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Final Report on the Safety Assessment of Dimethicone Copolyol

Dimethicone Copolyols are chemically and physically inert ingredients used in cosmetics in a concentration range of less than or equal to 0.1–10%. This compound is, at most, slightly toxic to the rat when administered orally or dermally in a single dose. Copolyols were not primary skin or ocular irritants in the rabbit and gave no evidence of subchronic oral toxicity when fed to rats.

Clinical studies showed that these Copolyols are neither primary skin irritants nor sensitizers when tested at a 100% concentration.

On the basis of the available information presented in this report, it is concluded that Dimethicone Copolyol is safe as a cosmetic ingredient in the present practices of use and concentration.

DIMETHICONE Copolyol belongs to a class of synthetic chemicals referred to as the silicones. Silicone materials related to Dimethicone Copolyol include dimethicones (straight-chain polymers of methylated siloxanes), cyclomethicones (cyclized dimethicones), simethicones (silica-activated dimethicones), and cyclo-copolyols (cyclized Dimethicone Copolyols). Because a great deal of the chemical and biological literature focused on the broader class of Silicones and not on Dimethicone Copolyol per se, data relating to Silicones have also been included in the report.

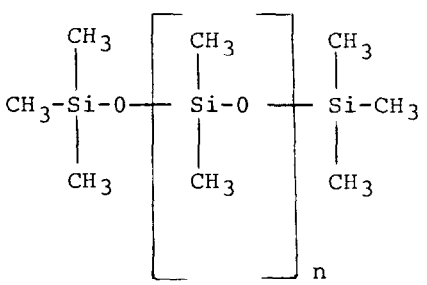
CHEMICAL AND PHYSICAL PROPERTIES

Definition

Dimethicone Copolyol is a polymer of dimethylsiloxane with polyoxyethylene and/or polyoxypropylene side chains.[1] It may also be defined as dimethicone that has been co-polymerized with polyalkoxy chains. Dimethicone Copolyol is also known as dimethylsiloxane-glycol copolymer.[1]

Structure

Dimethicones are long linear chains of dimethylpolysiloxane which have been end-blocked by trimethylsilyl groups. The generalized structure of Dimethicones is seen below where n can range from zero to over 10,000.[1,2]



Dimethicone can be prepared according to the following set of reactions. Silicon is reacted with an alkyl halide in the vapor phase in the presence of a silver or copper catalyst.[3]

$$Si + 2RCl \xrightarrow{Ag \text{ or } Cu} R_2SiCl_2$$

The resulting product is dialkyl dichlorosilane. Alternatively, this latter compound can be synthesized in a Grignard reaction using alkyl trichlorosilane as the initial reactant.

$$RSiCl_3 + RMgX \longrightarrow R_2SiCl_2 + MgXCl$$

When dialkyl dichlorosilane is placed in cold water, it is hydrolyzed to dialkyl dihydroxy silane. This latter compound is also referred to as dialkyl silane diol because of the carbon-like nature of silicon.

$$R_2SiCl_2 + 2H_2O \xrightarrow{\text{Hydrolysis}} HO\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}OH + 2HCl$$

Dimerization readily takes place between two of these dihydroxy (or diol) compounds wherein a water molecule is split out between contiguous hydroxy groups.

$$2\ HO\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}OH \xrightarrow{\text{Dimerization}} HO\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}O\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}OH + H_2O$$

Additional reactions can occur at either end of the molecule such that a linear polymer of alternating silicon and oxygen atoms is formed. The two terminals are still bounded by reactive hydroxyl groups and can undergo further chain elongation.

$$n\ HO\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}OH \xrightarrow{\text{Polymerization}} HO\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}O\left[\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}O\right]_{n-2}\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}OH + (n-1)H_2O$$

Dialkyl polysiloxane dihydroxide (DPD)

The reaction is quenched by end blocking these terminal hydroxyl groups with trimethylsilane (TMS).

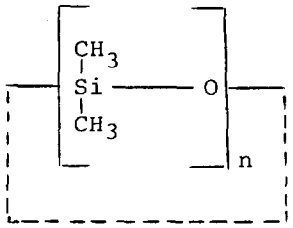
$$2(CH_3)_3SiH + DPD \xrightarrow{\text{Quenching}} CH_3\text{-}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{Si}}\text{-}O\left[\underset{\displaystyle R}{\overset{\displaystyle R}{Si}}\text{-}O\right]_{n}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{Si}}\text{-}CH_3$$

(TMS)

If the R moieties are methyl radicals, then the resulting end product is dimethylpolysiloxane (Dimethicone). Dimethicones conform to the molecular formula:[3]

$$(CH_3)_{2n+2}O_{n-1}Si$$

Cyclomethicones are cyclic dimethyl polysiloxane compounds. The generalized structure of Cyclomethicones is seen below where n can range from 3 to 8.[1]

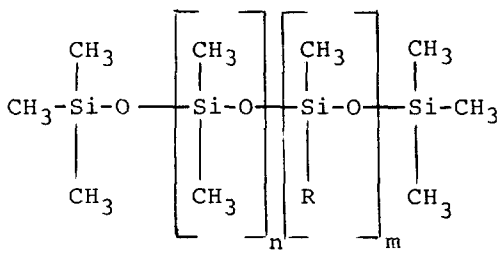


Cyclomethicones conform to the molecular formula:

$$(CH_3)_{2n}O_nSi_n$$

Simethicone is activated Dimethicone; it is a mixture of silica gel and Dimethicone.[1] Silica gel is the precipitate extracted from acidified sodium silicate.[4] There are 200–350 dimethylsiloxane subunits (n value) per Dimethicone molecule used in Simethicone.[1]

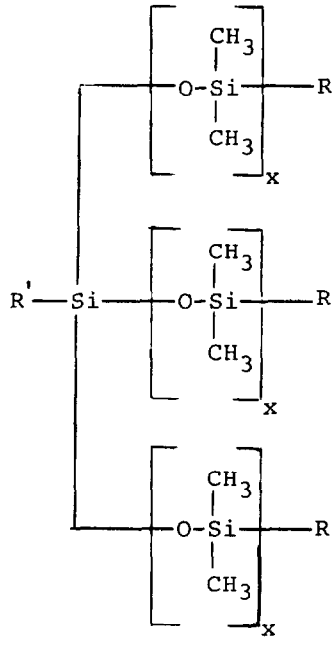
Dimethicone Copolyols are derived from Dimethicone polymers having molecule weights ranging from 250 to several million. Dimethicone Copolyols are of two broad types. Type A Copolymers are copolymers of Dimethicone with pendant side chains of polyethylene glycol (PEG), polypropylene glycol (PPG) or block polymers of polyoxyethylene/polyoxypropylene which are added through silicon–carbon bonds. Weight ratios of polyoxyalkylene:Dimethicone vary from 27:73 to 80:20. The block polymer side chains usually have a PEG:PPG ratio of 1:1. The generalized structure of Type A Copolyol is seen below where R is a polyoxyalkylene radical.[1,5,6]



Type A Copolyol

Type A Copolyols can be cyclized to form cyclo-Copolyols.

Type B Copolyols conform to the branched structure presented below where R is a polyoxyalkylene group and R′ is a lower alkyl group. The Type B Copolyols are differentiated from each other according to the nature of the R side chains.[1,5,6]



Physical Properties

Silicone fluids have an oily or waxy constitution depending upon viscosity.[7] Table 1 lists a variety of physical characteristics of 18 common Silicone compounds.[8-11]

Silicones are insoluble in water, carbinol, cyclohexanol, dimethyl phthalate, ethylene glycol, methanol, and paraffin oil. They are only partially soluble in acetone, butanol, dioxane, ethanol, heptadecanol, isopropanol, and o-dichlorobenzene. Silicones are soluble in amyl acetate, benzene, chlorobenzene, chloroform, deutero-chloroform, carbon tetrachloride, ethylene dichloride, ethyl ether, 2-ethylhexanol, gasoline, hexyl ether, kerosene, methyl chloride, methyl ether, methyl ethyl ketone, mineral oil, naphtha, perchloroethylene, toluene, trichloroethylene, ethyl caprylate, methyl and propyl laurates, methyl undecylate, and ethyl pelargonate.[7,8,12-16] Some higher molecule weight grades of Dimethicone Copolyols are sold as 10% active solutions in Cyclomethicone.[6]

Dimethicone (0.65 cs viscosity) and Cyclomethicones (2.5 and 6.0 cs) have low surface tension values of 19–21 dynes/cm^2.[17] All three have relatively high vapor pressures and evaporate readily.[9,10,16,17]

Increasing the concentration of cyclic dimethylpolysiloxane (tetramer or pentamer) in a formulation (antiperspirant stick) from 25 to 75% leads to a corresponding increase in the coefficient of friction from approximately 285 to about 345 $\mu \times 10^3$ (-GL-)^3.[10]

Dimethicone Copolyols contain both hydrophilic (polyglycol) and lipophilic (silicone, alkyl) moieties making them surface active agents. Surfactant properties vary according to the relative amount of the hydrophilic and lipophilic parts of the molecule.[5]

Many other properties of the silicone fluids have been reported.[7]

Reactivity

Silicones are inert compounds resistant to chemical, physical, biological, and microbiological degradation within the realm of cosmetic preparation, storage and use. They are stable for long periods of time at temperatures up to 150°C. At 250°C, in the presence of air, viscosity increases.[7]

Silicone fluids are not affected chemically by aqueous solution of hydrochloric, sulfuric, nitric,

TABLE 1. PHYSICAL CHARACTERISTICS OF SEVERAL COMMON SILICONE COMPOUNDS.[8-11]

Class/Chemical name	*Formula*	*M.W.*	*Visc. (cs)*	*Flash Pt. (°C)*	*M. Pt. (°C)*	*B. Pt. (°C)*[a]	*Sp. Grav.*	*Ref. Index*[b]	*Phase*	*Freezing Pt. (°C)*
A. *Dimethicone*										
1. Hexamethyl-disiloxane	$(CH_3)_6OSi_2$	162	0.65	−1	–	99.5[1]	0.7606	1.3748^{25}	Fluid	−68
2. Octamethyl-trisiloxane	$(CH_3)_8O_2Si_3$	237	–	–	−80	153[1]	0.8200	1.3848^{20}	Fluid	–
3. Decamethyl-tetrasiloxane	$(CH_3)_{10}O_3Si_4$	310	1.5	71	–	192[1]	0.852	1.387^{25}	Fluid	–
4. Dodecamethyl-pentasiloxane	$(CH_3)_{12}O_4Si_5$	385	2.0	91	−80	230[1]	0.8755	1.3925^{20}	Fluid	−84
5. Tetradeca-methylhexa-siloxane	$(CH_3)_{14}O_5Si_6$	459	–	–	−100	142^{20}	0.8910	1.3948^{20}	Fluid	–
6. Octadeca-methylocta-siloxane	$(CH_3)_{18}O_7Si_8$	607	–	–	–	153[5.1]	0.913	1.3970^{20}	Fluid	–
7. Eicosamethyl-nonasiloxane	$(CH_3)_{20}O_8Si_9$	665	–	–	–	173[4.9]	0.918	1.3980^{20}	Fluid	–
8. Docosamethyl-decasiloxane	$(CH_3)_{22}O_9Si_{10}$	756	–	–	–	183[41]	0.925	1.3988^{20}	–	–
9. Dimethylpoly-siloxane I	–	–	50	274	–	N.D.[c]	0.955	1.402^{25}	–	−55
10. Dimethylpoly-siloxane II	–	–	350	316	–	N.D.	0.972	1.4032^{25}	–	−53
11. Dimethylpoly-siloxane III	–	–	12,500	316	–	N.D.	0.973	1.4035^{25}	–	−46

TABLE 1. (Continued).

Class/Chemical name	*Formula*	*M.W.*	*Visc. (cs)*	*Flash Pt. (°C)*	*M. Pt. (°C)*	*B. Pt. (°C)*[a]	*Sp. Grav.*	*Ref. Index*[b]	*Phase*	*Freezing Pt. (°C)*
B. *Cyclomethicones*										
12. Octamethylcyclotetrasiloxane	$(CH_3)_8O_4Si_4$	297	–	–	−43	–	0.9558	1.3968^{20}[d]	Oily liq.	–
13. Dodecamethylcyclohexasiloxane	$(CH_3)_{12}O_6Si_6$	445	–	–	−3	245[1]	0.9672	1.4015^{20}	Oily liq.	–
14. Tetradecamethylcycloheptasiloxane	$(CH_3)_{14}O_7Si_7$	519	–	–	–	–	0.9730	1.4040^{20}	Oily liq.	–
15. Hexadecamethylcyclooctasiloxane	$(CH_3)_{16}O_8Si_8$	593	–	–	–	–	–	1.4060^{20}	Oily liq.	–
16. Octadecamethylcycolnonasiloxane	$(CH_3)_{18}O_9Si_9$	667	–	–	–	188^{20}	–	1.4070^{20}	Oily liq.	–
C. *Copolyol*										
17. Dimethylphenylmethylpolysiloxane	$[(CH_3)_3SiO]_2$ $[(CH_3)_2SiO]_n$ $[Ph(CH_3)SiO]_m$[e]	–	115	316	–	N.D.	1.068	1.494^{25}	Fluid	–
D. *Cyclo-Copolyol*										
18. Dimethylphenylmethylcyclosiloxane	$(PhCH_3SiO)_x$ $[(CH_3)_2SiO]_y$[f]	–	20	168	–	$180^{.004}$	1.058	1.489^{25}	–	–

[a]Atmosphere at which B. pt. was determined.
[b]°C.
[c]Not distillable.
[d]also = 1.3800 at 60 °C.
[e](n + m) = 10–15.
[f](x + y) = 3–8.

citric or fatty acids, hydrogen peroxide, sulfur dioxide, molten sulfur, metallic salt solutions, liquid ammonia, ammonium hydroxide, paraffin hydrocarbons, and phenol. Concentrated sulfuric and phosphoric acids will cause depolymerization with eventual dissolution of the entire polymer. Concentrated nitric acid oxidizes this polymer. Exposure to dry hydrochloric acid splits the siloxane bond and lowers the viscosity of the fluid. The organic groups on silicon react with dry chlorine resulting in increased viscosity.[7]

Analytical Methods

Several methods have been described for the quantitative determination of silicone levels.[15] These include volumetric and gravimetric assays, visible and UV determinations, potentiometric titration and IR and atomic absorption spectroscopy. Newer techniques are proton magnetic resonance, nuclear magnetic resonance and optical emission spectroscopies.[9,14,15]

Quantitative analysis for dimethylpolysiloxane can be performed by proton magnetic resonance spectroscopy. The method is sensitive for Dimethicone determination over a range of n = 10 to 350.[15]

An optical emission spectroscopic technique has been reported. The procedure is accurate for concentrations down to 5 mg/ml with an estimated precision of ± 10% of the standard deviation.[9]

Impurities

Information relative to impurities and to the addition of antioxidants and preservatives to the Dimethicones was not available.[6]

USE

Purpose and Extent of Use in Cosmetics

Dimethicone Copolyol surfactants are used in cosmetics as surface tension depressants, wetting agents, emulsifiers, and foam builders. They improve wetting characteristics of skin lotions and shave formulations, and promote foam volume and wetting in aerosol shave creams and shampoos. Dimethicone Copolyols are plasticizers in hair sprays, and lubricants in shave preparations.[5]

Table 2 lists product types and the number of product formulations containing Dimethicone Copolyol. Voluntary filing of such information with the FDA by cosmetic manufacturers, packers and distributors, conforms to the preset concentration ranges and product types as described in 21 CRF Part 720. In 1976, FDA reported that Dimethicone Copolyol was an ingredient in 164 cosmetic formulations at concentrations ranging from less than or equal to 0.1% up to 10%.[18]

Potential Interactions with Other Cosmetic Ingredients

Silicones are stable and unreactive within the normal physiochemical limitations to which cosmetics are subjected, and "show good compatability" with other cosmetic materials.[7,17] There are no reported chemical interactions of Dimethicone Copolyol or silicones with other cosmetic ingredients.

Cyclomethicone is the only reported diluent or solvent for Dimethicone Copolyol.[6]

Surfaces to which Commonly Applied

Cosmetic products containing Dimethicone Copolyol (Table 2) are applied to, or have the potential to come in contact with, the face (makeups, rouges, foundations, paste masks, shaving creams, and lotions), the scalp (hair conditioners and sprays, shampoos, and wave sets), the axillae (deodorants), the skin in general (colognes, fresheners, moisturizers, and suntan preparations) and the eyes (shampoos and aerosol hair sprays).[18]

TABLE 2. PRODUCT FORMULATION DATA ON DIMETHICONE COPOLYOL.[a]

Cosmetic Product Type	*Concentration (percent)*	*No. of product formulations*
Colognes and toilet waters	>0.1-1	1
Other fragrance preparations	>0.1-1	2
Hair conditioners	>0.1-1	11
	≤0.1	1
Hair sprays (aerosol fixatives)	>0.1-1	19
	≤0.1	41
Shampoos (noncoloring)	>1-5	3
	>0.1-1	4
Tonics, dressings and other hair grooming aids	≤0.1	2
Wave sets	>1-5	2
	>0.1-1	13
	≤0.1	10
Other hair preparations	>1-5	1
	>0.1-1	7
	≤0.1	3
Hair shampoos (coloring)	>0.1-1	6
Foundations	>0.1-1	2
Makeup bases	>5-10	1
Rouges	>0.1-1	1
Other makeup preparations	>0.1-1	2
Deodorants (underarm)	>0.1-1	2
Other personal cleanliness products	>0.1-1	1
Aftershave lotions	>0.1-1	2
Shaving cream (aerosol, brushless, and lather)	>0.1-1	6
Other shaving preparation products	>0.1-1	2
Face, body, and hand (excluding shaving preparations)	>0.1-1	1
Moisturizing	>1-5	2
Paste masks (mud packs)	>1-5	7
	>0.1-1	1
Skin fresheners	>0.1-1	1
Other skin care preparations	>0.1-1	1
Suntan gels, creams, and liquids	>1-5	6
	Total	164

[a]From Ref. 18.

Frequency and Duration of Application

Product formulations containing Dimethicone Copolyol can be applied on a daily basis (deodorants, makeup and shaving products) or occasionally (suntan, moisturizing, and hair products). The duration of application may range from a few minutes (shampoos, shaving creams, volatile colognes, and lotions) to several hours (suntan preparations, deodorants, and makeup). Use of cosmetic products containing Dimethicone Copolyol may extend over a period of years.

Noncosmetic Uses

Both dimethicone and simethicone are used in oral drug preparations to control flatulence.[19] The antiflatulent property of dimethicone is greatly inhanced by addition of 6% colloidal silica.[20] Dimethicone and simethicone are also used in gastrointestinal drugs as antifoaming agents.[19,21]

Dimethicone may be used as a direct food additive (defoaming agent) under the Federal Food, Drug and Cosmetic Act, if it meets the following specifications: (a) "substantially free" from hydrolyzable chloride and alkoxy moieties, (b) viscosity 300–600 cs at 25°C, (c) refractive index

range of 1.400–1.404 at 25°C, (d) maximum loss of 18% at 200°C for 4 h and (e) maximum concentration of 100 ppm (but zero in milk and foods for infants and invalids).[22] Dimethicone (viscosity greater than 300 cs) may also be used under the Food, Drug and Cosmetic Act as a component of surface lubricants having incidental food contact; regulations limit such use as an indirect food additive to 1 ppm.[23]

Silicone fluids which are chemically related to the Copolyols are used as vehicles for the intramuscular administration of drugs[24] and as suspension media for smallpox vaccines.[25] A vaginal silastic (Dimethicone) sponge, permeated with 0.25% of a prostaglandin (PGF) ester, has been used to abort successfully nine out of nine women in early second trimester pregnancy.[26] Dimethicone has been used as a vehicle to dissolve and stabilize prednisolone and aspirin for up to eight weeks of storage at temperatures from 4 to 45°C.[27,28]

Solid-phase silicone products are used for the binding and slow release of various pharmacologic agents.[29] The majority of these preparations take the form of intrauterine, subdermal, or subcutaneous implants.[30-38] Most of the studied agents are contraceptive steroid hormones such as progesterone, norprogesterone, norgestrel, norethindrone acetate, megastrol acetate, estrone, pregnadiene, and testosterone.[30-38] Other solid silicones have been reportedly used to form elastic masses for dental impressions.[39]

Silicone fluids appear to protect the skin when applied topically.[40] Some have been used in lotions for the treatment of various dermatoses.[41] Injectable silicone fluids are used in cosmetic surgery for soft tissue augmentation as in facial hemiatrophy, wrinkle eradication, and mammary augmentation.[42]

BIOLOGICAL PROPERTIES

General Effects

Dimethicone appears to increase poly-, di-, and monosaccharide absorption in humans when administered orally (140–240 mg). Patients with a variety of diseases that reduce intestinal carbohydrate absorption were given a mixture of pancreatin and SiO_2-activated Dimethicone (three doses of 1 or 2 g/day). The patients were greatly improved within 12 weeks. The mechanism for the enhanced sugar absorption was not detailed.[43]

Dimethicone fluid is resistant to chemical and physical degradation. As a possible corollary, it also appears to be unaffected by and to have little effect on living systems. There are no known organisms that can proliferate in, alter or digest dimethicone. An apparent lack of acute pharmacodynamic effects is demonstrated by the following study.[44]

Dimethicone fluid having a viscosity of 350 centistokes has been used experimentally to preserve rat skin allografts. Skin intended for grafting, completely immersed in such media, survived with no indication of adverse effects. Besides being nontoxic, dimethicone fluid appears to protect tissue from autolysis and microbial degradation (but not from the deleterious effects of freezing). Suprapannicular skin patches, cut down to the panniculus carnosus of the tela subcutanea, were excised from the flanks of female rats, placed in dimethicone fluid (350 cs) and stored at −9.5 , 4°, 12°, or 21°C for various periods of time. Dimethicone fluid affords no protection from injury by freezing (−9.5°C); skin patches become necrotic within 24 h. However, refrigeration in dimethicone fluid at 4° or 12°C for four or five days, respectively, had no harmful effect on skin allografts. All patches were successfully transplanted and behaved like freshly excised tissue. Even at room temperatures (21°C), excised skin patches survived up to three days without any indication of degradation, injury or toxicity. Biopsies for histopathological analysis of viability of cellular and fibrous constituents were taken at various times from the tissue samples both during storage in the dimethicone fluid and after allografting. Additional monitoring of the grafted skin included evaluations of graft vascularization, reinstatement of blood flow and tissue survival. At the times and temperatures (except freezing) indicated above, no harmful effects were found.[44]

Dimethicone fluid (350 cs) was tested for its antigenicity and histologic response in the guinea pig. No detectable antibody production was elicited. The average molecular weight of the fluid was ap-

proximately 10 kd, placing it within the normal weight range of polypeptide and polysaccharide antigens. Six animals were initially injected subcutaneously in the foot pad with 0.5 ml of dimethicone fluid mixed (1:1) with complete Freund's adjuvant (mineral oil, fatty acid esters and dried, heat-inactivated mycobacteria). This mixture was then injected weekly for three weeks into the foot pad (0.05 ml) and subcutaneously in the flank (1.0 ml). Two additional four-dose (3:1 dimethicone to adjuvant) courses were administered subcutaneously in the flank at a rate of 12.0 ml/week. Serial blood samples were taken by cardiac puncture before, during and 5, 10, and 15 weeks after the injection regimen. Serum samples were assayed for antibody using four techniques: passive cutaneous anaphylaxis, Ouchterlony gel diffusion, and immediate and delayed cutaneous hypersensitivity. The latter two in vivo assays involved injecting intradermally a challenge volume of 0.1 ml of the undiluted dimethicone and observing for skin reaction at 20 minutes and at 24, 48, and 72 h. No indication of antibody production was found in any of the assay systems. Histological examination of the guinea pig tissue indicated granuloma formation at the injection sites along with popliteal lymph node enlargement. Small intercellular spaces, partially walled off by macrophages, were found in the hepatic, splenic, and pulmonary parenchyma. These spaces were presumed to contain dimethicone fluid although this assumption could not be proven cytochemically as there are no known stains specific for dimethicone. The spaces did not contain any of the components of the Freund's adjuvant since special stains are available for these components and since none of the tissues in question took up any of these stains. No suggestion of intracellar uptake and accumulation of the dimethicone was made.[45]

A more recent study by Hobbs et al.[2] does suggest that there is little or no cellular accumulation of dimethicone fluids in fish and birds. A dimethicone (300 cs, 2g ^{14}C-labeled fluid/13.33 ml, 280 μCi/g activity) residue study was carried out on bluegill sunfish. Two groups of 30 young fish were each placed in 30-liter tanks of water containing 1 or 10 ppm of labeled (1.26 or 12.6 μCi) dimethicone fluid. Fish were sacrificed at 0, 1, 3, 5, 7, 14, 21, and 30 days and tissue samples were radioassayed for dimethicone. These fish were exposed triply to the labeled compound: transepithelial exposure in the gut, transbranchial exposure in the gills and transdermal exposure across the skin. Nevertheless, no tissue accumulation of labeled dimethicone was found for either dose level for up to 30 days of continuous exposure.

The same investigators conducted a comparable study on 96 young chickens. After being fed a normal diet for the first 24 weeks following hatching, the birds were divided into three equal groups receiving diets supplemented with 200, 1000, or 5000 ppm of dimethicone (100 cs), respectively. Eggs were collected regularly from the laying hens in each group and analyzed for dimethicone residue; no accumulation was observed. At the end of the dosing period, half of the chickens were sacrificed; the remaining birds, placed back on the normal diet, were sacrificed 30 days later. Liver, kidney, fat, and muscle samples from each chicken were assayed for dimethicone residue; none was found. It was concluded that there was no measurable accumulation of dimethicone in the flesh of these chickens and that there was no significant migration of dimethicone from hen to egg. Residues of dimethicone in all samples analyzed were below the limit for quantitative determination.[2]

Hobbs and associates[2] showed that ^{14}C-labeled dimethicone (300 cs, 15% emulsion) is not broken down detectably by sewage microorganisms. They added 180 mg of the labeled material (50.4 μCi) to 18-liter tanks containing settled sewage and monitored the system for 70 days for radioactivity, pH, and bacterial flora. Control tanks containing a labeled hydrocarbon instead of dimethicone were set up. The control compound was degraded extensively. There was no measurable biodegradation of the dimethicone material.

Dimethicone and simethicone fluids can protect the rat gastric mucosa from the irritant effects of aspirin.[20]

Absorption, Metabolism, and Excretion

Silicone compounds do not easily cross membrane barriers.[46] They are not absorbed through the skin.[47,48] Silicones are not readily absorbed through the gut and are not extensively deposited in

tissues when they do gain access to the body.[47,49,50] Carbon-14 labeled dimethicone fluid, injected into the hind legs of rats, was not metabolized but was stored principally in the gut.[48] Dimethicone fluids are not degraded by microbial systems.[2,51] Their chemical inertness is highly contributory to the apparent lack of metabolism.

In a study by Hine et al.[46] anesthesized rats were administered intraperitoneal or intracisternal injections of undiluted ^{14}C labeled dimethicone. The labeled material was injected intraperitoneally at single doses/animal of 15 or 100 μCi, or injected intracisternally at single doses/animal of 5 or 6 μCi. Urine and feces were collected daily for 25 or 45 days, after which time the animals were sacrificed. Tissue samples of all major organs were removed from each animal. Feces, urine, carcass and tissues were then assayed for radioactivity by liquid scintillation counting. Twenty-five days after each of three rats received intraperitoneal injection of 15 μCi, an average of 51% of the labeled material appeared in adipose tissues, whereas 27% and 15% were distributed in the gut tissues and the liver, respectively; none of the labeled material was recovered in the urine or feces. No ^{14}C-labeled dimethicone was found in the expired air (collected over a 24-hour period) of the single animal which received 100 μCi intraperitoneally. Forty-five days after 5 μCi was injected into the cisternae magnae of each of six rats, an average of 92% was recovered in the carcass, urine, or feces. Forty-five days after intracisternal injection of 6 μCi, an average of 82% was distributed in the CNS (41%, 31%, and 10% in the brain, vertebral column, and spinal cord, respectively) with small amounts of the labeled dimethicone deposited in fat (8%) and liver (1%) tissue.

Toxicology of Dimethicone Copolyols

General Studies

Acute toxicity

Oral: Seven undiluted Dimethicone Copolyol A (DMCA) or Copolyol B (DMCB) ingredients were tested in the rat for acute oral toxicity as specified in Table 3.[52-58] The lowest LD50 values reported for DMCA and DMCB were 12.3 and 11.3 ml/kg, respectively.[54,58]

Dermal: Two groups of four rats each were exposed topically to DMCA or DMCB. A single dose per rat was placed on a prepared skin site which was then occluded. The resulting acute dermal LD50s were greater than 16 and 20 ml/kg for DMCA and DMCB, respectively.[52,58] Similar studies on five other Copolyols were carried out in the rabbit.[53-57] There were no deaths in any study; the corresponding LD50 values are listed in Table 4.

Primary Skin Irritation: Two undiluted DMCA samples were tested for primary skin irritation potential according to the FHSA regulations and scored by the Draize method. The resulting primary irritation scores were 1.6 and 2.7 (maximum of 8.0) for DMCA 190 and 193, respectively, indicating that the two Copolyols are "not skin irritants."[56,57]

Five other undiluted Copolyols were tested as potential skin irritants in the rabbit. Aliquots of 0.01 ml of sample were applied to the uncovered skin for 24 h. Irritation was graded according to the scoring system found in Table 5. No sample was found to be a skin irritant (Table 6).[52-55,58]

TABLE 3. ACUTE ORAL TOXICITY.

Ingredient	*No. of rats*	*Dose range*	*LD50*	*Ref.*
DMCB 520	5	16.2–30.8 g/kg	22.3 g/kg	52
DMCA 522	5	9.13–16.7 ml/kg	12.3 ml/kg	58
DMCA 7500	5	64 ml/kg	>64 ml/kg	55
DMCA 190	16[a]	10.2–34.6 g/kg	28.2 g/kg	56
DMCA 193	16[a]	10.2–34.6 g/kg	>34.6 g/kg	57
DMCB 530	15	15.0–25.8 ml/kg	19.7 ml/kg	53
DMCB 531	15	7.0–18.3 ml/kg	11.3 ml/kg	54

[a]Fasted 16 h.

TABLE 4. ACUTE DERMAL TOXICITY.

Ingredient	*No. and species of animals*	*LD50*	*Ref.*
DMCB 520	4 rats	>20 ml/kg	52
DMCA 522	4 rats	>16 ml/kg	58
DMCA 7500	4 rabbits	>20 ml/kg	55
DMCA 190	10 rabbits	>2 g/kg	56
DMCA 193	10 rabbits	>2 g/kg	57
DMCB 530	2 rabbits	>20 ml/kg	53
DMCB 531	4 rabbits	>20 ml/kg	54

TABLE 5. SKIN IRRITATION SCORING SYSTEM.[a]

Irritation index	*Observation*
1, 2	Undiluted sample causes only capillary injection.
3, 4	Undiluted sample causes only slight erythema.
5	Undiluted sample causes erythema and slight edema.
6	Undiluted sample causes necrosis.
7–10	10% solution causes necrosis.

[a]From Ref. 5.

TABLE 6. PRIMARY SKIN IRRITATION IN RABBITS.

Ingredient	*Irritation index*[a]	*Ref.*
DMCB 520	1	52
DMCA 522	1	58
DMCA 7500	3	55
DMCB 530	3	53
DMCB 531	2	54

[a]See Table 5.

TABLE 7. EYE IRRITATION SCORING SYSTEM.[a]

Irritation index	*Observation*
1, 2	0.5 ml undiluted sample does not cause severe injury.
3–5	0.005 ml undiluted sample does not cause severe injury.
6–7	0.005 ml undiluted sample or excess 40% solution causes severe injury.
8, 9	Excess 5% solution causes severe injury.
10	Excess 1% solution causes severe injury.

[a]From Ref. 5.

TABLE 8. OCULAR IRRITATION IN RABBITS.

Ingredient	*Irritation level*	*Irritation index*[a]	*Ref.*
DMCB 520	None	1	52
DMCA 522	None	1	58
DMCA 7500	None	1	55
DMCB 530	Trace	2	53
DMCB 531	Trace	2	54

[a]See Table 7.

Ocular Irritation: Undiluted DMCA was tested in the rabbit for eye irritation potential according to FHSA requirements. Scoring was according to the Draize method. The 24-, 48-, and 72-hour eye irritation scores were 7.9, 0.7, and 0.0, respectively.[56] Undiluted DMCA 193 was similarly tested; 24-, 48-, and 72-hour scores were 3.0, 0.0 and 0.0, respectively.[57]

Five other undiluted Copolyols (0.5 ml) were tested as potential ocular irritants in groups of five rabbits each. Unstained eyes were scored immediately and after 24 h. Eye irritation was graded according to the scoring system found in Table 7. No sample was found to be an eye irritant (Table 8).[52-55,58]

Inhalation: Groups of six rats each were exposed to atmospheres containing various Dimethicone Copolyols for several exposure times and temperatures (Table 9).[52-55] The data indicate that little inhalation hazard exists at ambient temperatures.

Subchronic toxicity

Oral: Four groups of five rats each were fed diets containing 1% or 4% DMCB for 89 days. The doses were reported to be 0.64 and 2.88 g/kg/day in males and 0.74 and 3.08 g/kg/day in females. There were no mortalities or deleterious effects in any group.[52]

Dermal: Undiluted DMCA 190 was tested in a 28-day percutaneous toxicity study on ten male rabbits each receiving 200 mg/kg/day. None of the identified test or control animals died. There were no untoward behavioral reactions. Slight to moderate erythema and edema were found at the application sites after two treatments and thereafter. No other gross pathological alterations in tissues or organs were observed. No differences from control were found in mean testes/body weight ratios. Histopathologically, 1/10 rabbits showed a depression in spermatogenesis; all control animals were normal.[59]

TABLE 9. INHALATION TOXICITY IN THE RAT.

Ingredient	*Exposure time(h)*	*Bubbler temp.(°C)*	*Maximum chamber (°C)*	*Chamber size(L)*	*Chamber*[a] *conc. (mg/L)*	*Mortality*	*Ref.*
DMCB 520	8	50–70	–	–	0.031 (5% in water)	0/6	52
DMCB 520	8	50–70	–	–	Conc. vapor	1/6	52
DMCA 7500	8	23	–	9	0.158	0/6	55
DMCA 7500	2	170	27	9	20.77	0/6	55
DMCA 7500	4	170	27	9	23.47	2/6	55
DMCA 7500	8	170	27	9	–	6/6	55
DMCB 530	8	21	–	9	0.235	0/6	53
DMCB 530	8	150	24.5	9	–	0/6	53
DMCB 531	8	22	–	120	–	0/6	54
DMCB 531	4	170	26	120	4.5	0/6	54

[a]Airflow rate through bubble: 2.5 L/min.

A similar test on undiluted DMCA 193 was run on ten rabbits; none died. There were no gross behavioral or pathological alterations. The mean testes/body weight ratios were not different from control. Spermatogenesis was depressed in 2/10 control and 2/10 test animals.[60]

Clinical Assessment of Safety

Primary skin irritation

Twenty-four hour occlusive insult patch tests were conducted with 40% Dimethicone Copolyol in aqueous solution and undiluted Dimethicone Copolyol on 19 and 20 subjects, respectively. In the group exposed to the 40% concentration, 18 subjects showed no irritation whereas one subject exhibited minimal irritation; the one reactor's score was 0.5 out of a maximum possible score of 4.0. The investigator concluded that 40% Dimethicone Copolyol in aqueous solution caused "an acceptably low level" of primary skin irritation.[61] None of the 200 subjects exposed to the undiluted material exhibited any irritation.[62]

Skin irritation and sensitization

A repeated insult patch test on 22 Caucasian males aged 18–55, 14 Black males aged 19–52, and 14 Caucasian females aged 20–23 was conducted on undiluted DMCA 190. Each person had oval adhesive sensitizing patches (1″ × 1¼″) applied to the same site every other day for a total of nine patches (18 days). Each patch was removed after 24 h exposure and the site scored. A single challenge patch was applied to a new site adjacent to the induction site two weeks after the last sensitizing application. Scoring of irritation was according to the Draize criteria. All scores were zero indicating no evidence of skin irritation, "fatiguing" or sensitization.[63] Undiluted DMCA 193 elicited no skin irritation or sensitization when tested on the same subjects and in the same manner as DMCA 190.[64]

In a repeated insult occlusive patch test on 201 subjects, Dimethicone Copolyol was found to be "essentially nonirritating." There were no reactions to the challenge application which were suggestive of sensitization. No further details were given.[65]

Toxicology of Silicone Fluids

General Studies

Acute toxicity

Oral: Rowe et al.[66] administered dimethylpolysiloxane (0.65, 2.0, 50, and 75 cs) or methylphenylpolysiloxane (35 or 350 cs) fluid to guinea pigs in a single dose via gavage. Mineral oil was used as a control. Several of the fluids as well as the control oil produced a laxative action on the test animals (Table 10).

Intravenous: Dogs were given intravenous infusions of two Dimethicone fluids of different viscosity. The lower viscosity compound was well tolerated by the animals. The fluid was apparently retained in the liver and lungs and blocked the reticuloendothelial system. The higher viscosity fluid produced pulmonary emboli resulting in the death of the animals. No other details were given.[58]

Intraperitoneal: The silicone fluids listed in Table 10 were administered to rats in single intraperitoneal doses of 0.1, 0.3, 1.0, 3.0, or 10.0 ml/kg. The animals were observed for 90 days. The only deaths that occurred in the study were for the three highest doses of the lowest viscosity fluid (0.65 cs). Extensive adhesions of the peritoneal viscera were found in these animals. Nodules of silicone fluid were found in the omenta and on the surface of the spleen, liver and diaphragm. No inflammation was found in any animal.[66]

This experiment was repeated using groups of five male rats each. Hexamethyldisiloxane was given intraperitoneally at 0.1, 0.5, or 1.0 ml/rat. The other fluids listed in Table 10 were administered similarly at 0.5 or 1.0 ml/rat. Several of the hexamethyldisiloxane-dosed animals became moribund and were sacrificed within the first week; all displayed extensive adhesions and other evidence of local irritation. At 90 days post-injection, the rest of the animals were sacrificed. In the hexamethyldisiloxane-treated rats, there was evidence of widespread local irritation. All other silicone fluids tested produced no reaction.[66]

Hawthorne et al.[67] injected dimethicone fluid (350 cs) intraperitoneally into four strains of rats.

TABLE 10. SINGLE ORAL DOSE OF SILICONE FLUID IN THE GUINEA PIG.[a]

Sample	Viscosity in cs	Dose (ml/kg)	Mortality ratio	Laxative effect (h) 2.5	8	24	48
DC 200 Fluid (Hexamethyldisiloxane)	0.65	3	0/7				
	0.65	10	0/7				
	0.65	30	0/7				
	0.65	50	1/10				
DC 200 Fluid (dodecamethylpentasiloxane)	2.0	10	0/3		+		
	2.0	30	0/6		++		
	2.0	50	3/3				
DC 200 Fluid	50	10	0/2	+++	+++	+++	+
	50	30	0/6	+++	+++	+++	+++
	50	50	0/3				
DC 550 Fluid	75	3	0/3				
	75	10	0/3	+	+	+	
	75	30	0/6		++	+++	+++
DC 702 Fluid	35	3	0/3				
	35	10	0/3	+	++	+++	
	35	30	0/6		++	+++	++
DC 200 Fluid	350	5	0/2			+	
	350	10	0/5		+	+	
	350	30	0/6		+	+	
	350	50	0/3			++	++
Min. Oil U.S.P.		10	0/2	++	++	+++	+
		30	0/3	+++	+++	+++	+

[a]From Ref. 66.

The volume administered ranged from 14 to 62 ml; the time of sacrifice ranged from 3 to 12 months post-injection. A variety of hematological tests were run. No significant differences in total and differential leukocyte counts, hemoglobin content, and hematocrit were found. Histologic examination of blood smears revealed no indication of silicone phagocytosis by leukocytes. However, erythrocytes in six rats were found to contain multiple small vacuoles, possibly containing dimethicone in the peripheral cytoplasm nine months after treatment.

Rats were injected intraperitoneally with dimethicone fluid (350 cs) at two to three or 16 ml/animal. Each animal had previously undergone abdominal surgery during which peritoneal adhesions were experimentally induced. The incidence and severity of adhesions were greatly reduced in the group receiving the 16 ml of dimethicone fluid. The authors concluded that the diminished adhesion formation was caused by mechanical separation of the traumatized serosal surfaces and not to the silicone fluid providing a protective surface coating.[68]

Intradermal: Rowe et al.[66] gave single, intradermal injections (0.1 ml) in the depilated back of rabbits of each of the silicone fluids listed in Table 10. Only hexamethyldisiloxane caused visible irritation characterized by edema, inflammation and necrosis at the injection site.

Subcutaneous: Rowe and associates[66] injected subcutaneously the silicones (0.1 ml) listed in Table 10 into the backs of rabbits. At 48 h, only the hexamethyldisiloxane-treated animals gave indication of appreciable irritation at the injection site. At autopsy 13 days later, the same sites displayed marked irritation.

Cutler and colleagues[69] injected mice subcutaneously with a simethicone antifoam compound (94% polydimethylsiloxane fluid, 6% silicone dioxide). Each weanling mouse received 0.2 ml of the

compound. All surviving mice were sacrificed at 80 weeks of age. No silicone was found in the liver, kidneys, spleen, or perirenal adipose tissue. Cysts remained at the injection sites throughout the lifespan of many of the mice.

Inhalation: Oxygen and CO_2 are very soluble in some silicone fluids.[7,70] Goldfish can survive in oxygenated silicone liquid for several weeks.[70]

A hexamethyldisiloxane vapor inhalation study was conducted on guinea pigs. The animals were found to tolerate up to 25,000 ppm for 30 min. However, a saturation concentration of approximately 40,000 ppm caused death by respiratory failure within 15–20 min.[66]

Intraspinal and Intracisternal: A viscous silicone fluid (12,500 cs) or saline was injected spinally into monkeys, rabbits, and rats. The first two species were injected in the subdural space at the level of the fourth lumbar vertebra; the rats were injected in the cisterna magna. All animals received one injection, were closely observed for 30 or 90 days and were then sacrificed for gross and micropathologic study (Table 11).[46] Each animal was observed daily for the first 14 days and weekly thereafter for overt signs of central nervous system (CNS) problems. The following assessments were made: general behavior, righting reflex, grasping ability, muscle tone, stimulation of nociceptive reflexes, food and water consumption, and the presence of corneal and light reflexes. No deviations from normality were observed for any of these neurological parameters. No gross pathological changes were observed. Histologic analysis revealed the following results. For all rat and monkey studies, no changes were seen in spinal cord, brain, cerebellum, or meninges. Two silicone-treated rabbits in Group 6 showed indication of mild "central nervous system inflammation." Bacterial infection was the probable cause for one of these inflammations. The other rabbit had slight perivascular cuffing along with small foci of chronic inflammatory cells in the cerebrum and cerebellum. No lesions were found in the meninges or spinal cord. The tissue of the other four rabbits appeared normal. One silicone-treated rabbit in Group 8 showed a lesion (1 mm in diameter) in the pia arachnoid and subjacent cerebrum. This consisted of round cell infiltration of the pia. There was cuffing of the cerebellar arteries. One saline-treated rabbit in Group 7 showed perivascular and meningeal inflammation in the hind brain; a similarly treated animal in Group 9 showed a small necrotic granuloma in the cerebrum with involvement of the adjacent meninges.[46]

Eye Irritation: Rowe and associates[66] instilled the seven undiluted silicone fluids (viscosity range 0.65–12,500 cs) listed in Table 12 into the eyes of rabbits. These materials had only a transitory effect on the eye. No corneal damage was demonstrated using fluorescein dye.

Subchronic/chronic toxicity

Oral: Cutler et al.[69] fed simethicone (94% polydimethylsiloxane, 6 percent silicon dioxide) at either 0.25% or 2.5% of the total diet (approximately 580 or 5800 mg/kg/day) to mice for 76 weeks post-weanling. The only significant difference from control found in mortality rates was for female

TABLE 11. TEST GROUPS FOR SPINALLY-TREATED ANIMALS.[a]

Group	*No. and species of animals*	*Substance*	*Amount (ml)*	*Days*
1	4 rats	Silicone	0.05	30
2	4 rats	Silicone	0.10	30
3	4 rats	Saline	0.10	30
4	4 rats	Silicone	0.05	90
5	4 rats	Saline	0.10	90
6	6 rabbits	Silicone	0.30	30
7	4 rabbits	Saline	0.30	30
8	4 rabbits	Silicone	0.30	90
9	3 rabbits	Saline	0.30	90
10	6 monkeys	Silicone	0.50	90
11	3 monkeys	Saline	0.50	90

[a]From Ref. 46.

TABLE 12. SUMMARY OF EYE IRRITATION STUDIES.[a]

Sample	Viscosity in cstks at 25°C	Occurrence and Persistence of Irritation					
		Immed.	1 h	4 h	8 h	24 h	48 h
DC 200 Fluid	0.65	+	0	0	0	0	0
DC 200 Fluid	2.0	0	0	0	0	0	0
DC 200 Fluid	50.0	0	+	+	+	0	0
DC 550 Fluid	75.0	0	0	+	+	0	0
DC 702 Fluid	35.0	0	0	+	+	0	0
DC 200 Fluid	350.0	0	+	+	+	+	0
DC 200 Fluid	12,500	0	+	+	+	+	0

[a]From Ref. 66.

mice (2.5% group) at Week 76 of the study; there were 19/48 deaths in the treated group and 8/50 in the control group. Histopathological examination revealed a significant increase in the incidence of superficial gastric ulcers in male mice in the 0.25% group when compared with control animals. Female mice given the 2.5% diet had a significantly lower incidence of atrophic uteri than control mice.

McDonald et al.[71] supplemented the diet of weanling rats with 1% levels of polydimethylsiloxane (50, 350, 1000, 10,000, or 60,000 cs) for 90 days. No significant differences from control animals were found with respect to body weight, leukocyte counts, hemoglobin levels and gross or micropathology.

Hobbs et al.[2] fed a polydimethylsiloxane (100 cs) to mallard ducks and bobwhite quail for eight days. The test material was incorporated into the normal laboratory diet at levels of 312, 625, 1250, 2500, or 5000 ppm. The LC50 was reported to be greater than 5000 ppm for each species.

The same silicone fluid was included in the diets (200, 1000, or 5000 ppm) of white leghorn chickens for 24 weeks. No adverse effects on body weight or food consumption were found. No differences were observed between test and control chickens at autopsy.[2]

Rowe et al.[66] administered DC 200 fluid (350 cs) via gavage to female rats in repeated doses. Twenty administrations of 1.0, 2.0, 5.0, 10.0, or 20.0 g/kg were made to five rats each over the course of 28 days. All test animals grew as well as the controls. No significant differences were found in hematological and bone marrow studies. There were no differences found in organ weights. No microscopic abnormalities were found in the test animals.

Inhalation: The same researchers[66] repeatedly exposed 10 rats and eight guinea pigs to hexamethyldisiloxane vapors (4400 ppm). The rats were exposed 7 h at a time for 15 times in 18 days; the guinea pigs received 20 exposures of the same duration in 26 days. Similar groups served as controls but received no exposure. Body and organ weights among test and control groups were essentially the same. All tissues were grossly and microscopically normal.

Dermal: Rowe et al.[66] applied various silicones (see Table 10) to the ears and abdomen of an unspecified number of rabbits 20 times in 30 days. No irritation developed even for the volatile hexamethyldisiloxane which is a good solvent.

Special Studies

Reproduction

Kennedy et al.[51] conducted two separate three-phase reproductive studies using dimethicone fluid (350 cs). The three phases were general reproductive performance, embryogenesis, and peri- and postnatal performance. Rats were used in all three phases; rabbits were also used in Phase II (teratogenesis). The animals were injected subcutaneously with dimethicone (20 or 200 mg/kg) or with sesame oil (200 mg/kg). Males were injected thrice weekly for 10 weeks and females daily for two weeks prior to mating. Postmortum Caesarean sections were performed on half of the pregnant

females on the 13th day of gestation. The number of live and dead pups and the number of implant sites were recorded. The rest of the females carried their litters to term and nursed their pups for 20 days. Dosing continued through weaning after which time all dams and pups were sacrificed. All pups were subjected to detailed gross examination.

The treated male rats were not affected in appearance or behavior, weight gain or food intake, or in genital development. No genital abnormalities were seen in the treated females that underwent Caesarean section. The average number of implant sites and viable fetuses was slightly higher than for control animals. The ratio, implant sites/viable fetuses, suggested no effect on resorption incidence. There were no dead fetuses. No pups showed abnormal flexion. The average gestation period and the mean body weight of pups at parturition and at weaning were not significantly different among the three test groups. The viability indices (pup survival between days 0 and 4) were all normal. The lactation indices (pup survival at 21 days) were low for all groups, especially for the controls. Neither the dams nor pups showed any indication of abnormal behavior. No gross anatomical abnormalities were found at sacrifice for any group.[51]

In Phase II, 156 adult rats were housed, two females and one male per cage. The males were removed three days later (Day 0 of the teratogenesis study). All 104 females were pregnant and were injected subcutaneously with 1000 mg/kg sesame oil (control) or with 20, 200, or 1000 mg/kg of dimethicone fluid once daily from Day 6 to 16. At Day 20, the dams were sacrificed and the fetuses taken by post mortum Caesarean section. The mean number of implant sites and viable pups was not significantly lower in the treated groups than in the control group. The treatment did not cause increased resorption or fetal mortality. There was no difference in mean body weights between test and control pups. Approximately two-thirds of the pups were stained with Alizarin red S and the fetal skeletons examined for anomalies. Some problems were reported with respect to the development of the sternebrae (fetal segments of the sterum which eventually fuse to form the adult corpus sterni). The percentage of pups with incompletely developed sternebrae was 27%, 17.5%, 31%, and 40% for the control, 20, 200, and 1000 mg/kg dimethicone-treated groups, respectively. Bipartite sternebrae was found in 8%, 26%, 16%, and 37% of the pups in the same groups.[51]

A rabbit study was carried out as part of Phase II. Sixty does were mated; the pregnant females were divided into groups of 15 and administered subcutaneously 20, 200, or 1000 mg/kg dimethicone fluid once daily from Day 6 to 18. Controls were injected with 1000 mg/kg of sesame oil. Postmortum Caesarean section was made on Day 29. The average number of implantation sites was statistically the same for the control, 200 and 1000 mg/kg groups (8.8, 9.9 and 8.2/dam). The average was only 6.7/dam for the 20 mg/kg group. In utero mortality was significantly higher than control for all treated groups; the percent of fetal mortality was 0%, 8%, 14% and 12% for the control, 20, 200, and 1000 mg/kg silicone-treated groups, respectively. Mean litter weights were comparable for all groups. No major differences among the groups were found in the development of fetal skeletons.[51]

In Phase III, 80 female rats were mated and divided into four groups. The injection regimen (as before) began on Day 15 and continued throughout lactation. The dams cast their litters naturally. All indices among the four groups were comparable: gestation (percent of pregnancies leading to litters cast alive), viability (percent of pups cast alive that lived at least four days) and lactation (percent of pups alive at day four that lived to weanling 17 days later). There was a higher in utero mortality rate among the animals in the 200 and 1000 mg/kg dimethicone groups than among the 20 mg/kg and controls. The percent dead were 8%, 22%, 3%, and 2.4, respectively.[51]

A similar second 3-phase study was run at the same time as the first study. The second study results were comparable to those cited above except that there was no indication of the fetotoxicity seen before. There were no stillborn pups. There were no adverse effects on reproductive performance or on the weights, number or survival of pups. The Phase II rabbit study was expanded to include dermal studies in which 10% of the total surface area (shaven backs) of the animals was exposed to silicone fluid. Additionally, corn oil as well as sesame oil was used to solubilize some of the test material. Two of the 76 pups treated with 200 mg/kg dimethicone dissolved in sesame oil had *talipes varus* (clubfoot, heel turned inward) which is at or above the maximum limit expected in a

control population. However, there was no *talipes varus* at the 1000 mg/kg dose. There was no incidence of *talipes valgus.*[51]

The same investigators ran similar studies with two less viscous fluids (DC 700-7 cs and DC 225-10 cs). The 7 cs fluid was tested on rats for teratologic potential at 300 and 1000 mg/kg/day given by gavage on gestation Days 6–19. The 10 cs fluid was administered dermally at 200 mg/kg (1:5 in corn oil) to rabbits. Neither silicone fluid caused any type of teratogenic activity.[51]

Mutagenesis

A mutagenesis study with silicone fluid (7 cs) was conducted using albino mice. Either 5 or 10 g/kg silicone fluid was injected once intraperitoneally. Methyl methanesulfonate (50 mg) was used as a positive control. Mutation rates were determined on the basis of both early resorptions and decreases in viable embryos. No evidence for dominant lethal mutagenic activity was found for the test fluids.[51]

Clinical Studies

Solid silicone (drug-releasing implants) and liquid silicone (skin augmentation injections) have been used for several years. The absence of extensive adverse reaction to these silicones may suggest indirectly that they are relatively nontoxic substances. However, Jeyasselan et al.[38] have reported a local tissue response to a solid-dimethicone implant in one of 50 women studied. In this single case, microscopic examination of the tissue surrounding the implant showed a connective tissue response with progressive condensation and maturation of collagen associated with chronic inflammatory cell reaction. This reaction was predominantly of the mononuclear and foreign body giant cellular type. Neovascularization of the system in the area was also noted, but no anaplastic (cell reversion) changes in the fibroblasts were seen.

Silicones are used in creams for the treatment of several dermatoses. Such problems as subacute and chronic housewive's eczema, contact dermatitis of the hands, uncomplicated diaper rash, periaural dermatitis, certain hyperkeratotic dermatoses and other skin conditions that do not respond to conventional medicants have responded favorably to lotions containing from 1.5% to 30% silicone fluid.[40,41,72]

Subchronic percutaneous absorption studies on several silicones were carried out on three groups of volunteers (5 subjects/group). The subjects were exposed to dimethylpolysiloxane (100 cs), tris-(trimethylsiloxy)-phenylsilane (15 cs), or trifluoropropylmethylpolysiloxane (300 cs) once daily for 10 conseuctive days. The fluid (50 mg/kg) was spread evenly over the entire back of each subject and left in contact with the skin for 20 h, after which time any remaining material was removed. Blood and urine samples were collected and analyzed for silicone content for comparison with pretest values. There was no statistically significant increase in silicone levels in either blood or urine. Under these conditions, little or no silicone was absorbed through the skin.[9]

SUMMARY

Dimethicones are polymers of methylsiloxane. Dimethicone Copolyols are Dimethicones copolymerized with polyalkoxy chains. The Copolyols are chemically and physically inert ingredients used in cosmetics in a concentration range of less than or equal to 0.1–10% as surface tension depressants, wetting agents, emulsifiers, foam builders, plasticizers, and lubricants. Copolyol-containing products may be applied to all surfaces of the body on an occasional or daily basis over a period of years.

Silicone compounds do not easily cross membrane barriers and are not absorbed through the skin. Silicones are not metabolized by the body or by microorganisms. Silicone fluids are relatively innocuous when administered orally and parenterally.

Dimethicone Copolyols were at most slightly toxic to the rat when administered orally in a single dose. Single dermal application of Copolyols to rats and rabbits were practically nontoxic. Copolyols were not primary skin or ocular irritants in the rabbit. Inhalation studies at ambient temperatures in the rat indicated that little hazard exists. An 89-day feeding study in the rat using two concentrations of a Copolyol B gave no evidence of subchronic oral toxicity. Subchronic dermal

tests in the rabbit using two undiluted Copolyol A ingredients showed little effect other than slight to moderate skin irritation at the application sites.

Clinical studies on a total of 39 subjects indicated that both 40% Dimethicone Copolyol in aqueous solution and undiluted Dimethicone Copolyol are not primary skin irritants.

Fifty subjects showed no indication of skin irritation or sensitization when tested with undiluted Dimethicone Copolyol A ingredients. An unspecified concentration of Dimethicone Copolyol was found to be nonirritating and nonsensitizing when tested on 201 volunteers.

CONCLUSION

On the basis of the available information presented in this report, the Panel concludes that Dimethicone Copolyol is safe as a cosmetic ingredient in the present practices of use and concentration.

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