Final Report on the Safety Assessment of Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone[1]

Dimethicone is a fluid mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units. Methicone is a linear monomethyl polysiloxane. The other dimethicones and methicones covered in this review are siloxane polymers of Dimethicone and Methicone. Most of these ingredients function as conditioning agents in cosmetic formulations at current concentrations of use of $\leq$15%. Clinical and animal absorption studies reported that Dimethicone was not absorbed following oral or dermal exposure. Dimethicone, Methicone, and Vinyldimethicone were not acutely toxic following oral exposure. No adverse reactions were found in rabbits following short-term dermal dosing with 6% to 79% Dimethicone, yet adverse effects were noted with a hand cream formulation containing 1% Dimethicone, suggesting something else in the preparation was toxic. Mice and rats were dosed for 90 days with up to 10% Dimethicone without adverse effect. Dimethicone did not produce adverse effects in acute and short-term inhalation-route studies, Methicone and Vinyldimethicone were negative in acute exposure studies using rats, but Hexyl Methicone was toxic to rats at 5 mg/L delivered in small particle (mean diameter of 0.29 μ) aerosols. Most dermal irritation studies using rabbits classified Dimethicone as a minimal irritant. Dimethicone (tested undiluted and at 79%) was not a sensitizer in four assays using mice and guinea pigs. It was not a sensitizer at 5.0% in a clinical repeated insult patch test using 83 panelists. Most ocular irritation studies using rabbits classified Dimethicone as a mild to minimal irritant. Dimethicone was tested in numerous oral-dose (using rats) and dermal-dose (using rats, rabbits, and monkeys) reproductive and developmental toxicity studies. In a few studies, treated males had significantly decreased body weight and/or decreased testes or seminal vesicles weights. No treatment-related adverse findings were noted in dosed pregnant females or fetuses. Dimethicone was negative in all genotoxicity assays. It was negative in both an oral (tested at 91%) and dermal (tested at an unknown concentration) dose carcinogenicity assay using mice. The Cosmetic Ingredient Review (CIR) Expert Panel considered it unlikely that any of these polymers would be significantly absorbed into the skin due to their large molecular weight. Although adverse effects were noted in one inhalation study with small aerosol particles, the expected particle sizes for cosmetic products would primarily be in the range of 60 to 80 μ, and less than 1% would be under 10 μ, which is an upper limit for respirable particles. Overall, the safety test data support the safety of these ingredients at the concentrations they are known to be used in cosmetic formulations. Accordingly, the CIR Expert Panel was of the opinion that Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are safe as used in cosmetic formulations.

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[1]Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. This report was prepared by Bindu Nair, with the assistance of Amy R. Elmore, both former CIR staff.

Address correspondence to F. Alan Andersen, Cosmetic Ingredient Review Director, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

INTRODUCTION

This report is a compilation of data relevant to assessing the safety of Stearoxy Dimethicone, Dimethicone, Methicone,

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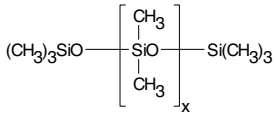
Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone for use in cosmetic formulations. Almost all of the studies were done on Dimethicone identified under the CAS no. 63148-62-9 and defined as "dimethyl silicones and siloxanes." Heading names are used to identify studies that were done on other ingredients.

CHEMISTRY

Definition and Structure

Stearoxy Dimethicone (CAS no. 68554-53-0) is a polymer of dimethylpolysiloxane end-blocked with stearoxy groups. No structure is available. Synonyms include Dimethylsiloxane·Methylstearoxysiloxane Copolymer; Dimethyl Siloxy Stearoxy Siloxane Polymer; Poly(dimethylsiloxy) Stearoxysiloxane; Siloxanes and Silicones, Dimethyl, (Octadecyloxy)-Terminated; and Stearoxymethylpolysiloxane (Wenninger, Canterbery, and McEwen 2000).

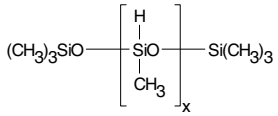
Dimethicone (CAS no. 9006-65-9, 63148-62-9, and 9016-00-6) is a mixture of fully methylated linear siloxane polymers $\mathbf{[-(CH_3)_2SiO-]}_x$ end-blocked with trimethylsiloxy units $\mathbf{[-(CH_3)_3SiO-]}$. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000; Committee on Revision of the United States Pharmacopeial Convention 1995):



Dimethicone

Synonyms include Dimethylpolysiloxane; Dimethyl Silicone; Highly Polymerized Methyl Polysiloxane (1) and (2); Methyl Polysiloxane; Poly[oxy(dimethylsilylene)], α-(trimethylsilyl)-ω-methyl-; Silicone L-45 (Wenninger, Canterbery, and McEwen 2000), and α-(trimethylsilyl)-ω-methylpolydimethylsiloxane poly[oxy(dimethylsilylene)] (Committee on Revision of the United States Pharmacopeial Convention 1995). The Food and Agriculture Organization (FAO) of the World Health Organization (WHO) also lists the following three synonyms: Dimethylsilicone Fluid, Dimethylsilicone Oil, and Poly(dimethylsiloxane) (FAO/WHO 1994).

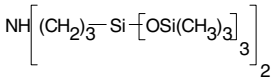
Methicone (CAS no. 9004-73-3) is a linear monomethyl polysiloxane. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Methicone

Synonyms include Hydrogen Methyl Polysiloxane, Methyl Hydrogen Polysiloxane, and Poly[oxy(methylsilylene)] (Wenninger, Canterbery, and McEwen 2000).

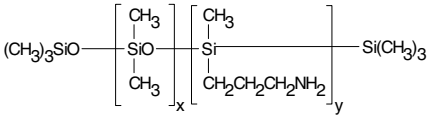
Amino Bispropyl Dimethicone is a substituted siloxane amine that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Amino Bispropyl Dimethicone

No synonyms for Amino Bispropyl Dimethicone were found.

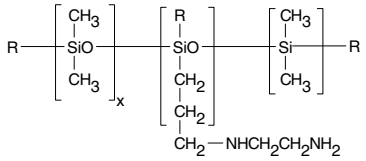
Aminopropyl Dimethicone is a silicone polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Aminopropyl Dimethicone

No synonyms for Aminopropyl Dimethicone were found.

Amodimethicone is a silicone polymer end blocked with amino functional groups. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



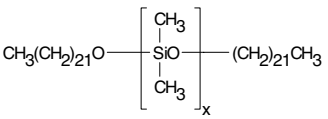
Amodimethicone

where R represents OH or CH3

Synonyms for Amodimethicone include Aminoethylaminopropylsiloxane · Dimethylsiloxane Copolymer Emulsion (Wenninger, Canterbery, and McEwen 2000).

Amodimethicone Hydroxystearate is the salt of Amodimethicone (q.v.) and Hydroxystearic Acid (q.v.) (Wenninger, Canterbery, and McEwen 2000). No structure was available and no synonyms were found.

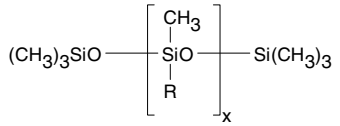
Behenoxy Dimethicone is a dimethyl siloxane polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Behenoxy Dimethicone

No synonyms for Behenoxy Dimethicone were found.

C24–28 Alkyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

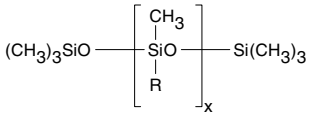


C24-28 Alkyl Methicone

where R represents the C24-28 alkyl group

No synonyms for C24–28 Alkyl Methicone were found.

C30–45 Alkyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

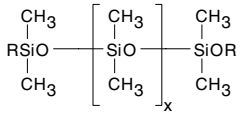


C30-45 Alkyl Methicone

where R represents the C30-45 alkyl group

No synonyms for C30–45 Alkyl Methicone were found.

C30–45 Alkyl Dimethicone is a silicone polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):

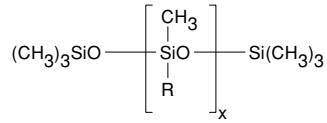


C30-45 Alkyl Dimethicone

where R represents the C30-45 alkyl group

No synonyms for C30–45 Alkyl Dimethicone were found.

Cetearyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

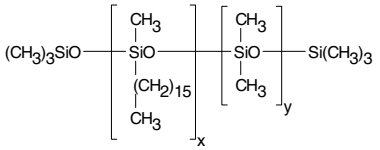


Cetearyl Methicone

where R represents the C16-18 alkyl group

No synonyms for Cetearyl Methicone were found.

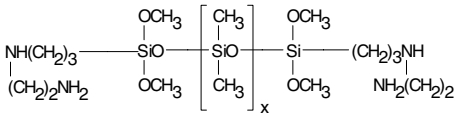
Cetyl Dimethicone is a dimethyl siloxane polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



Cetyl Dimethicone

No synonyms for Cetyl Dimethicone were found.

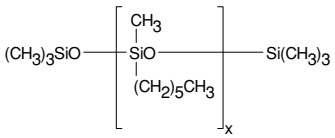
Dimethyoxysilyl Ethylenediaminopropyl Dimethicone (CAS no. 71750-80-6) is the silicone polymer that conforms generally to the formula:



Dimethyoxysilyl Ethylenediaminopropyl Dimethicone

Synonyms include Siloxanes and Silicones, Dimethyl, Mono-[[3-[(2-aminoethyl)amino]propyl]dimethoxysilyl]oxy-terminated (Wenninger, Canterbery, and McEwen 2000).

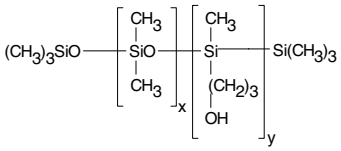
Hexyl Methicone (CAS no. 1873-90-1) is the silicone polymer that conforms to the formula:



Hexyl Methicone

Synonyms for Hexyl Methicone include trisiloxane, 3-Hexyl-1,1,1,3,5,5,5-Heptamethyl- (Pepe, Wenninger, and McEwen 2002), and 1,1,1,3,5,5,5-Heptamethyl-6-Hexyltrisiloxane (IIT Research Institute 1994).

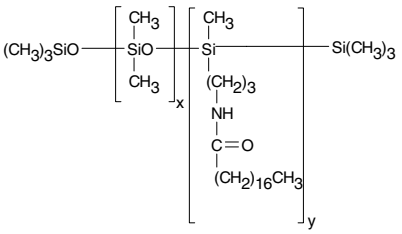
Hydroxypropyldimethicone (CAS no. 102782-61-6) is the silicone polymer that conforms generally to the formula:



Hydroxypropyldimethicone

A synonym is Siloxanes and Silicones, Dimethyl, 3-Hydroxypropyl Methyl (Wenninger, Canterbery, and McEwen 2000).

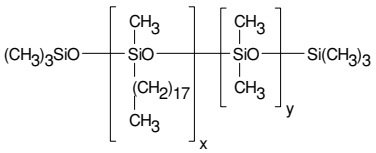
Stearamidopropyl Dimethicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



Stearamidopropyl Dimethicone

No synonyms for Stearamidopropyl Dimethicone were found.

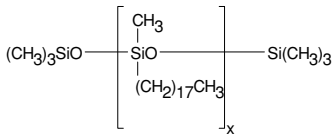
Stearyl Dimethicone is the silicone polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Stearyl Dimethicone

No synonyms for Stearyl Dimethicone were found.

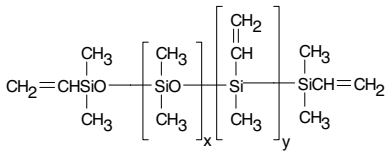
Stearyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



Stearyl Methicone

No synonyms for Stearyl Methicone were found.

Vinyldimethicone is a polymer of dimethylsiloxane containing vinyl functional groups. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Vinyldimethicone

The Registry of Toxic Effects of Chemical Substances (RTECS 1998) identifies "vinyl dimethylsiloxy-terminated polydimethylsiloxane" with the CAS no. 68083-19-2.

Physical and Chemical Properties

Dimethicone is a white, almost odorless fluid polymer. The Cosmetic, Toiletry, and Fragrance Association (CTFA) specifications for Dimethicone state that the color and odor are specified by the buyer. Also specified by the buyer are the refractive index at 25°C (within the range of 1.4000 to 1.4035), and the kinematic viscosity (provided that the specified mean viscosity at 25°C is not less than 20 centistokes [cs] and not greater than 60,000 cs, and that the specification limits are not greater than ±5% of the specified mean). It contains 98.5% to 101.1% Dimethicone and the total acid number is 0.01 maximum (Nikitakis and McEwen 1990).

One supplier of Dimethicone noted that 100 and 350 cs fluids are generally used for cosmetics (Dow Corning no date).

The National Formulary specifies that Dimethicone have a nominal viscosity in the discrete range between 20 and 12,500 cs and contain between 97.0% and 103.0% of polydimethylsiloxane. Minimum and maximum viscosity cs values were established for nominal viscosity cs values of 20, 100, 200, 350, 500, 1000, and 12500. The specific gravity ranged from 0.946 for the 20-cs nominal viscosity to 0.975 for the 1000-cs nominal viscosity (specific gravity values were not given for the 12500-cs nominal viscosity). The refractive index ranged from 1.3980 for the 20-cs nominal viscosity to 1.4055 for the 12500-cs nominal viscosity (Committee of Revision of the United States Pharmacopeial Convention 1995).

Method of Manufacture

Stearoxy Dimethicone is produced by the reaction of dichloropolydimethylsiloxane with stearyl alcohol (Goldschmidt Chemical Corp. 1998).

Dimethicone is produced by polymerization/equilibration (Goldschmidt Chemical Corp. 1998).

Cetyl Dimethicone is produced by hydrosilylation of C_{16} alpha-olefins (Goldschmidt Chemical Corp. 1998).

Stearyl Dimethicone is produced by hydrosilylation of C_{18} alpha-olefins (Goldschmidt Chemical Corp. 1998).

Manufacturing methods were not available for other ingredients.

Impurities

One supplier of these ingredients noted that Stearoxy Dimethicone, Dimethicone, Cetyl Dimethicone, and Stearyl Dimethicone contain no antioxidants or preservatives. Heavy metals are at 5 ppm maximum, and D4/D5 cyclomethicone is at less than 1% (Goldschmidt Chemical Corp. 1998).

USE

Cosmetic

The functions of Stearoxy Dimethicone and the related cosmetic ingredients are listed in Table 1. Almost all function as conditioning agents for either the hair or skin; the exceptions are Stearamidopropyl Dimethicone (corrosion inhibitor, film former) and Vinyldimethicone (chemical additive). In addition to being conditioning agents, Dimethicone and Cetyl Dimethicone also function as antifoaming agents. C24–28 Alkyl Methicone and C30–45 Alkyl Methicone are also viscosity-increasing agents—nonaqueous (Pepe, Wenninger, and McEwen 2002). One supplier noted that Stearoxy Dimethicone, Cetyl Dimethicone, and Stearyl Dimethicone are also used as "spreading agents" (Goldschmidt Chemical Corp. 1998).

Seven of the 20 ingredients were reported to the Food and Drug Administration (FDA) as in use in January 1998 (FDA 1998). These seven were used in a total of 1884 formulations (Table 2). Two uses of C14–20 polyalkylmethicone were also reported to the FDA, although this ingredient is not listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe, Wenninger, and McEwen 2002).

Recent data submitted to the Cosmetic Ingredient Review (CIR) from one source indicated use of Stearoxy Dimethicone at ≤3.0%, Dimethicone at ≤15%, Cetyl Dimethicone at ≤3.0%, and Stearyl Dimethicone at ≤5.0% (Goldschmidt Chemical

TABLE 1
Cosmetic function of Dimethicones and Methicones

Ingredient	Function[1]	Used in 1998[2]
Stearoxy Dimethicone	Skin-conditioning agent—emollient; spreading agent[3]	Yes
Dimethicone	Antifoaming agent; skin-conditioning agent—emollient	Yes
Methicone	Skin-conditioning agent—occlusive	
Amino Bispropyl Dimethicone	Hair-conditioning agent	
Aminopropyl Dimethicone	Hair-conditioning agent	
Amodimethicone	Hair-conditioning agent	Yes
Amodimethicone Hydroxystearate	Hair-conditioning agent	
Behenoxy Dimethicone	Skin-conditioning agent—emollient	Yes
C24–28 Alkyl Methicone	Skin-conditioning agent—emollient; viscosity increasing agent—nonaqueous	
C30–45 Alkyl Methicone	Skin-conditioning agent—occlusive; viscosity increasing agent—nonaqueous	
C30–45 Alkyl Dimethicone	Skin-conditioning agent—occlusive	
Cetearyl Methicone	Skin-conditioning agent—occlusive	Yes
Cetyl Dimethicone	Antifoaming agent; skin-conditioning agent—occlusive; spreading agent[3]	Yes
Dimethoxysilyl Ethylenediaminopropyl Dimethicone	Hair-conditioning agent	
Hexyl Methicone	Skin-conditioning agent—emollient	
Hydroxypropyldimethicone	Hair-conditioning agent; skin-conditioning agent—miscellaneous	
Stearamidopropyl Dimethicone	Corrosion inhibitor; film former	
Stearyl Dimethicone	Skin-conditioning agent—occlusive; spreading agent[3]	Yes
Stearyl methicone	Skin-conditioning agent—occlusive	
Vinyldimethicone	Chemical additive	

[1]Pepe, Wenninger, and McEwen 2002.
[2]FDA 1998.
[3]Goldschmidt Chemical Corp. 1998.

Corp. 1998). Concentration of use data provided by the CTFA are given in Table 2 (CTFA 1999).

Current concentrations of use may be compared with historical data from industry reports to FDA in 1984 in which Stearoxy Dimethicone was used at $\leq$5% (51 uses total), Dimethicone was used predominately at $\leq$25%, with one use at 25% to 50% (1012 uses total), Methicone was used in two formulations at $\leq$1% but also in one formulation at $>$50%, and Amodimethicone was used in nine products at unknown concentrations (FDA 1984).

According to the Ministry of Health, Labor and Welfare (MHLW) in Japan, Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are not restricted in any manner in cosmetic formulations (MHLW 2001).

Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are not listed in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Commission, 2003).

TABLE 2
Product formulation data

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Stearoxy Dimethicone		
Eye shadow (506)	—	3%
Eye lotion (18)	—	2%
Hair spray (aerosol fixative) (261)	—	0.1%
Tonics, dressings, and other hair-grooming aids (549)	—	0.2%
Foundations (287)	—	0.7%
Lipstick (790)	—	3%
Face powders (250)	1	—
Makeup bases (132)	1	0.9%
Skin cleansing (653)	1	0.5%
Face and neck skin care (excluding shaving) (263)	3	2%
Body and hand skin care (excluding shaving) (796)	7	2%
Moisturizing creams, lotions, powders, and sprays (excluding shaving preparations) (769)	5	2%
Night skin care (188)	1	—
Other skin care preparations (692)	2	—
Suntan gels, creams, and liquids (136)	—	3%
1998 total for Stearoxy Dimethicone	21	
Dimethicone		
Baby lotions, oils, powders, and creams (53)	7	2%
Other baby products (29)	1	2%
Bath oils, tablets, and salts (124)	1	—
Bubble baths (200)	1	—
Other bath preparations (159)	4	—
Eyebrow pencil (91)	1	13%
Eyeliner (514)	6	1%–5%
Eye shadow (506)	55	1%–10%
Eye lotion (18)	5	0.5%–1%
Eye makeup remover (84)	2	4%
Mascara (167)	20	0.3%–4%
Other eye makeup preparations (120)	22	—
Colognes and toilet waters (656)	3	—
Sachets (28)	1	—
Perfumes (28)	—	16%
Other fragrance preparations (148)	30	5%–6%
Hair conditioners (636)	103	0.2%–10%
Hair sprays (aerosol fixatives) (261)	23	0.2%–0.6%
Hair straighteners (63)	1	—
Permanent waves (192)	2	—
Rinses (noncoloring) (40)	4	0.4%–3%
Shampoos (noncoloring) (860)	72	0.08%–4%
Tonics, dressings, and other hair-grooming aids (549)	28	1%–10%
Wave sets (55)	1	—
Other hair preparations (276)	15	10%–80%
Hair dyes and colors (1572)	1	—
Hair tints (54)	28	—

(Continued on next page)

TABLE 2
Product formulation data *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Other hair-coloring preparations (59)	—	0.5%
Blushers (all types) (238)	86	3%–23%
Face powders (250)	87	0.3%–30%
Foundations (287)	122	1%–16%
Lipstick (790)	12	0.6%–20%
Makeup bases (132)	11	4%–23%
Rouges (12)	1	1%
Makeup fixatives (11)	2	24%
Other makeup preparations (135)	14	3%
Basecoats and undercoats (48)	3	0.001%
Cuticle softeners (19)	2	—
Nail creams and lotions (17)	4	0.6%–1%
Nail extenders (<4)	1	0.001%
Nail polish and enamel (80)	16	0.001%–3%
Other manicuring preparations (61)	10	—
Other oral hygiene products (6)	—	0.001%
Bath soaps and detergents (385)	6	0.5%–0.8%
Deodorants (underarm) (250)	9	0.5%–23%
Other personal cleanliness products (291)	30	3%
Aftershave lotion (216)	18	0.5%–2%
Preshave lotions (all types) (14)	1	—
Shaving cream (139)	8	0.5%–1%
Other shaving preparation products (60)	5	3%
Cleansing (653)	43	0.07%–3%
Depilatories (28)	—	0.5%–3%
Face and neck skin care (excluding shaving) (263)	63	0.0001%–10%
Body and hand skin care (excluding shaving) (796)	228	0.5%–10%
Foot powders and sprays (35)	8	—
Moisturizing (769)	200	0.5%—10%
Night skin care (188)	41	1%–2%
Paste masks (mud packs) (255)	13	2%
Skin fresheners (184)	2	0.3%–5%
Other skin care preparations (692)	111	5%
Suntan gels, creams, and liquids (136)	27	1%–15%
Indoor tanning preparations (62)	29	1%–5%
Other suntan preparations (38)	9	4%
1998 total for Dimethicone	1695	
Amodimethicone		
Colognes and toilet waters (656)	1	—
Hair conditioners (636)	67	0.7%–3%
Hair sprays (aerosol fixatives) (261)	2	—
Hair straighteners (63)	2	0.6%
Permanent waves (192)	18	—
Rinses (noncoloring) (40)	1	—
Shampoos (noncoloring) (860)	5	—
Tonics, dressings, and other hair-grooming aids (549)	9	0.0004%–0.7%

(Continued on next page)

TABLE 2
Product formulation data (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Other hair preparations (276)	17	—
Hair dyes and colors (1572)	41	—
Hair bleaches (113)	1	—
Other hair-coloring preparations (59)	1	2%
Hair lighteners with color (6)	1	—
Wave sets (55)	—	0.7%
1998 total for Amodimethicone	166	
Behenoxy Dimethicone		
Foundations (287)	—	2%
Face and neck creams, powders, lotions and sprays (excluding shaving preparations) (263)	—	2%
Paste masks (mud packs) (255)	—	3%
Hair conditioners (636)	1	—
Other hair preparations (276)	2	—
Suntan gels, creams, and liquids (136)	—	2%
1998 total for Behenoxy dimethicone	3	
C14–20 Polyalkylmethicone[a]		
Eyebrow pencil (91)	1	—
Lipstick (790)	1	—
1998 total for C14-20 Polyalkylmethicone	2	
C24–28 Alkyl Dimethicone		
Lipstick (790)	—	2%
1998 total for C24–28 Alkyl Methicone	—	
C30–45 Alkyl Dimethicone		
Suntan gels, creams, and liquids (136)	—	2%
1998 total for C30–45 Alkyl Methicone	—	
Cetearyl Methicone		
Face and neck creams, powders, lotions and sprays (excluding shaving preparations) (263)	—	0.5%
Lipstick (790)	1	0.6%–1%
1998 total for Cetearyl Methicone	1	
Cetyl Dimethicone		
Eye shadow (506)	1	—
Mascara (167)	2	0.5%
Other eye makeup preparations (120)	2	—
Tonics, dressings, and other hair-grooming aids (549)	1	—
Blushers (all types) (238)	5	4%–10%
Face powders (250)	2	0.9%–3%
Foundations (287)	2	6%
Lipstick (790)	—	4%–5%
Makeup bases (132)	4	—
Other makeup preparations (135)	2	4%
Cleansing (653)	1	—
Face and neck skin care (excluding shaving) (263)	1	—
Body and hand skin care (excluding shaving) (796)	1	2%
Moisturizing (769)	2	—

(Continued on next page)

TABLE 2
Product formulation data (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Suntan gels, creams, and liquids (136)	—	2%
Other suntan preparations (38)	1	—
1998 total for Cetyl Dimethicone	27	
Stearyl Dimethicone		
Mascara (167)	2	0.8%
Eye shadow (506)	—	1%–6%
Makeup bases (132)	—	6%
Makeup fixatives (11)	—	5%
Foundations (287)	1	1%–6%
Lipstick (790)	2	4%–6%
Blushers (all types) (238)	—	6%
Moisturizing (769)	1	—
Paste masks (mud packs) (255)	1	—
Other skin preparations (692)	—	4%
Suntan gels, creams, and liquids (136)	—	4%
1998 total for Stearyl Dimethicone	7	
Methicone		
Baby lotions, oils, powder, and creams (53)	—	0.3%
Eyebrow pencil (91)	—	0.2%–0.9%
Eyeliner (514)	—	0.05%–0.8%
Eye shadow (506)	—	0.05%–0.9%
Eye makeup remover (84)	—	0.05%
Mascara (167)	—	0.1%–0.2%
Other eye makeup preparations (120)	—	0.02%
Other hair coloring preparations (59)	—	0.3%
Blushers (all types) (238)	—	0.5%–0.9%
Face powders (250)	—	0.08%–5%
Foundations (287)	—	0.03%–2%
Lipstick (790)	—	0.06%
Makeup bases (132)	—	0.7%
Makeup fixatives (11)	—	0.6%
Other makeup preparations (135)	—	0.01%
Nail polish and enamel (80)	—	0.009%
Body and hand skin care (excluding shaving) (796)	—	0.3%
1998 total for Methicone	0	

[a]C14–20 Polyalkylmethicone is not listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger, Canterbery, and McEwen 2000).

Noncosmetic

Food

In 1979, the Joint Expert Committee on Food Additives (JECFA) of the WHO established an acceptable daily intake (ADI) level for Dimethicone of 0 to 1.5 mg/kg body weight. The ADI applied, "only to compounds with a relative molecular mass in the range of 200–300" (FAO/WHO 1994).

The Select Committee of GRAS Substances (SCOGS) of the Federation of American Societies for Experimental Biology (FASEB) evaluated the safety of Dimethicone (under the name methylpolysilicones) for food use. The Select Committee was of the opinion:

> The bulk of food grade methylpolysilicones consists of high molecular weight compounds which are not absorbed to any appreciable extent from the intestinal tract. However, these silicones may also contain some low molecular weight (<1000) polymers which might be absorbed. Prudence dictates that food grade specifications should be modified to minimize the presence of absorbable components.

The Select Committee concluded that there was no evidence that demonstrated or suggested grounds to suspect that Dimethicone was hazard to the public when used at levels, "that are now current or that might be reasonably expected in the future." At the time, daily intake was estimated at 0.1 μg/kg/body weight (FASEB 1981).

The FDA has included "siloxanes and silicones, dimethyl . . ." as acceptable defoaming agents in the manufacture of paper and paperboard for use in packaging, transporting, or holding food. The regulation appears in the Code of Federal Regulations (CFR) at 21 CFR §176.210.

Pharmaceutical

The FDA has proposed classifying Dimethicone as Category 1 (recognized as safe and effective) for use as a skin protectant up to 30% in infants, children, and adults with the labeling: *Warning. Not to be applied over puncture wounds, infections, or lacerations* (FDA 1978). The FDA has also proposed Dimethicone as Category 1 in the treatment and prevention of diaper rash (FDA 1990).

At one time, Dimethicone was used in antacid formulations (Locock 1971). Now, simethicone (not contained in this report) is used (Harvey 1990).

GENERAL BIOLOGY

Dimethicone Absorption and Excretion

Oral Delivery—Animal Studies

Dow Corning Corp. (1956) orally administered an antifoam compound containing 28% [^{14}C]-Dimethicone to two lactating dogs (25 g given to ~9-kg animals) and one albino rat (0.58 g given to ~170-g animal, sex not given). No evidence of assimilation was observed in the rat. Traces of siloxanes were found throughout the body of both dogs. It was estimated that 0.0001% of the dose had been absorbed from the gastrointestinal (GI) tract.

The University of Birmingham (1968) reported a study in which four beagle dogs (two of each sex) were fed an antifoam compound (91% Dimethicone) at a dose of 300 mg/kg/day for 120 days. The material was mixed with a small amount of meat and given prior to the main meal to ensure that all of the dose was eaten. Total silicon consumption was between 300 and 500 g. A control group received untreated feed. Urine and feces were collected periodically. At the end of dosing, dogs were fed untreated feed for 5 days and then killed. Blood samples were taken and major organs were weighed and examined for microscopic and histopathologic changes and for silicon content. Average output of urinary silicate was not increased in treated dogs. Fecal silicon output was approximately equal to the amount ingested. Silicon was not detected in any organ. One dosed male had a healed gastric ulcer. The spleen of one dosed female had areas of atrophy with wide fibrous trabeculation. The other treated female had a slightly reddened rugae in an area of the stomach and adherent mucus in the intestine, but was microscopically normal. The antifoam compound was considered not absorbed by beagle dogs.

Dow Corning Corp. (1972a) gave a 41.8-mg/kg oral dose of [^{14}C]-Dimethicone (360 fluid with a specific activity of 0.5 mCi/g) to a male rhesus monkey. The animal was held in a unit that prevented respiratory air from being contaminated with volatile products from feces and urine. Air, feces, and urine were analyzed. Virtually all radioactive label was found in the feces. By 70.5 h after dosing, 65.4% of the dose was recovered in the feces. An additional 27.3% of the dose was recovered over the next hour, with only trace amounts after that. Analysis of toluene extracts of the fecal samples established that Dimethicone was excreted unchanged.

Dow Corning Corp. (1989a) gave male Sprague-Dawley rats a single oral dose of [^{14}C]-Dimethicone fluid (either 35 or 1000 cs, with unspecified specific activity) at either 250 or 2500 mg/kg. In a repeated-dose study, rats were fed 0.5% or 5.0% Dimethicone for 13 days followed by a single oral dose of the radioactive Dimethicone at either 250 or 2500 mg/kg. Plasma, excreta, organs, and tissues were collected at 4, 8, 24, and 48 h post dosing and analyzed for radioactivity via liquid scintillation spectrophotometry. Most of the test material was found in the GI tract at 4 and 8 h and in the feces at 24 and 48 h after administration of [^{14}C]-Dimethicone fluid. Anal leakage was observed with the 35 cs fluid at the 2500-mg/kg dose. Trace activity was detected in the urine and scattered tissue samples until 8 h; no activity was detected in tissues or organs at 48 h. Dimethicone was considered to be rapidly excreted from the GI tract following gavage.

Oral Delivery—Human Studies

In a report from the University of Birmingham (1967a), four subjects were instructed to ingest a capsule containing 376.5 mg silicone (an antifoam product containing 91% Dimethicone) twice a day for 10 days. Two subjects completed the protocol. Daily fecal samples were collected from the two during the last 3 days of the dosing period, and 24-h urine samples were collected from all four during the last 5 days. Fecal analysis detected a silicone output that was slightly greater than the intake. The authors considered that the short sampling time had not established a quanitative balance between oral intake and fecal output. No significant increase in soluble silicate was detected in the urine. In studies with other species, the authors stated that almost 99% and 82.5% of the administered silicone was recovered in the 4-day feces of rats and rabbits, respectively. They concluded that Dimethicone was unlikely to be absorbed from the GI tract of humans, rats, and rabbits.

Dow Corning Corp. (1974) studied the absorption and elimination of silicon contained in two Dimethicone antifoam preparations in human tests. Each of the two samples was given as a single oral dose of 100 mg/kg to six humans or as a single dose (100 mg/kg) of an emulsion (30 mg/kg solids) to five humans. Total and organosoluble urinary silicon output (for 72 h post administration) and organosoluble silicon output in expired

air (8-h value) were measured. The compound that contained <0.22% low-molecular-weight polymers (in 91% Dimethicone) did not produce a significant increase in total or organosoluble urinary silicon. Further, no organosilicon compounds were detected in the expired air. An increase in all three parameters was observed with the second compound, which contained 10% low-molecular-weight polymers (in 93% Dimethicone). The urine contained 1.8% and 3.3% of the administered dose of the compound and emulsion, respectively. The expired air contained approximately 0.25% of the given dose. It was suggested that the increased silicon concentrations found with the second Dimethicone sample represented organosoluble silicon rather than inorganic silicon (silica). Approximately 25% of the urinary silicon was an unidentified form of a soluble organosilicon compound. The exhaled material contained primarily octamethylcyclotetrasiloxane and small amounts of decamethylcyclopentasiloxane.

Dermal Delivery—Human Studies

Hobbs, Fancher, and Calandra (1972) applied a 100 cs Dimethicone fluid (TX-225) once daily (50 mg/kg) to the back of five Caucasian males for 10 days. The material was evenly distributed over the entire back surface and no special covering was required. After 20 h of exposure, the excess material was rinsed off. Daily logs of diet were maintained and subjects were asked to refrain from eating raw leafy vegetables during the study. Subjects provided samples of home drinking water and beer, so that dietary silicon contributions could be quantified.

Absorption was measured as silicon in blood and urine. Baseline concentrations were established for several days (up to 25) prior to dosing. Samples were taken on days 1, 3, 6, 8, and 10 during the dosing period. No significant difference between pretest and test urinary silicon concentrations were found in four subjects. One subject had increased urinary silicon ($p = 0.05$) that was attributed to a large value on day 10, accompanied by large urine output on that day. Another two subjects had consistently greater total urinary silicon concentrations throughout the study compared to other subjects. The finding was attributed to relatively high concentrations of silicon in the subjects' home drinking water, high beer intake, and generally greater urine output. Statistical analysis of group data indicated no significant increase in urine silicon concentrations. No increase in blood silicon concentrations was noted in any subjects. The investigators concluded that there was no evidence of dermal absorption of Dimethicone (Hobbs, Fancher, and Calandra 1972).

Absorption Enhancement by Dimethicone

Two clinical studies investigated the effects of various lipophilic vehicles on the skin penetration of methyl nicotinate. Dimethicone 100 was selected as the standard because it was not expected to exert "specific vehicle effects" due to its high molecular weight (6700 Da). As expected, Dimethicone did not alter drug penetration (Leopold and Lippold 1995; Leopold and Maibach 1996).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Dimethicone

The acute oral LD_{50} values for various Dimethicone samples, summarized in Table 3, are consistent with the conclusion that Dimethicone is not acutely toxic.

Methicone

Methicone (as L-31) had an oral LD_{50} of >64 ml/kg in male albino rats. No deaths occurred in five rats given that dose (Mellon Institute 1993).

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) had an oral LD_{50} of >16.0 ml/kg in 10 Sprague Dawley rats. Greasy-textured fur was noted. One rat had pneumonia, and pleuritis was observed at necropsy (Myers and Ballantyne 1993).

Short-Term Oral Toxicity

Dimethicone

MacDonald, Lanier, and Deichmann (1960) fed groups of 50 Sprague-Dawley rats (10 of each sex) 1% Dimethicone at one of five viscosities, 30, 350, 1000, 10000, and 60000 cs, for 90 days. A control group received untreated feed. Rats were killed after the dosing period and examined for gross lesions. Feed consumption, weight gain, hematological parameters (total and differential leukocyte counts, hematocrit, and hemoglobin measured on days 45 and 90), organ weights (heart, lungs, liver, spleen, kidneys, and testes), microscopic examination (spleen, kidneys, liver, testes/ovaries, uterus, aorta, stomach, intestines) were similar between dosed and control rats. One rat of the 60,000-cs group had an aggregation of leukocytes in the myocardium of the right ventricle of the heart. Varying degrees of inflammation were noted in the lungs.

In a study at the University of Birmingham (1967b), groups of 20 rats (10 of each sex) were fed 0.1% or 1% of an antifoam preparation containing 91% Dimethicone for 90 days. It was estimated that rats consumed almost 22.5 g of the compound during the dosing period. Rats were then transferred to a control diet and a 24-h urine specimen was collected for silicate content analysis. Rats were killed after 2 weeks of feeding the control diet and were necropsied. Blood samples were taken from the caudal vein and the lungs; any detectable lymphoid tissue was examined microscopically. The liver, kidneys, spleen, testes, and intestine were analyzed for silicone content.

No significant differences were observed in body weight gain, serum parameters (sodium, potassium, serum glutamic oxaloacetic transaminase [SGOT], serum pyruvic glutamic transaminase [SPGT], total protein, albumin, globulin, hemoglobin concentration, packed cell volume [PCV], total white cells, polymorphonuclear leukocytes, eosinophils, lymphocytes, and monocytes), urine-concentrating ability, protein content,

TABLE 3
Acute oral toxicity of Dimethicone

Dimethicone sample	Oral LD_{50}	Reference
	Mice	
35% aqueous dispersion as TX 184A and 184B	>10.0 ml/kg	Hill Top Research 1967
	Rats	
3.26% in a caulking compound	26.85 g/kg	Food and Drug Research Labs 1978
3.26% in a caulking compound	>17.22 g/kg (approximate) Substance blocked airways	Food and Drug Research Labs 1979a
6.9% in rubber adhesive sealant	>8.49 g/kg (approximate) Substance blocked airways	Food and Drug Research Labs 1979b
15% in emulsion	12.3 ml/kg (males) 6.50 ml/kg (females)	Bushy Run Research Center 1984
15.7% in a rubber adhesive sealant	23.12 g/kg (approximate) Substance blocked airways	Food and Drug Research Labs 1980
15.7% in caulking	6.98 g/kg	Food and Drug Research Labs 1981
35.0% in emulsion	>40 ml/kg	Food and Drug Research Labs 1977a
38.0% in emulsion	>40 ml/kg	Food and Drug Research Labs 1977b
50% aqueous dispersion	>10.0 ml/kg	Dow Corning Corp. 1972b
81.8% in a putty	21.2 g/kg	Food and Drug Research Labs 1977c
85.8% in putty	19.9 g/kg	Food and Drug Research Labs 1977d
85.8% in a putty (given as a 75% suspension in 95% ethanol)	31.9 g/kg (discounting ethanol effects)	Food and Drug Research Labs 1977e
XF-1-3753	>10.0 g/kg	Dow Corning Corp. 1970
XF-2-1075	>15.4 g/kg	Dow Corning Corp. 1975
X2-1133 heat-transfer fluid	≥15.4 g/kg	Dow Corning Corp. 1977
X2-1162 heat-transfer fluid	≥15.4 g/kg	Dow Corning Corp. 1978a
Heat-transfer fluid	≥15.4 g/kg	Dow Corning Corp. 1978b
Trade compound (>90% Dimethicone)	>17 g/kg	Springborn Labs 1991
	Guinea pigs	
Two 35% aqueous dispersions	>30.0 g/kg	Dow Corning Corp. 1949
Two 35% aqueous emulsions	>10.0 g/kg	Dow Corning Corp. 1950

silicate concentration, or organ weight. Male rats of the 1% group weighed significantly more ($p < 0.05$) than controls at the time of necropsy. No changes were noted at microscopic examination. Silicone was not detected in the spleen, kidneys, liver, testes, or intestine (University of Birmingham 1967b).

Atlas Chemical Industries (1969) fed an antifoam compound containing 95% Dimethicone to groups of six dogs (three of each sex) at concentrations of 120, 380, or 1200 mg/kg/day for 90 days. Body weight gain, serum chemistry parameters (urea, nitrogen, glucose, sodium, potassium, chloride, cholesterol, alkaline phosphatase, and SGOT), hematology parameters (PCV, hemoglobin, sedimentation rate, leukocyte count, differential count, and plasma prothrombin time [PTT]), urinary parameters, and gross and microscopic examination of tissues and organs were similar to controls groups.

Dow Corning Corp. (1972c) described Dimethicone fluids that contain low-molecular-weight linear and cyclic dimethylpolysiloxanes as "ubiquitous trace components" and conducted a study of the effects of a 4-week oral exposure to 20-cs Dimethicone fluid using rats. The study measured changes in organ weight, thyroid function, and tissue elemental silicon accumulation. Rats were fed either the 20 cs fluid containing not more than 0.04% linear/cyclic dimethylpolysiloxanes (where number of Si atoms ≤ 6) or a "spiked" solution containing 5% each of four linear/cyclic dimethylpolysiloxanes. Controls were sham-dosed. No changes were noted with respect to final body weights or organ weights. Whole body oxygen consumption was not altered by treatment. Changes were seen in serum total cholesterol concentrations, but were not consistent with regard to compound, sex, or route of administration. The authors observed that females accumulated more organosiloxane-derived silicone in depot fat than males. Administration of cyclic compounds resulted in greater fat silicone concentrations in fat compared to administration of linear compounds.

Dow Corning Corp. (1989b) investigated silicon oil as a low-calorie alternative to traditional edible oils. Groups of 30 CD-1 mice (15 of each sex) were fed diets containing 5% and 10% Dimethicone fluid for 90 days. A control group received

untreated feed. Mice were killed at the end of dosing and major organs were collected, weighed, and examined for microscopic lesions. No signs of toxicity, changes in behavior, or mortality were seen in any group. Mean body weights were comparable between treated and control mice. Treated mice consumed significantly more feed; the increased intake was considered to compensate for the non-nutritive components of the diet. Anal leakage was observed in treated mice and was greatest in females of the 10% group, but stool consistency was similar to controls. Organ weights were similar and no microscopic lesions were observed.

At the Dow Corning Corp. (1989c), groups of 40 Sprague-Dawley rats (20 of each sex) were fed 1%, 5%, or 10% Dimethicone at one of three viscosities, 35, 350, and 1,000 cs (total of nine treatment groups) for 90 days. Two control groups received untreated feed. Blood samples were obtained by cardiac puncture from 20 rats of each group (10 of each sex) and urine was collected from 10 of these 20 rats (5 of each sex) at the end of the study. All rats were killed and major organs were collected, weighed, and examined for microscopic lesions.

No signs of toxicity or changes in behavior were observed. One control female and two treated male rats were moribund and were killed. The authors did not consider the deaths treatment related. Slight-to-marked anal leakage was observed in rats of the 10% group; leakage decreased with increasing viscosity. Slight leakage was also observed in rats of the 5% group. Stool consistency was similar to controls. Although occasionally body weight increase was significantly greater in treated male rats, most of the mean body weight data was comparable between treated and control groups. Treated rats consumed more feed and, as in the mouse study, the finding was considered a compensatory response to the non-nutritive components of the diet.

Changes in blood, clinical chemistry, bone marrow, or urinary parameters were observed occasionally but were not considered biologically significant. Some mean absolute and relative organ weights were significantly different between treated and controls, but the findings were not considered of biological or toxicological significance.

Treatment-related changes were observed in the eyes (corneal opacities and neovascularization). Some rats also had mineralization of the cornea. Mild chronic inflammation of the cornea was observed microscopically. The ocular findings were not dose dependent and could have resulted from direct irritation from the Dimethicone fluid in the feed. Three lymphomas were observed in treated males (two lymphocytic lymphomas in the 10%, 1000-cs group, and one undifferentiated lymphoma in the 1%, 35-cs group). The neoplasms were not considered treatment related because the incidence was within that of the historical control and the incidence was not duplicated in the follow-up study (described below) using a larger group of rats (Dow Corning Corp. 1989c).

Because of the lymphomas seen in the study described above, male rats were selected for further study (Dow Corning Corp. 1989d). Groups of 100 were fed 10% Dimethicone fluid at one of three viscosities (35, 350, and 1000 cs) for 90 days. Two control groups received untreated feed. At the end of dosing all rats were killed, major organs and blood were collected and examined for microscopic and hematologic changes. No overt signs of toxicity or behavioral changes were observed. Two treated rats were killed; one was moribund. A statistically significant difference in mean body weight was observed between rats of the 35-cs group and one control group, but was not considered treatment related. Like earlier studies, treated rats had significantly greater mean feed consumption. No significant changes were observed in hematology parameters or at necropsy and histopathologic examination.

Subchronic Oral Toxicity

Dimethicone

Child, Paquin, and Deichmann (1951) reported a study in which groups of two mongrel dogs were fed Dimethicone (83% in an antifoam compound) at 0.3, 1.0, or 3.0 g/kg/day in ground horse meat 5 days per week for 3 months. A control group was fed untreated horse meat. Afterwards, dogs were fed the Dimethicone in commercial dog food for another 3 months. Dogs were killed at the end of the study; organs and tissues were weighed and examined for microscopic lesions. Both dogs of the 3.0-g/kg group had a thin layer of viscid, gray material covering the intestinal tract and enlarged lymphoid aggregates of the small intestine. The liver of dosed dogs had pigment deposits that were revealed to be bile; quantities deposited in the Kupffer and hepatic cells were directly related to the daily dosing. The authors concluded that the antifoam compound would be harmless should traces be absorbed by humans "from time to time."

Dow Corning Corp. (1954a) fed an antifoam compound (83% Dimethicone) in an emulsion to rats at concentrations of 0.1%, 0.3%, and 1.0% for 120 days. No adverse effect was noted in growth, appearance, behavior, mortality, hematologic parameters, or blood urea nitrogen (BUN). An increase in the spleen and liver weight was noted in rats of the 1.0% group.

Chronic Oral Toxicity

Dimethicone

Rowe, Spencer, and Bass (1950) fed 0.3% (by weight) Dimethicone antifoam compound to groups of 50 Wistar rats (25 of each sex) for 2 years. A control group received untreated feed. Rats were killed at the end of the study. Gross appearance, behavior, growth, and survival were comparable between treated and control animals. Treated rats had greater weight gains compared to controls. No significant differences were observed in the weights of the heart, liver, kidneys, spleen, and testes. BUN and hepatic lipid values were comparable. At microscopic examination, pulmonary lesions, changes in the ovaries and uterus, and mild fatty changes in the liver and tubular epithelium of the kidneys were observed in all treated rats.

Carson, Weinberg, and Oser (1966) fed Dimethicone, as it appeared in a fluid (50 or 350 cs) or in an antifoam compound, as 1% of the diet to groups of rats (for 1 year) and rabbits (for 8 months). The number of animals was not stated. Control groups received untreated feed. Feed and water were available ad libitum. Blood and urine samples were taken periodically. Necropsy was done at the end of dosing. No adverse effects were observed. At the same time, additional groups of rats and rabbits received Dimethicone plus 0.8% cholesterol. The control group for this portion of the study received the cholesterol-supplemented feed. Adverse effects were observed in animals fed cholesterol (both with and without Dimethicone) compared to basal controls. The changes were attributed to the cholesterol.

Acute Dermal Toxicity

Dimethicone

Bushy Run Research Center (1984) reported that a commercial emulsion containing 15% Dimethicone had a dermal LD_{50} of approximately 16.0 ml/kg in rabbits. At that dose, Dimethicone killed 2/5 males and 2/5 females. A Dimethicone dose of 8.0 ml/kg killed 1/5 males and 0/5 females.

Hazleton France (1988a) applied a colorless slightly viscous liquid containing Dimethicone (2008 mg/kg; 2.07 ml/kg volume applied) to the clipped skin of 10 Sprague-Dawley rats (5 of each sex). The exposure area was approximately 10% of the total body surface. The concentration of Dimethicone in the liquid was unreported. The site was covered for 24 h of exposure and then rinsed with water. Observations were made at 15 min, 1 h, 2 h, 4 h, and then once daily for 14 days. Necropsy was done at the end of the study. No adverse reactions were noted. The dermal LD_{50} was $>$2008 mg/kg.

Springborn Labs (1991) applied a trade mixture (containing $>$90% Dimethicone) in a single dermal application (2000 mg/kg) to a group of 10 rabbits (5 of each sex). Rabbits were killed on day 15 and necropsied. Decreased feed consumption, diarrhea, mucoid/soft stool, and application site dermal irritation were observed. No changes were noted at necropsy. The acute dermal LD_{50} was $>$2000 mg/kg.

Methicone

Methicone (as L-31) had a dermal LD_{50} of $>$20 ml/kg in albino rabbits. The dose was the maximum amount of fluid that could be kept in contact with the skin under impervious covering. At that dose (24-h contact), none of four rabbits died and no irritation was noted (Mellon Institute 1993).

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) had a dermal LD_{50} of $>$16.0 ml/kg in New Zealand white rabbits. The rabbits (five of each sex) had received a 24-h occlusive exposure to the single dose and were observed for 14 days. Erythema and edema were noted, but no signs of systemic effects were observed. No gross lesions were noted at necropsy (Myers and Ballantyne 1993).

Short-Term Dermal Toxicity

Dimethicone

Dow Corning Corp. (1969) reported that three formulations intended for application to the feet, containing 6%, 11%, or 25% Dimethicone, were applied daily (2000 mg/kg) to clipped sites on male rabbits for 7 days. A control group was treated with a formulation containing 22% Dimethicone. Another control group was left untreated. Rabbits were killed at the end of the study and observed for gross lesions. No adverse reactions, effects on body weights, or pathologic changes were noted.

As described earlier, Dow Corning Corp. (1972c) conducted a study of the effects of a 4-week oral exposure to 20-cs Dimethicone fluid using rats. Rats also were dermally dosed with either the 20 cs fluid containing not more than 0.04% linear/cyclic dimethylpolysiloxanes (where number of Si atoms $\leq$ 6) or a "spiked" solution containing 5% each of four linear/cyclic dimethylpolysiloxanes. Controls were sham-dosed. The study measured changes in organ weight, thyroid function, and tissue elemental silicon accumulation. No changes were noted with respect to final body weights or organ weights. Whole body oxygen consumption was not altered by treatment. Changes were seen in serum total cholesterol concentrations, but were not consistent with regard to compound, sex, or route of administration. Dermal dosing resulted in less silicon accumulation in the fat than did oral administration.

Acute Inhalation Toxicity

Dimethicone

Hazleton Labs (1953) exposed two dogs, seven guinea pigs, and seven rats to a "200 fluid" aerosol (containing unspecified concentration of Dimethicone) at a concentration of 2.12 mg/L for 6 h. No particle size was reported. Three guinea pigs died during the study. At the end of dosing, almost all of the animals were killed for necropsy and collection of tissues. One dog was observed for an additional month before it was killed. Hyperventilation, excitability, and salivation were noted during exposure. All animals killed immediately after dosing had hyperemic lungs with hemorrhagic areas. At microscopic examination edema, hemorrhage, and mild interstitial irritation of the lungs were found. The dog killed 1 month later had small areas of dark coloration of the lungs, but microscopic findings were similar to those found in animals that had been immediately killed. The authors concluded that this fluid produced only minimal signs of toxicity and was essentially nontoxic.

Methicone

Methicone (as L-31) generated as a concentrated vapor caused no mortality when six female albino rats were exposed for 8 h. The calculated concentration was 0.78 mg/L. Rats appeared normal throughout the subsequent 2-week observation

period and no remarkable lesions were noted at necropsy. No further details were given (Mellon Institute 1993).

Hexyl Methicone

Aerosolized Hexyl Methicone was administered by whole-body inhalation exposure to groups of 10 Fischer F344/N rats (5 of each sex) for a 4-h exposure. The initial target dose was 5.0 mg/L (5.08 mg/L achieved) with particles having a mass median aerodynamic diameter (MMAD) of 0.27 μm. All exposed rats died within 24 h. A second exposure was done using a 2.0 mg/ml dose with an MMAD of 0.29 μm. Four males died within 2 h of exposure; the remaining six rats survived the 14-day observation period. A third exposure was then conducted with a targeted dose of 1.0 mg/L (0.95 mg/L achieved), with an MMAD of 0.27 μm. Two males died immediately after the exposure; the remaining rats survived through the observation period. Dyspnea and decreased activity or hypoactivity were clinically observed in surviving rats immediately after exposure. Lesions at necropsy of rats that died included dark red or mottled lungs and/or fluid filled trachea; no unusual findings were noted at necropsy of rats that had survived the observation period. The calculated LC_{50} was 1.12 mg/L for males, between 2.0 and 5.0 mg/L for females, and 1.8 mg/L for the combined sexes (IIT Research Institute 1994).

Vinyldimethicone

Sprague Dawley rats were placed in a sealed chamber and exposed for 6 h to a near-saturation vapor of a substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2). No particle size was reported. Rats were observed for 14 days after exposure. No deaths or gross lesions were observed. No further details were provided (Myers and Ballantyne 1993).

Short-Term Dermal Toxicity

Dimethicone

A cat, rabbit, guinea pig, two rats, and four mice were sprayed for 4 hours with an atomizer containing 10 ml/kg of a Dimethicone sample. The sample contained approximately 110 siloxane units and its viscosity was 140 cs at 20°C. No particle size was reported; but the atomizer output was described as a thick fog that settled rapidly on the animals and the cage. The treatment was repeated 29 days later. The cat, rabbit, guinea pig, and rats had no adverse effects from the exposure. Weight gain was normal during the exposure and 6-week postdosing observation periods, the urine was free from protein, and the blood had no changes in hemoglobin content or in erythrocyte and leukocyte counts. All four mice died. The first died after 20 exposures and the others died during the postdosing period. None were examined microscopically. The authors stated that there was a relatively high mortality rate in mice in the laboratory at the time and that the link between the treatment and deaths was not certain. Overall, the authors concluded that inhalation of silicone oil was harmless (Gloxhuber and Hecht 1955).

Vaginal Irritation

Dimethicone

A mucoadhesive paste (53% Dimethicone) was introduced (0.5 g) via syringe into the vaginal cavity of six albino rabbits. Two control rabbits were dosed with a sodium chloride solution. Tissue was scored according to the Draize scale (maximum score of 8) at 24, 48, and 72 h post dosing. Erythema was noted in three rabbits at 24 h, and in one rabbit at 48 h after treatment. None had erythema at 72 h. No edema or signs of toxicity were observed. The irritation score for the paste was 0.22 (Toxikon Corp. 1991).

Dermal Irritation

Dimethicone

Hazleton Labs (1975) reported a preliminary skin irritation study using six adult albino rabbits (species/sex not stated). A Dimethicone fluid (0.5 ml) was applied for 24 h under occlusive patches to an intact and abraded site (clipped of hair) on each of two rabbits. Sites were scored for erythema and edema at the time of patch removal (24 h) and again 48 h later. The maximum score was 8.0. The authors reported a primary irritation index (PII) of 6.54 and concluded that the material was a severe irritatnt to rabbit skin.

CTFA (1977a) reported no reactions when a Dimethicone sample (100%) was applied in a 24-h patch to the clipped backs of eight rabbits, four with abraded backs.

Dow Corning Corp. (1978a) evaluated intact and abraded sites on rabbits exposed to three heat-transfer fluids (for industrial use) at 24 and 72 h (presumably on a 0–8 scale). The protocol used to test was not reported. The three fluids had PII scores of 0.1, 0.0, and 0.0, respectively (Dow Corning Corp. 1977, 1978a, 1978b). Based on unreported findings, the investigators stated that one fluid, "may be absorbed through the skin in acutely toxic amounts" and recommended dermal absorption toxicity testing.

The Bushy Run Research Center (1984) reported that a 4-h occlusive exposure to 0.5 ml of a commercial emulsion (15% Dimethicone) produced moderate erythema in all six rabbits tested and minor-to-moderate edema in four. The erythema persisted in most of the rabbits for 10 days (rabbits were observed for 21 days). Desquamation developed within 7 days. One rabbit died on day 21; the death was not considered treatment related.

Hazleton France (1989) applied AK 350 (containing an unreported amount of Dimethicone) for 4 h on each of two sites on six New Zealand white rabbits. No irritation was reported at the 1 h scoring or the 72 h scoring.

Springborn Labs (1991) reported a study in which a trade mixture (containing >90% Dimethicone) were applied for 4 h on each of two sites on six New Zealand white rabbits. Slight-to-well-defined erythema and very slight edema was observed at almost all test sites at the 1-h scoring. The irritation diminished with time and had cleared by the 72 h scoring (last scoring). The calculated PII was 0.40. The maximum score was 8.0.

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) was applied in a 4-h occlusive patch (0.5-ml dose) to the clipped, intact dorsal skin of six New Zealand white rabbits (2 to 3.5 kg, sex not given). Sites were scored using the Draize scale for 7 days. The PII was 0.0 (maximum possible = 8.0). No irritation was observed (Myers and Ballantyne 1993).

Cumulative Dermal Irritation

Dimethicone

Dow Corning Corp. (1949) applied two mold release emulsions each containing 35% Dimethicone (Type P and XE-18) in 10 applications over 14 days to the external ears and shaved abdomen of rabbits. The number of rabbits used and actual exposure time were not reported. No reactions were observed in the pinna, but both emulsions produced slight "simple" irritation to the abdomen. In a follow-up study, Dow Corning Corp. (1950) reported that another two 35% aqueous emulsions, tested under similar conditions, produced similar reactions.

Dow Corning Corp. (1953) reported that Dimethicone (as XF-409) applied to the intact skin of the external ear or abdomen of rabbits (number not stated) for a total of 10 applications produced very slight hyperemia after prolonged contact for several days.

Dow Corning Corp. (1954b) reported four irritation studies in which Dimethicone 200 fluid, tested at 99 parts (as XF1-3753) and as a 50% aqueous dispersion (as XEF-4-3561) was applied to three sites: the intact external ear (10 applications), the intact abdomen (10 applications), and abraded abdomen (3 applications) on an unspecified number of rabbits. Exposure time was not reported. The authors concluded that Dimethicone did not produce irritation in these studies.

Gloxhuber and Hecht (1955) painted a rabbit's external ear once daily for 60 consecutive working days with a Dimethicone sample. The sample contained approximately 110 siloxane units and its viscosity was 140 cs at 20°C. No changes were noted compared to the untreated pinna.

These same authors painted the ears of three rabbits twice daily with a 40% Dimethicone emulsion (60 cs at 20°C). One rabbit died on day 10; the death was not considered treatment related. The other two rabbits were painted 60 and 100 times, respectively, without adverse effect (Gloxhuber and Hecht 1955).

Hill Top Research (1967) applied two 35% Dimethicone aqueous dispersions (TX-184A and TX-184B) for an unspecified amount of time to two rabbits. Sites were evaluated for 15 days. No irritation was observed.

Dow Corning Corp. (1975) reported that when tested as a hydraulic fluid (99.7% as XF-21075), Dimethicone produced no reaction in the external ear, hyperemia after the sixth application to the intact abdomen that became moderate with slight edema after the ninth application, and slight hyperemia after the first application to the abraded abdomen.

CTFA (1977b) reported that Dimethicone (100%), applied to the clipped skin of three male Hartley guinea pigs once a day for 3 consecutive days (it was not stated whether or not the site was covered), produced no reaction.

Irritation Barrier

Dimethicone

A cream containing 10% Dimethicone was investigated as a barrier against dermal irritation. The cream was applied to one side of the clipped back of female guinea pigs. Plastic syringe reservoirs containing the irritants toluene, mineral oil, sodium hydroxide, and sodium lauryl sulfate (SLS) were applied for exposure times of 2 or 24 h. Each irritant was tested on three guinea pigs. Punch biopsies were taken from the test site and were examined for pathologic changes. The cream did not significantly protect against irritation by toluene or sodium hydroxide. It did protect against SLS-induced irritation when the SLS had been applied in a hydrophobic phase, but not when a water solution was used. The cream protected against mineral oil-induced skin changes (Mahmoud, Lachapelle, and van Neste 1984).

Dermal Sensitization

Dimethicone

Dow Corning Corp. (1985) applied a gel containing 79% Dimethicone (Q7-2167/68) to the clipped and depilated backs of 10 male Hartley albino guinea pigs. Four 48-h occlusive patches (0.1 ml) were applied in 10 days. At the third application, 0.2 ml Freund's complete adjuvant (FCA) was injected intradermally near the test site. Sites were evaluated at the time of patch removal. Following a 10-day nontreatment period, guinea pigs were challenged at an unexposed site. Challenge reactions were evaluated at 24, 48, and 72 h postapplication. Positive- and negative-control groups (five guinea pigs in each group) were maintained. Hyperemia and edema were each scored on 0–4 scales. Observations during induction were not reported. No reactions were observed at challenge.

Hazleton France (1989) tested a trade mixture (containing >90% Dimethicone) using the Magnusson-Kligman protocol. On induction day 1, groups of 20 Dunkin-Hartley guinea pigs (10 of each sex) received three series of two injections consisting of (1) FCA alone, (2) a 50% *w/w* solution of the test article alone, and (3) FCA plus test article. Because pretesting established that the test article was not an irritant, an SLS patch was applied on day 8. A 48-h occlusive patch of the test material as supplied was applied on day 9. Following an 11-day nontreatment period, a 24-h patch of the test article was applied to a previously unexposed site. Challenge sites were evaluated 24 and 48 h after patch removal. A control group was treated with water. No reactions were observed at challenge.

National Institute of Environmental Health Sciences (1990) reported a study in which Dimethicone fluid was applied (20 μl) to shaved and dermabraded dorsal sites on sixteen female B6C3F$_1$ mice daily for 8 days. Seven days later, mice were

challenged on the dorsal and ventral sides of the left external ear. A hypersensitivity reaction was measured by both the radioisotopic incorporation assay ([^{125}I]-Iododeoxyuridine (IUDR) was injected into the tail vein of all mice the day before challenge) and the mouse ear swelling test (MEST). Following the MEST test, all mice were killed except for eight of the Dimethicone group. The challenged and untreated external ears of killed mice were biopsied and counted in a gamma counter. Seven days later, the eight remaining mice were joined with another group of eight mice that had been treated with saline for 5 days. All of these mice were challenged with an application of Dimethicone on the left external ear and again analyzed by the MEST assay for 2 days. The authors concluded that Dimethicone did not produce a contact hypersensitivity reaction.

Dow Corning Corp. (1991) tested a Dimethicone liquid (Q7-2867) following a modified split-adjuvant protocol. The liquid (0.2 ml) was applied under gauze to 10 male Hartley guinea pigs. Four 48-h occlusive patches were applied in 10 days. FCA was injected at the third application and application of the fourth patch occurred 72 h later. Following a 12-day nontreatment period, a 24-h challenge patch was applied to an unexposed site. Challenge reactions were evaluated at 24, 48, and 72 h post application. Two negative-control groups (saline and alcohol), one positive-control group, and a vehicle-control group were maintained. No irritation was noted during induction, and the Dimethicone liquid did not produce any reactions at challenge.

Ocular Toxicity

Dimethicone

Dow Corning Corp. (1953) reported that Dimethicone (as XF-409) produced very slight pain and irritation for a few hours after instillation into rabbit eyes (number not stated) regardless of whether the eye was subsequently rinsed or unrinsed.

Dow Corning Corp. (1954b) tested Dimethicone as 200 fluid in four studies using rabbits. Dimethicone was reported to produce a slight conjunctival irritation that subsided in 24 h when tested undiluted in rinsed and unrinsed eyes.

Another study (Dow Corning Corp. 1957a) observed essentially no irritation when electrical-grade silicone fluid was tested undiluted, although slight pain and conjunctivitis, which subsided in 24 h, were noted when the electrical-grade silicone fluid was instilled as a 10% solution in propylene glycol. Treated and untreated electrical-grade fluid instilled as a single dose or daily for 5 days produced conjunctival irritation that was slow to heal; the irritation was more severe following repeated exposure (Dow Corning Corp. 1957b).

Dow Corning Corp. (1959) reported very slight but definite conjunctival irritation in another repeated-dose study using rabbits, but details were not available.

Dow Corning Corp. (1968) stated that Dimethicone at 10% and 29% in trade formulations produced essentially no irritation. Slight conjunctivitis or iritis was noted with 35%, but lesions had cleared in 24 h.

Dow Corning Corp. (1970) stated that Dimethicone (as XF-1-3753) produced a very slight conjunctival reponse in a rabbit that subsided within 24 h.

Dow Corning Corp. (1972b) stated that Dimethicone, as a 50% aqueous dispersion (XEF-4-3561), produced slight conjunctivitis in rabbits at 1 h; the conjunctivitis cleared by 24 h.

Dow Corning Corp. (1975) stated that Dimethicone (as XF 2-1075) produced essentially no response when tested in rinsed and unrinsed rabbit eyes.

Hazleton Labs (1975) reported that although Dimethicone (50% in SM2080) was a mild irritant to rabbit eyes following a 2- or 4-s rinsing, it was a severe irritant to unrinsed eyes.

CTFA (1977c) reported that Dimethicone produced a conjunctival reaction when instilled into one conjunctival sac of each of three rabbits. The total score was 4.7 (maximum 110). It was considered a "minimal irritant."

Dow Corning Corp. (1977, 1978a, 1978b) tested three heat-transfer fluids (containing Dimethicone) on six rabbits. The protocol used was not reported but the conjunctiva, cornea, and iris were observed 24 h, 48 h, 72 h, and 7 days after exposure. Two fluids produced no reaction (Dow Corning Corp. 1978a, 1978b), the third produced conjunctival redness in all rabbits and conjunctival chemosis in two rabbits at the 24-h observation (Dow Corning Corp. 1977). The chemosis had cleared by 48 h, whereas the redness persisted through the 72-h scoring, but cleared by day 7. The cornea and iris were not affected.

The Bushy Run Research Center (1984) reported that a 0.1-ml dose of a trade mixture (15% Dimethicone) produced moderate corneal injury, iritis, and conjunctival irritation in all of the six rabbits. A 0.01-ml dose produced moderate conjunctival irritation in all rabbits and moderate iritis in two. A 0.005-ml dose produced minor to moderate conjunctival irritation in all rabbits that cleared in five of six rabbits by 72 h.

Hazleton France (1989) reported that Dimethicone (a major component of trade mixture) was a slight irritant when instilled into one eye of six rabbits followed by a 72-h observation period.

Springborn Labs (1991) instilled 0.1 ml of a trade mixture (containing >90% Dimethicone) into one eye of each of six rabbits, followed by a 7-day observation period. The authors concluded that Dimethicone was a nonirritant based on the European Commission evaluation criteria.

Five 35% aqueous emulsions tested separately produced slight conjunctivitis in rabbits that cleared within 2 days with no corneal damage, although one emulsion produced "immediate and painful irritation" when first instilled (Dow Corning Corp. 1950).

Methicone

Three undiluted methicone oils were each instilled (0.1 ml) into one conjunctival sac of each of two albino rabbits (sex, species, body weights were not given). The contralateral eye served as the control. One dosed eye was rinsed 20 s after exposure with tap water for one min; the other dosed eye was not rinsed. Eyes were examined by a hand slit lamp at 1 and 4 h, and

at 1, 2, and 3 days. None of the three oils produced corneal injury; DF 1040 produced minimal congestion of the iris at 1 h; and all produced mild conjunctival redness that lasted up to 2 days (Dupont De Nemours & Co. 1966).

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) was instilled (0.1 ml undiluted) into the lower conjunctival sac of one eye of six New Zealand rabbits. Eyes were scored for 7 days using the Draize scale. Minor conjunctivitis was noted; the conjunctivitis cleared within 1 to 2 days. The maximum mean score was 6.0 (Myers and Ballantyne 1993).

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Oral

Dimethicone

The Food and Drug Research Labs (1966) tested Dimethicone-containing fluids in oral studies to investigate possible atrophic changes in rat seminal vesicles. The test material was administered directly into the stomach of 10 male Sprague-Dawley rats at a dose of 3.3 ml/kg/day for 6 days. A control group received saline. Feed and water were available ad libitum. Rats were killed at the end of dosing and necropsy was performed. Final body weight and the weight of the seminal vesicles were measured. A Dimethicone sample (TX-158F) produced a significant reduction in the average seminal vesicle to body weight ratio but not in absolute organ weight. Two other Dimethicone samples had no adverse effect.

Atlas Chemical Industries (1970) reported a study in which a medical grade antifoam compound (93% Dimethicone) was given orally to pregnant Wistar rats on gestational days (GDs) 6 to 15 at doses of 0.38, 1.20, and 3.80 g/kg/day. The highest dose was selected to represent 70 times the recommended clinical dose for the treatment of intestinal gas and 1000 times that recommended to treat peptic ulcers. A control group received tap water. Rats were examined by laparotomy on GD 20 at which time fetuses were removed from the uterus. Dams were killed and the ovaries were examined for corpora lutea. The authors concluded that Dimethicone at any dose did not induce significant differences in fetal viability at laparotomy, resorptions, average weight, and gross external, soft tissue, and skeletal anomalies.

Siddiqui (1994) fed an antifoam compound (food-grade Dimethicone) to time-mated New Zealand white rabbits at concentrations of 0%, 0.5%, 1.0%, and 2.5% on GDs 6 to 19. Females were observed daily for clinical signs of toxicity. On gravid day 29, confirmed-pregnant females (20 to 22 per group) were evaluated for gestational outcome. Each live fetus was examined for external, visceral, and skeletal malformations. No overt signs of toxicity in the dams, and no statistically significant differences in feed consumption were observed between treated and control rabbits. No adverse effects were noted in mean maternal body weight or liver weight. The incidence of resorptions among the total fetal population was not altered by feeding the antifoam compound. Male and female pup weights were not affected by the maternal treatment. No significant treatment related adverse effects in the incidence of external, visceral, or skeletal abnormalities were observed.

Dermal

Dimethicone

Kennedy et al. (1976) applied 200 mg/kg Dimethicone (medical grade fluid, 350 cs; suspended in either corn oil or sesame oil in a 1:5 ratio) to the shaved backs of groups of 15 pregnant rabbits on GDs 6 to 18. Other groups received subcutaneous injections of 20, 200, or 1000 mg/kg Dimethicone (diluted in sesame oil, or undiluted at the highest dose). Vehicle control groups were treated with corn oil or sesame oil. Litters were delivered by cesarean section on day 29. The uterus and other genital organs of each dam were inspected. Implantation sites and live and dead pups were counted. Live pups were incubated for 24 h and then killed. Dead pups and two thirds of those killed were cleared and stained for skeletal examination. The remaining pups were necropsied. The investigators considered that the vehicles, corn, and sesame oil had an effect on the incidence of resorptions. No treatment-related fetal abnormalities were found. The incidence of talipes varus in the 200-mg/kg group was at or above the upper limit for historical controls, but the abnormality was not detected at the 1000 mg/kg dose.

Following the same protocol, these authors applied Dimethicone (225 fluid, 10 cs) suspended in corn oil (1:5) (200 mg/kg) to the shaven backs of groups of 15 pregnant rabbits on GDs 6 to 18. Treatment did not affect maternal body weight, weight gains, number of implantation or resorption sites, or viable fetuses. Umbilical hernia was noted in one pup each of the treated and control group; one treated pup had talipes varus. No other abnormalities were observed and 24-h survival was comparable between treated and control pups (Kennedy et al. 1976).

In a study by an unknown author, retrieved from the National Technical Information Service (NTIS 1987a), motor oil containing an unspecified amount of Dimethicone was applied undiluted to the shaved backs of the parental (P_1) and first (F_1) generation of Sprague-Dawley rats, 7 days a week for an 8 week premating period, 3-week mating period, and throughout gestation and lactation. Doses applied were 0.1, 0.4, and 1.5 ml/kg. Twenty pregnant P_1 females from each dose group underwent natural parturition; the remaining 20 were killed on GD 13 and the uteri content was examined for implants. A single male and female were selected from each F_1 litter to produce the F_2 generation; dermal treatment began one day after weaning. All F_1 females were allowed a natural parturition. P_1 and F_1 males were killed at the end of mating. F_2 rats were not treated and were killed at weaning.

No statistically significant difference was detected in the mortality or survival rates in F_1 litters on day 0 (parturition). However, mortality after day 0 was significantly decreased in the

0.4- and 1.5-ml/kg groups. In contrast, mortality in the F_2 litter was significantly increased in the 0.4-ml/kg group on day 0. Body weights and weight gains were significantly reduced in adult F_1 male rats of the 1.5-ml/kg group beginning on week 7 and continuing throughout the mating period. Absolute testes weight was also significantly reduced in these males, but the relative testes to body weight ratio was not significantly different from controls.

Gestating dam body weights were significantly increased in the 0.1- and 0.4-ml/kg group compared to sham controls. No significant differences were noted in F_1 or F_2 litter body weight or body weight gains. External appearance and microscopic features of the F_1 and F_2 skeletal systems were comparable to controls. Mild dermal irritation was observed in P_1 and F_1 rats. Mild epidermal acanthosis was observed in P_1 and F_1 rats of the 1.5-ml/kg group. According to the authors, the motor oil did not induce any significant alterations in the reproductive performance of either the P_1 or F_1 generation (NTIS 1987a).

In a study by an unknown author, retrieved from the National Technical Information Service (NTIS 1987b), motor oil containing an unknown concentration of Dimethicone was applied undiluted (1.5 ml/kg) to the shaved back of 20 timed-pregnant Sprague-Dawley rats on GDs 6 to 15. A sham-control was maintained. No deaths occurred during the study. Mean dam and litter body weight, pup viability, incidence of external, soft tissue, and skeletal abnormalities were comparable between treated and control animals.

GENOTOXICITY

Dimethicone

Mutagenicity studies done on Dimethicone are summarized in Table 4. Dimethicone, tested pure or in a trade mixture, was not mutagenic in either in vitro studies using bacterial or mammalian cells, or in vivo studies using mammalian systems.

CARCINOGENICITY

Oral

Dimethicone

Cutler et al. (1974) fed an antifoam compound containing 91% Dimethicone at 0.25% and 2.5% to groups of 100 outbred mice (50 of each sex) for 76 weeks. Another group received a single subcutaneous injection of the test material (0.2 ml) into the left flank. Silicone exposure was calculated to be 520 and 5200 mg/kg/day for the 0.25% and 2.5% oral dose groups, respectively, and 201 mg for the subcutaneous injection group. A control group for the oral-dose study was fed untreated feed and a control group for the injection study received an injection of liquid paraffin. Mice were killed at 80 weeks and necropsied.

Microscopic examination was done on any organ that appeared abnormal and sections from the lungs, heart, stomach, small intestine, spleen, liver, and kidneys from 20 mice of each group were examined. The liver, kidneys, spleen, and perirenal fat of five mice that had been subcutaneously injected were analyzed for silicon. Ten mice of the 2.5% oral dose group were analyzed for whole-body silicon content.

Survival to week 80 was significantly ($p < 0.05$) less than controls for female mice fed 2.5% silicone (however, four had died from cage flooding, and the parameter was not significant when these deaths were excluded) and male mice injected with silicone (however, mice had been killed after the appearance of subcutaneous fibromas). A significantly greater percentage of males injected with silicone developed injection site cysts, had hair loss; a smaller proportion had silicone deposits in the urinary bladder.

Males of the 0.25% diet group had increased incidence of superficial ulceration of the stomach and females of this group had an increased incidence of lymphoid hyperplasia. Neither change was noted in the 2.5% diet group and thus was not considered treatment related. A reduced incidence of uterine atrophy was noted in the females of the 2.5% dietary group. No increase in the number of malignant or benign neoplasms was observed in mice that received silicone in the feed or by injection, compared to controls. In some instances, the incidence of certain benign neoplasms was lower in dosed mice, compared to controls. Analysis of tissue failed to detect silicone in samples obtained from orally dosed or subcutaneously injected mice (Cutler et al. 1974).

Dermal

Dimethicone

In a study by an unknown author, retrieved from the National Technical Information Service (NTIS 1987c), a motor oil containing an unspecified amount of Dimethicone was applied undiluted (50 μl) to the shaved skin of 50 male C3H/HeN mice, twice weekly for life. The sites were not covered and the test material was not mechanically spread after its application. A sham-control group had 120 male mice. The study was terminated when the survival rate for each group reached $\leq$10%. Mice were necropsied, and tissue samples of the application site and stomach were prepared for microscopic examination.

Five control mice died accidentally during the study and were excluded from statistical analysis. The median life span was 79.5 weeks for treated mice and 79.0 weeks for control mice. Mean time-to-death and mortality rates were comparable between treated and control mice. At certain observations, treated mice had significantly greater mean body weight and body weight gains compared to control mice. The differences were not considered treatment related or of biological significance. The final effective number (number of mice alive at week 60 plus the number of dead mice with neoplasms prior to week 60) was 44 treated mice and 91 control mice.

No application site dermal neoplasms were microscopically confirmed in treated or control mice. Ulceration at the application site was observed in 8.0% of treated mice compared to 2.6% of control mice. One treated mouse had a palpable skin mass at the application site during week 65, which regressed by week 67. Epidermal hyperplasia at the application site was more evident

TABLE 4
Genotoxicity testing on Dimethicone

Test	Protocol and Dimethicone dose*	Results	Reference
Bacterial cell			
Ames assay: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Dimethicone (pure) tested at 33.3, 100, 333.3, 1000, 3333.3, and 10000 μg/plate ± S9	Negative	SRI International 1980
Ames assay: *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Dimethicone (fluid at 100 and 1000 cs) tested at 0.5, 5, 100, and 500 μg/plate ± S9	Negative	Dow Corning Corp 1978c
Ames assay: *S. typhimurium* TA98, TA100, TA1535, TA1537	Dimethicone mixture (unknown conc) tested at 50, 158, 500, 1580, and 5000 μg/plate ± S9	Negative	NTIS 1988
S. typhimurium TA98, TA100, TA1535, TA1537, TA 1538	Trade mixture (to contain >90% Dimethicone) tested at 1, 5, 10, 50, 100 μl/plate ± S9	Negative	Hazleton France 1988b
S. typhimurium TA98, TA100, TA1535, TA1537 and *Escherchia coli* WP2	Surfactant containing 3 wt.% Dimethicone was tested in ethanol at 100, 333, 1000, 3333, and 5000 μg/plate ± S9	Negative	Microbiological Associates 1994
Bacterial reverse mutation: *S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2	Ethanol extractions of CU-7439 (<0.1% Dimethicone) tested at 312.5, 625, 1250, 2500, and 5000 μg/plate ± S9	Negative	Dow Corning Corp 1989e
Bacterial reverse mutation	X2-5169 (10% Dimethicone)	Negative	Dow Corning Corp 1986a
Bacterial reverse mutation	X2-3379 (28% Dimethicone)	Negative	Dow Corning Corp 1990a
Bacterial reverse mutation	X3-9626 (49% Dimethicone)	Negative	Dow Corning Corp 1986b
Bacterial reverse mutation	X2-3320 (59% Dimethicone)	Negative	Dow Corning Corp 1990b
Bacterial reverse mutation	Q7-2159A gel (79% Dimethicone)	Negative	Dow Corning Corp 1986c
Bacterial reverse mutation	Q7-2867	Negative	Dow Corning Corp 1990c
Mammalian cell line			
BALB/C-3T3 mouse cell transformation assay	Q7-2159A gel (79% Dimethicone) tested at 500, 1000, and 2000 μg/ml ± S9	Negative	Dow Corning Corp 1986d
BALB/C-3T3 mouse cell transformation assay	Q7-2167/68 gel (79% Dimethicone) tested at 1250, 2500, 5000, and 10000 μg/ml ± S9	Negative	Dow Corning Corp 1989f
Chinese hamster ovary (CHO) chromosome aberration assay	Q7-2167/68 gel (79% Dimethicone) tested at 625, 1250, 2500, 5000, and 10000 μg/ml ± S9	Negative	Dow Corning Corp 1989g
CHO/HGPRT forward mutation assay	Q7-2159A gel (79% Dimethicone) tested at 31.3, 62.5, 125, 250, 500, and 1000 μg/ml ± S9	Negative	Dow Corning Corp 1986e
CHO/HGPRT forward mutation assay	Q7-2167/68 gel (79% Dimethicone) tested at 312.5, 625, 1250, 2500, 5000, and 10000 μg/ml ± S9	Negative	Dow Corning Corp 1989h

(Continued on next page)

TABLE 4
Genotoxicity testing on Dimethicone *(Continued)*

Test	Protocol and Dimethicone dose*	Results	Reference
Mammalian system			
Micronucleus test using Swiss/Webster mice	Ten mice (5 of each sex) received a single intraperitoneal injection of an extract of Q7-2159A gel (79% Dimethicone) in tissue culture fluid (dose 5 g/kg)—peripheral blood samples were taken at 24, 48, and 72 h post dosing. Micronuclei per 1000 polychromatic erythrocytes counted	Negative	Dow Corning Corp 1986f
Micronucleus test using CD-1 mice	Groups of 10 mice (5 of each sex) received a single intraperitoneal injection of an extract of Q7-2167/68 gel (79% Dimethicone) in ethanol (sterile water dilutions of the ethanol extract were made to obtain doses** of 1.25, 2.0, and 2.5 g/kg)—peripheral blood samples were taken at 24, 48, and 72 h post dosing. Micronuclei counted	Negative	Dow Corning Corp 1989i

*All studies used CAS no. 63148-62-9 to identify dimethyl silicones and siloxanes except for SRI International (1980), which used CAS no. 9006-65-9; all studies maintained appropriate positive- and negative-control groups; S9 activation prepared from an adult male rat liver; HGPRT (hypoxanthine guanine phosphoribosyl transferase) locus.

**Linear dimethylsiloxane at doses of 0.005, 0.008, and 0.01 g/kg; dimethyl cyclics at 0.01 to 0.02 g/kg.

in treated mice (17/50) than in control mice (1/115), suggesting to the author slight dermal irritation (NTIS 1987c).

CLINICAL ASSESSMENT OF SAFETY

Oral

Dimethicone

Bio-Research Labs (1985a) tested 350 cs Dimethicone fluid as a food additive. In a preliminary study, six men received the additive as 1% of the diet for 5 days (15 g), followed by a 2-day "washout" period. Subjects then received the additive as 2% of the diet for another 5 days (30 g), followed by another washout period. Blood, urine, and fecal samples were collected to assess absorption of selected nutrients. No anal leakage or major GI disturbances were reported. An increased frequency of bowel movements was reported. No changes in protein, carbohydrates, or vitamin A, D, or E were observed.

Bio-Research Labs (1985b) conducted a subsequent study in which seven male subjects received the additive in ascending doses of 2%, 3%, 4%, and 5% of the diet by weight for five consecutive 3-day periods. After this phase of the study, a bolus dose was given. One subject was withdrawn due to inability to produce a fecal specimen until day 6. Three subjects were placed on control diets on day 10 after 3 days at the 3% dose because they experienced anal leakage. Another subject experienced leakage after the first day on the 4% diet; the next day (day 11), this subject, as well as the remaining two subjects, were all placed on the control diet. On day 14, all subjects received a bolus dose of 30 g of the additive (equal to the 2% daily intake dose) and the control diet was continued for another two days. No anal leakage was observed following the bolus.

Subjects experienced flatulence during the study but no other significant discomfort. An increase in the frequency of bowel movements was noted. No significant changes in vitamin K absorption, as estimated by serum prothrombin time and partial thromboplastin time values, were observed. A decrease in mean platelet count was noted following introduction of the test material, but the count returned to baseline values post study. An increase in the percentage of neutrophil count, accompanied by a decrease in the percentage of lymphocyte count with a slight decease in total white blood cell count, was observed post study. Post study mean SGOT, SGPT, and BUN were decreased 14% to 16% from prestudy values. Post study mean values for alkaline phosphatase increased 8%, and total serum bilirubin

increased 54% (this increase was almost entirely accounted for by one subject). Weight loss of 2.7 to 5 kg was observed in three subjects. The significance of the clinical findings was not known (Bio-Research Labs 1985b).

Dermal Irritation

Dimethicone

Dimethicone, applied in a 24-h occlusive patch to the forearm, produced no irritation in 54 men (CTFA 1981).

Dermal Sensitization

Dimethicone

Hill Top Research (1984) conducted a repeated-insult patch test (RIPT) with a solution containing 5.0% *w/v* active Dimethicone in cyclomethicone. During induction, 10 24-h patches containing 0.3 ml of the test material were applied to the same site on the arm of 103 Caucasian subjects. Twenty subjects were withdrawn before study termination due to noncompliance unrelated to the test material. Subjects were challenged at an unexposed site. Sites were scored on a scale of 0 to 5. Patch application was either terminated or moved to another site if any reaction >1 was observed. The protocol was followed except for isolated instances of site scorings being conducted later than prescribed. Reactions were all ≤ 1. The investigators concluded that the test substance was neither an irritant nor a sensitizer.

Therapeutic

Dimethicone

Johnson (1976) tested a cream consisting of 2.5% Dimethicone in a hydrophilic base as an alternative to steroid creams in the treatment of allergic contact dermatitis. The cream contained no pharmacologically active ingredient. Participants included 56 patients with cutaneous disease considered "likely to respond" to an inactive cream, as well as 19 patients who were considered "not likely to respond." The panel consisted of 47 males and 28 females ranging in age from less than 2 years to 78 years old. Patients (or their parents/caregivers) were instructed to apply the cream to the affected area(s) four times per day for 14 days as well as after the affected areas had been washed. Panelists were instructed to avoid other therapy for the cutaneous disease.

The cutaneous disease characterized by dryness, roughness, scaling, and cracking of the skin were either cleared or improved by the therapy (46 of the 56 "likely responders"). Symptomatic relief and lessened discomfort was noted in some of the 19 "unlikely responders." The nonactive cream was considered a viable alternative in the treatment of cutaneous disease that did not require steroid therapy (Johnson 1976).

SUMMARY

Dimethicone is a fluid mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units. Methicone is a linear monomethyl polysiloxane. The other dimethicones and methicones covered in this review are siloxane polymers of Dimethicone and Methicone. Most of the data reviewed in this report are studies of Dimethicone.

Almost all of the 20 ingredients function as conditioning agents in cosmetic formulations. FDA reported seven of the ingredients used in 1998 in a total of 1884 formulations; CTFA reported 10 uses. The highest current concentration of use was 15%.

Dimethicone has both food and over-the-counter topical drug use. Its use in foods is limited by molecular weight.

Clinical and animal absorption studies generally reported that Dimethicone was not absorbed following oral or dermal exposure, although some absorption was seen in humans following ingestion of a Dimethicone sample containing low-molecular-weight polymers.

Dimethicone, Methicone, and Vinyldimethicone were not acutely toxic following oral exposure. Mice and rats were dosed for 90 days with up to 10% Dimethicone without adverse effect. Changes in body weight or spleen weight were observed in some rat studies. Anal leakage was noted when Dimethicone fluids of low viscosity were used. Bile deposits in the Kupffer and hepatic cells were observed in dogs dosed with 3 g/kg/day for 6 months.

The dermal LD_{50} for Dimethicone was >2 g/kg in rats and rabbits. The dermal LD_{50} for Methicone was >20 ml/kg in rabbits. The dermal LD_{50} for Vinyldimethicone was >16 ml/kg in rabbits. No adverse reactions were found in rabbits following short-term dermal dosing with 6% to 79% Dimethicone. Adverse effects were noted with a hand cream formulation containing 1% Dimethicone (the other components of the cream were not disclosed).

Only limited inhalation toxicity data were available. A "200 fluid" did produce adverse effects in one study. Methicone and Vinyldimethicone were negative in acute exposure studies using rats. Hexyl Methicone did produce toxic effects in Fischer F344/N rats—the LC_{50} was 1.8 mg/L.

Most dermal irritation studies using rabbits classified Dimethicone as a minimal irritant. Studies that scored reactions according to the Draize scale reported PIIs of ≤ 2.8 (with test samples containing 5% to 100% Dimethicone).

Dimethicone (tested undiluted and at 79%) was not a sensitizer in four assays using mice and guinea pigs. It was not a sensitizer at 5.0% in a clinical RIPT using 83 panelists. Vinyldimethicone was not irritating to rabbits following a 4-h exposure.

Most ocular irritation studies using rabbits classified Dimethicone as a mild to minimal irritant. The most common finding was a conjunctival reaction. However, a few studies reported severe reactions. Similar to Dimethicone, Methicone and Vinyldimethicone also produced conjunctival reactions.

Dimethicone was tested in numerous oral-dose (using rats) and dermal-dose (using rats, rabbits, monkeys) reproductive and developmental toxicity studies. In a few studies, treated males had significantly decreased body weight and/or decreased testes or seminal vesicles weights.

No treatment-related adverse findings were noted in dosed pregnant females or fetuses.

Dimethicone was negative in all mutagenicity assays. It was negative in both an oral (tested at 91%) and dermal (tested an unknown concentration) dose carcinogenicity assay using mice.

DISCUSSION

The CIR Expert Panel considered it unlikely that any of these polymers would be significantly absorbed into the skin due to the large molecular weight of these polymers. Inhalation exposure, however, was of concern given the limited inhalation toxicity findings in the report. It was noted, however, that only a few of these ingredients are used in aerosol formulations and at a very low concentration. In addition, the Panel was informed that particles from cosmetic formulations containing these ingredients would not likely be inhaled. In particular, it was stated that expected particle sizes would primarily be in the range of 60 to 80 microns, and less than 1% would be under 10 microns, which is an upper limit for respirable particles. The Panel expects that the manufacture process for cosmetic formulations in which these ingredients are found and which may be inhaled would continue to produce particle size distributions that are not significantly respirable.

Overall, the safety test data in the report support the safety of these ingredients at the concentrations that they are known to be used in cosmetic formulations. Accordingly, the CIR Expert Panel was of the opinion that Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone may be used safely in cosmetic formulations.

CONCLUSION

Based on the available data, the CIR Panel concludes that Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30-45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are safe as used in cosmetic products.

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