl Trimethicone	Female Wistar rats	3/group	corn oil	OECD TG 423. Two groups were administered 2000 mg/kg bw (no control group), via gavage and were observed for 14 d prior to necropsy.	$LD_{50} \geq$ 2000 mg/kg. No mortality or clinical abnormalities were observed.	5
Phenyl Trimethicone	Rats (strain not specified)	NR (both males and females)	NS	OECD TG 401. Animals were administered 1000, 2500, or 5000 mg/kg bw of the test article, via gavage and observed for 7 d (necropsy not performed).	LD_{50} > 5000 mg/kg. No mortality or clinical abnormalities were observed.	5
78 - 82% Phenyl Trimethicone and 18 - 22% polysilicone-11	Wistar-derived albino rats	5/sex	none	The animals were given 5000 mg/kg bw of the test article, via gavage.	LD > 5000 mg/kg. No mortality or clinical abnormalities were observed.	24
Trimethylsiloxyphenyl Dimethicone	CD rats	5/sex	corn oil	Animals were administered a 2000 mg/kg bw dose, via gavage, at a constant volume-dosage of 10 ml/kg,	LD_{50} > 2000 mg/kg bw	13

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results	Reference
INHALATION						
Diphenyl Dimethicone	Albino rats	5/sex/group	none	Whole body exposure. The test article was vaporized during 5-min intervals, at 370 °C on an electric hot plate, housed within a bell jar (maintained at 25 - 30 °C) connected to an animal exposure chamber. Fresh air mixed with the heated vapors entered the exposure chamber at an airflow rate of 5 lb/in^2. Animals were exposed to either 5, 10, 23, 24, 42, 90, 101, 168, or 214 mg/l of the vaporized test article for 1 h. Exposure concentrations were calculated based on the volume of the chamber and the amount of Diphenyl Dimethicone being vaporized. Animals were observed for 14 d after exposure.	LC_{50}: 18 mg/l (estimated). Little or no respiratory distress was observed during the exposure period. One animal each from the 42 mg/l and 101 mg/l group died during the exposure period. Within 24 h after exposure, the following deaths occurred: 5 mg/l: none 10 mg/1: 3 animals 23 mg/l: 6 animals 24 mg/l: 7 animals 42 mg/l: 6 animals 90 mg/l: 8 animals 101 mg/l: 7 animals 168 mg/l: 3 animals 214 mg/l: 1 animal At higher volumes of dispensation (≥ 101 mg/l), residues accumulated on the hot plate. The lower conductivity of these concentrations was suspected to modify temperature and vaporization, thus, resulting in lower mortality than at intervening dose levels. Granular livers were seen in ~ 30% of the animals exposed to ≥ 24 mg/l. Severe and diffuse pulmonary hemorrhages accounted for most of the deaths. Pulmonary consolidation, varying from pinkish orange petechia to major involvement, was found in surviving animals.	[22]

N/A - not applicable; NR - none reported; OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
ORAL							
Diphenyl Dimethicone, 15%	10% polyethylene glycol 660 hydroxystearate, in purified water	Sprague-Dawley rats (10/sex)	90 d	0, 5, 20, or 80 mg/kg/d, via gavage	Subchronic oral toxicity study. The animals were observed daily for mortality and clinical abnormalities; body weights and food consumption were recorded weekly. Animals were killed at the end of treatment; post-mortem evaluation of animal organs and hematological parameters, including glucose, triglycerides, white blood cell counts, and prothrombin time, as well as urinalysis, were performed.	No deaths related to treatment with the test article occurred and no changes were observed in body weight and food consumption. Higher absolute and relative liver weights in animals given 80 mg/kg were considered to be treatment-related and were correlated with slight hepatocellular hypertrophy seen in 8 males and 10 females in the 80 mg/kg group; both effects were considered toxicologically significant. Liver enlargement was noted in 3 males from the 80 mg/kg group, which was attributed to treatment with the test article. Higher liver weight was noted in females from the 5 and 20 mg/kg/d groups, but these effects were not related to relevant microscopic findings and were therefore not considered toxicologically significant. Other statistically significant differences (including higher prothrombin time in males given 80 mg/kg and lower mean leukocyte counts in all the test group females) were not considered toxicologically significant, as they were minimal, without a dose-response relationship, did not exhibit any trend between the sexes, and individual values were within the expected historical range. The NOAEL was determined to be 20 mg/kg/d.	[25]

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Diphenylsiloxy Phenyl Trimethicone	corn oil	Wistar Han rats (5/sex)	28 d	0, 200, 600, or 1000 mg/kg bw, via gavage	OECD TG 407. Short-term oral toxicity study	A statistically significant reduction in body weight gain occurred in male rats from the 1000 mg/kg group (18 - 19%, when compared to controls) on day 8 and day 15 of observation. Significant reduction in body weight gain (48%, compared to controls) also occurred in female rats from the 600 and 1000 mg/kg groups on day 8. There were no reported treatment-related changes to food consumption in test animals. No treatment-related changes in hematology, clinical chemistry, urinalysis, or deaths occurred. Compared to controls, relative liver weights increased by 12, 22, and 18% for low-, mid-, and high-dose groups for the male rats, respectively, while relative liver weights increased by 23, 29, and 43% for low-, mid-, and high-dose groups for the female rats, respectively. Treatment-related microscopic liver changes, such as the following, were observed: hepatocellular hypertrophy (ranging from minimal to moderate degrees) in all test animals, increased incidence or severity of change in fatty tissue deposition in the livers of males from the high dose group and in all of the test females, and the increased incidence of bile duct production in males from the mid dose group and females from the low and mid dose groups. Minimal hypertrophic changes in the follicular epithelium of the thyroid gland were observed in 2 males from the low-dose group, 1 male from the mid-dose group, and 4 males from the high-dose group. The authors considered the hepatic hypertrophy adaptive, and the thyroid changes as secondary, and a result of the metabolic turnover of thyroid hormones. The NOAEL was determined to be > 1000 mg/kg.	[6,7]
Trimethylsiloxyphenyl Dimethicone	corn oil	CD rats (5/sex/group)	4 wk	0, 20, 150, 1000 mg/kg/d, via gavage	The test article was administered at a constant volume of 5 ml/kg bw. The animals were monitored for mortality, food and water consumption, and body weight throughout the study period. Hematological and blood chemistry samples were taken on day 29. Upon necropsy, the organ weights of the adrenals, liver, kidneys, and testes were calculated relative to bodyweight gain. Gross and histopathological examination of the adrenals, heart, kidneys, liver, spleen, and testes was performed.	No deaths or significant changes related to the test material were observed. The NOAEL was determined to be 1000 mg/kg/d.	[26]

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
INHALATION							
Phenyl Methicone, 9.2 cSt, 25 °C	N/A	1 cat, 2 guinea pigs, 2 rabbits, and 4 rats	10 d, for 7 h/d	67.4 mg/min, at a concentration of 0.52 mg/l	Animals were exposed, whole body, to the test article.	No animals died during and after exposure. Histopathological examination did reveal moderate degenerative changes in the livers of cats and guinea pigs. However, in the absence of control data, moderate degenerative changes in livers of the cats and guinea pigs were considered only circumstantially associated with siloxane exposure.	[27]

cSt – centistoke; N/A - not applicable; NOAEL - no-observable-adverse-effect-level; OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
ORAL						
Diphenylsiloxy Phenyl Trimethicone	corn oil	Sprague-Dawley rats (10/sex)	0, 100, 500, or 1000 mg/kg bw/d, via gavage	OECD TG 422. Males and females were treated with the test substance 2 wk prior to, and during, mating. One group which received no treatment served as negative controls. Males were treated for 92 d and were killed at the end of the treatment period, while dams were treated up until postpartum day 3. Males, pups, and dams which delivered were killed on day 4 postpartum; mated females which did not deliver were killed on day 25 or 26 of gestation.	No statistically significant changes in body weight, food consumption, or organ weights were observed. (Statistically significant changes in body weight for females during week 2 of gestation were not toxicologically significant.) No treatment-related effects were apparent for reproductive endpoints in the parents, including testis weight, epididymis weight, mean gestation length, mean number of corpora lutea, mean number of implantation sites, mean mating and fertility indices, nor were there effects observed in the offspring for gross pathology, mean litter size, mean litter weight, or mean ratio live births/litter size. The NOAEL for reproductive (both sexes) and developmental toxicity was determined to be ≥ 1000 mg/kg bw/d.	[6]
Phenyl Trimethicone	oil	Male Wistar rats (20/group)	0, 100, 300, or 1000 mg/kg bw, via gavage	The test article was administered 5 d/wk, over 4 wk. Animals were killed 24 h after the final dose, and testicles were weighed and examined microscopically.	No visible changes, body weight fluctuations, or deaths occurred during the course of the study. No effects on testicle weight or histology were observed. The NOAEL for effects on body weight, testicle weight, and histology was determined to be > 1000 mg/kg.	[5]

NOAEL - no-observable-adverse-effect-level; OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	Reference
IN VITRO						
Diphenylsiloxy Phenyl Trimethicone	ethanol	Up to 5000 µg/plate, with and without metabolic activation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 strains	OECD TG 471. Ames test	Not genotoxic	[6,7]
Diphenylsiloxy Phenyl Trimethicone	ethanol	Without metabolic activation: 0.025 – 0.3 µl/ml (4 h) 0.006 – 0.2 µl/ml (18 h) 0.013 – 0.1 µl/ml (28 h) With metabolic activation: 0.003 – 0.2 µl/ml (4 h) 0.040 – 5 µl/ml (4 h)	Chinese hamster lung (V79) cell line	OECD TG 473. Mammalian chromosomal aberration study. Appropriate positive and negative controls were used. Cells were treated prior to harvest with a metaphase-arresting substance, stained, and analyzed microscopically for induced cytotoxicity or the presence of chromatid-type and chromosome-type aberrations in cells undergoing metaphase.	Non-clastogenic. Cell numbers below 50% of the controls or poor metaphase quality were observed in cells treated with ≥ 0.15 µl/ml of the test substance in the absence of metabolic activation for 18 h. No statistically significant increase in the frequency of cells with chromosome aberrations was induced in either the absence or presence of metabolic activation.	[6,7]
Trimethylsiloxyphenyl Dimethicone	10% Tween 80 solution	1, 5, 10, 50, or 100 µl/plate	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 strains, with or without metabolic activation	Ames test	Not genotoxic	[28]

OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
ANIMAL						
Diphenyl Dimethicone, 100% pure	N/A	0.5 ml, applied neat	6 New Zealand white rabbits	Primary dermal irritation test. The test article was simultaneously applied to an abraded and unabraded test site, under occlusion, for 24 h. Mean scores from 24 and 72 h after application were used to determine the PII. Under study conditions, the test article was not considered to be a primary dermal irritant.	Not irritating; PII = 0.28	[29]
Diphenylsiloxy Phenyl Trimethicone, 100% pure	N/A	0.5 ml, applied neat	3 New Zealand white rabbits	OECD TG 404; primary skin irritation test. A semi-occlusive patch application of the test article was made for 4 h, and test sites were scored at 1, 24, 48, and 72 h after patch removal.	Not irritating	[30]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Diphenylsiloxy Phenyl Trimethicone	N/A	0.5 ml, applied neat	1 male and 2 female New Zealand white rabbits	OECD TG 404; dermal irritation study. A semi-occlusive patch application of the test article was made for 4 h, and test sites were scored at 24, 48, and 72 h after patch removal. Mean scores for erythema/eschar and edema were calculated for each animal from scores taken at the 3 time points.	Slightly irritating; non-irritating in another description. Very slight to well-defined erythema was noted in all 3 animals 1 h after patch removal. Mean erythema/eschar scores were 0.33 for both animal 1 and 2, and 0.67 for animal 3; no edema was observed. Very slight erythema persisted in all animals until the 24-h reading and was still present in 1 animal at the 48-h reading. The noted effects were reversible and no longer evident at the 72 h. In another description of the same study, GHS criteria were not met, and the test article was deemed non-irritating.	[6,7]
72 - 82% Phenyl Trimethicone 18 - 22% polysilicone-11	N/A	0.5 ml, applied neat	6 New Zealand white rabbits	In an acute skin irritation test, an occlusive application of the test material was made to intact and abraded skin on the shaved trunk (approximately 6 cm^2) for 24 h. Upon removal of the patch, test sites were gently wiped, and were scored for erythema and edema at 24 and 72 h after application.	Not irritating; PII = 0	[31]
Trimethylsiloxyphenyl Dimethicone	N/A	0.5 ml, applied neat	6 New Zealand white rabbits	OECD 404.; primary skin irritation test. A semi-occlusive application of the test article was made for 4h. Test sites were scored 1, 24, 48, and 72 hr after patch removal. Mean values were calculated from the evaluation of erythema and edema lesions at 24, 48, and 72 h.	Not irritating; mean values for erythema = 0.06; edema = 0	[32]
				HUMAN		
Lip color containing 9.06% Diphenyl Dimethicone	N/A	NS, applied neat	20 subjects	24-h, SIOPT. Irritation scores were made on a scale of 0 - 4 and PIIs were calculated. A liquid lip color was tested in tandem.	Not irritating; PII = 0	[33]
Ampoule containing 0.5% Diphenylsiloxy Phenyl Trimethicone	N/A	not specified, applied neat	20 subjects	24-h, SIOPT. Irritation scores were made on a scale of 0 - 4 and PIIs were calculated. A serum was tested in tandem.	Not irritating; PII = 0.03	[34]
SPF cream containing 3.2363% Phenyl Trimethicone	N/A	0.05 ml, applied neat	25 subjects	14-d cumulative irritation test. Occlusive, 15 mm^2 applications of the test material were made to a site on the upper arm or back for 14 d. Positive and negative control sites comprised 0.05 ml of 0.25% SLS or plain cotton, respectively. Test sites were graded daily after patch removal on a scale of 0 - 5.	Not irritating. Cumulative score and CII = 0. Control results were as expected.	[37]
Eye primer containing 10% Phenyl Trimethicone	N/A	not specified, applied neat	21 subjects	24-h, SIOPT. Performed as described previously. A mousse foundation was tested in tandem.	Not irritating; PII = 0	[35]
Shine gloss containing 5% Trimethylsiloxyphenyl Dimethicone	N/A	not specified, applied neat	18 subjects	24-h, SIOPT. Performed as described previously. A frizz shine spray was tested in tandem.	Not irritating; PII = 0	[36]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Serum containing 2% Trimethylsiloxyphenyl Dimethicone	N/A	200 µl, applied neat	28 subjects	15-d cumulative irritation test. Occlusive, 24-h applications of the test material (2 cm^2) were made to the back for 15 d. Positive and negative control sites comprised 200 µl of 0.25% SLS or plain cotton, respectively. Test sites were graded daily after patch removal on a scale of 0 - 4.	Not irritating. No reactions were observed in 27 subjects. Grade 1 reactions (mild redness) occurred twice in one participant, yielding a CII = 0.002 (negligible/non-significant irritation). Control results were as expected.	[38]
SENSITIZATION						
			ANIMAL			
Product containing 15% Diphenyl Dimethicone	acetone: olive oil (4:1 v/v)	25 ml; 2.5, 5, 10, 25, or 50%	Groups of 4 female CBA mice	OECD TG 429; LLNA. The test article was topically applied on days 1, 2, and 3 to one ear, while acetone:olive oil (vehicle control) was applied to the other ear. One group which received 25% α-hexylcinnamaldehyde in the acetone:olive oil mixture served as positive controls. Animals were observed for clinical and gross abnormalities for up to 6 d before being killed. Stimulation indices (SI) were calculated.	Not sensitizing. Two of 4 of animals in the 10% group died on day 3 and 1 of the animals in the 50% group died on day 6. These deaths were not attributed to the test article. No positive lymphoproliferative response (SI > 3) were noted at any tested concentration.	[39]
Diphenyl Dimethicone, 100% pure	N/A	NS, applied neat	6 male and 6 female Hartley albino guinea pigs	Buehler test. Animals received 3 topical, occluded applications of the test article over the 3-wk induction period. Five males and 5 females served as the control group (which received no treatment during induction). After 2 wk, a challenge application of the test article was made to an untreated site on both the test and control animals. Reactions were scored 7 and 24 h after each induction and challenge application, and also at 48 h following the challenge application. The test article was deemed a non-sensitizer.	Not sensitizing	[29]
Diphenylsiloxy Phenyl Trimethicone, 100% pure	acetone: olive oil (4:1 v/v)	25, 50, or 100% w/w	Groups of 4 female mice	LLNA. The test article was applied topically to the back of both left and right ear lobes for 3 consecutive days. A control group was treated only with the acetone:olive oil mixture. Five days after the first topical application the mice were intravenously injected with radio-labelled thymidine. The animals and were killed and lymph nodes were excised for evaluation approximately 5 h after injection.	25% group SI = 1 50% group SI = 2 100% group SI = 2.4 (An SI < 3 is non-sensitizing) No deaths occurred during the study period, and no clinical signs were observed in controls or animals in the 25% group. All mice in the 100% group exhibited slight ear swelling at both ear lobes on day 2, which persisted for 4 d. All mice in the 50 and 100% groups exhibited such results on day 3, which persisted for 3 d.	[30]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Diphenylsiloxy Phenyl Trimethicone	acetone: olive oil (4:1 v/v)	25, 50, or 100% w/w	Groups of 4 female CBA mice	OECD TG 429; LLNA. The test item was topically administered for an unspecified duration. Vehicle controls received the acetone:olive oil mixture, while animals treated previously with α-hexylcinnamaldehyde served as positive controls. Lymphocyte proliferative responses (measured as DPM/lymph node) and SIs (test/control ratio) were calculated for each group.	No evidence of induction of a lymphocyte proliferative response indicative of skin sensitization to the test substance was observed. Slight ear swelling was observed in test animals exposed to 100% of the test article on the second day of application. Animals exposed to 50 and 100% of the test article also exhibited slight erythema of the ear on the third day of application, which persisted until the end of the study.	[6,7]
Trimethylsiloxyphenyl Dimethicone	FCA	Intradermal injections during induction: -test article, as supplied -50% FCA in isotonic solution -50% test article in FCA and isotonic solution Intradermal challenge: 0.5 ml, applied neat Challenge: 0.5 ml, applied neat	Dunkin Hartley guinea pigs (10/sex/group)	OECD TG 406. On day 1, animals received 2 lots of 0.1 ml intradermal injections. Additionally, a 48-h, occlusive application of the undiluted test substance was made. As this application did not cause irritation, 0.5 ml of SLS (10% in paraffin oil) was applied to the skin on day 8. On day 9, a 48-h, occlusive application of the test article was made to an 8 cm^2 area where the injections were delivered. On day 22, an occlusive, 24-h challenge application of the undiluted test article was made to a 2 cm^2 area. Challenge sites were scored 24 and 48 h after patch removal. Controls received water during induction and were challenged with the test article.	Not sensitizing	[40]
				HUMAN		
Product containing 2% Diphenyl Dimethicone	N/A	0.02 ml, applied neat	111 subjects	Modified Marzulli-Maibach HRIPT. Nine occlusive applications were made to a 50 mm^2 area of the back using Finn chambers over a 3-wk period for 48- or 72-h. After a 13-d non-treatment period, a single 48-h challenge application was made to the induction site and a previous untreated site. Reactions were scored on a 0 - 4 irritation scale between 15 and 30 min of patch removal during both the induction and challenge phases; challenge phase reactions were additionally evaluated 48 h after application. An MII was calculated by dividing the sum of the quotations of the 9 induction readings by the number of subjects and readings performed. The test article did not demonstrate potential to produce irritation or cutaneous sensitization.	Not irritating or sensitizing; MII = 0.01	[41]
Ampoule containing 0.5% Diphenylsiloxy Phenyl Trimethicone	N/A	0.2 g, applied neat	112 subjects	HRIPT. Nine occlusive, 24-h applications of the test material were made over 3 wk. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24, 48, 72, and 96 h after application.	Not sensitizing Two subjects exhibited low level reactions during induction and 2 other subjects exhibited low level reactions during challenge.	[42]
Lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone	N/A	~ 0.1 - 0.15g, applied neat	109 subjects	HRIPT. Similar procedure as described above. The 24-h challenge application was scored 24 and 72 h after application.	Not irritating or sensitizing	[43]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Product containing 0.2% Phenyl Methicone	N/A	not specified, applied neat	107 subjects	Marzulli-Maibach HRIPT. Nine occlusive, 48-h induction applications were made using 8 mm Finn chambers to the same site over a 3-wk period. Induction sites were evaluated for dermal reactions immediately prior to application of the next patch. After a 2-wk non-treatment period, challenge applications were made to the original test site and a previously untreated site in the same manner as the induction applications. Challenge sites were scored 48, 72, and 96 h after application.	Not irritating or sensitizing	[44]
Product containing 20% Phenyl Trimethicone	N/A	0.1 - 0.15 g, applied neat	53 subjects	HRIPT. Nine occlusive, 24-h applications of the test material were made over 3 wk. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24 and 72 h after application.	Not irritating or sensitizing	[45]
Concealer containing 26.18% Phenyl Trimethicone	N/A	0.05 ml, applied neat	26 subjects	Maximization assay. Five, occlusive induction applications were made. Prior to each induction application, a 24-h application of 0.05 ml of 0.25% aqueous SLS was made. After removal of the SLS-pre-treatment patch, 0.5 ml of the test material was applied for 48 - 72 h using an occlusive patch. After a 10-d non-treatment period, subjects were pre-treated with 0.05 ml of 1 % aqueous SLS for 1 h on a novel site, prior to a 48-h challenge application, in the same manner as the induction applications. Challenge reactions were scored immediately after patch removal and 24 h later.	Not sensitizing No instances of contact allergy or irritation were observed.	[46]
Product containing 28.67% Phenyl Trimethicone	N/A	0.2 g, applied neat	203 subjects	HRIPT. The test material was applied to the skin using a 2 cm^2 absorbent pad for semi-occlusive, 24-h induction and challenge applications. Challenge reactions were scored 48 and 72 h after application.	Not sensitizing	[47]
Cream containing 3% Trimethylsiloxyphenyl Dimethicone	N/A	0.2 g, applied neat	103 subjects	HRIPT. The test material was applied using a 0.75 in^2 absorbent pad for the occlusive, 24-h induction and challenge applications. Challenge reactions were scored 24 and 72 h after application. The test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.	Not irritating or sensitizing	[48]
Product containing 38.006% Trimethylsiloxyphenyl Dimethicone	N/A	0.2 g, applied neat	205 subjects	HRIPT. The test material was applied using a 2 cm^2 absorbent pad for 24-h occlusive induction and challenge applications. Challenge reactions were scored 48 and 72 h after application.	Not sensitizing	[49]
Trimethylsiloxyphenyl Dimethicone, 100% pure	N/A	0.2 ml, applied neat	51 subjects	HRIPT. The test material was applied using a 0.75 in^2 absorbent pad for the 24-h induction and challenge applications. Challenge reactions were scored 24 and 72 h after application. The test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.	Not irritating or sensitizing	[50]

CII - cumulative irritation index; DCNB - 1-chloro-2, 4-dinitrobenzene; DPM - disintegrations per minute; FCA – Freund's Complete Adjuvant; GHS - Globally Harmonized System of classification; HRIPT - human repeat insult patch test; LLNA - local lymph node assay; MII - mean irritation index; N/A - not applicable; PDII - primary dermal irritation index; PII - primary irritation index; SI - stimulation index; SIOPT - single insult occlusive patch test; SLS - sodium lauryl sulfate

Table 9. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL						
Diphenyl Dimethicone	N/A	0.1 ml, undiluted	Groups of 3 albino rabbits	Ocular irritation test. Each animal had the test material instilled in the conjunctival sac of one eye. Treated eyes remained unwashed in the first group, were washed 2 s after exposure with 20 ml water in the second group, and were washed 4 s after exposure with 20 ml water in the third group. The eyes were examined, and irritation was scored 4 h, and 1, 2, 4, and 7 d after exposure.	Slightly, but transiently, irritating. A maximum score of 8 (out of the potential maximum of 110), indicating slight irritation, was observed only within 4 h in 1 animal from the second group. By the second or third day the eyes appeared normal, regardless of rinsing status.	[22]
Diphenylsiloxy Phenyl Trimethicone	N/A	0.1 ml, undiluted	1 male and 2 female New Zealand white rabbits	OECD TG 405; Acute ocular irritation study. Rabbit eyes were treated with the undiluted test article for 72 h.	Not irritating (according to GHS classification); slightly irritating according to Kay and Calandra criteria. Mild ocular changes, including reddening of the conjunctivae and sclerae, discharge, and chemosis were observed 1 h after instillation, but resolved within 24 h.	[6,7]
Phenyl Methicone	N/A	not specified	Rabbits (strain and number not specified)	Ocular irritation test. The test article (35 and 75 cSt viscous) was directly instilled into rabbit eyes and the eyes were observed for irritation from application for up to 48 h.	Not irritating Slight irritation, observed 4 and 8 h after exposure, subsequently subsided.	[27]
78 - 82% Phenyl Trimethicone 18 - 22% polysilicone-11	N/A	0.1 ml, undiluted	6 New Zealand white rabbits	Ocular irritation test. The test material was instilled on the everted lower lid of one eye, and the upper and lower eye lids were gently held together for 1 s before releasing. The contralateral, untreated eye served as control. The cornea, iris, and conjunctivae were evaluated according to the Draize method at 24 and 72 h post-instillation. A 2% fluorescein sodium solution, followed by saline solution wash was utilized as necessary.	Not irritating; MMTS = 0	[53]
Trimethylsiloxyphenyl Dimethicone	N/A	0.1 ml, undiluted	6 male New Zealand white rabbits	OECD TG 405. The test material was instilled as supplied, without rinsing, to the right eye. The left eye served as the untreated control. Eyes were examined 1, 24, 48, and 72 h after instillation. Mean values were calculated for ocular lesions in the conjunctiva, iris, and cornea 24, 48, and 72 h after instillation.	Slightly irritating; Mean values: Opacity to the cornea: 0 Congestion to the iris: 0.5 Chemosis and enanthema to the conjunctiva: 0.5 and 1.39	[54]

cSt – centistoke; GHS – Globally Harmonized System of classification; MMTS- maximum mean total score; OECD- Organisation for Economic Cooperation and Development; TG- test guideline

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