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Final Report on the Safety Assessment of Carbomers-934, -910, -934P, -940, -941, and -962

The Carbomers are synthetic, high molecular weight, nonlinear polymers of acrylic acid, cross-linked with a polyalkenyl polyether. The Carbomer polymers are used in cosmetics and emulsifying agents at concentrations up to 50%.

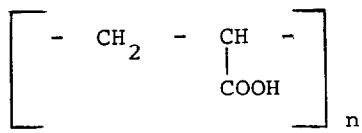
Acute oral animal studies showed that Carbomers-910, -934, -934P, -940, and -941 have low toxicities when ingested. Rabbits showed minimal skin irritation and zero to moderate eye irritation when tested with Carbomers-910 and -934. Subchronic feeding of rats and dogs with Carbomer-934 in the diet resulted in lower than normal body weights, but no pathological changes were observed. Dogs chronically fed Carbomer-934P manifested gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver.

Clinical studies with Carbomers showed that these polymers have low potential for skin irritation and sensitization at concentrations up to 100%. Carbomer-934 demonstrated low potential for phototoxicity and photocontact allergenicity.

On the basis of the available information presented and as qualified in the report, it is concluded that the Carbomers are safe as cosmetic ingredients.

CHEMICAL AND PHYSICAL PROPERTIES

The Carbomer resins (-910, -934, -934P, -940, -941, and -962) are synthetic, high molecular weight, nonlinear polymers of acrylic acid cross-linked with a polyalkenyl polyether. They are chemically similar to each other, differing only in ascending molecular weights (which range from Carbomer-910 to Carbomer-962). They contain between 98.7% and 99.9% acrylic acid. When dried at 80°C for one hour, they contain not less than 56.0% and not more than 68.0% carboxylic acid (−COOH) groups.[1-5] The general structural formula is:[6]



Carbomer-934 is reported to be a polymer of acrylic acid cross-linked with alkylsucrose: $CH_2 = CHCH_2$-O-sucrose.[6] Carbomer-934P is the pharmaceutical grade of Carbomer-934.[2] Carbomer-962 is the ammonium salt of Carbomer-941 and contains about 20% NH_3.[7] The exact compositions of the Carbomer polymers are proprietary information.[7]

Carbomers-910 and -962 are two new cosmetic ingredients, and they are not listed in the 1977 *CTFA Cosmetic Ingredient Dictionary*.[2] Carbomers-960 and -961, formerly used in cosmetics, are no longer produced.[8]

The Carbomers are white, fluffy powders with a slight characteristic odor.[5] They are highly ionic and slightly acidic; they are largely insoluble in water and in the majority of common solvents.[3,4] When neutralized with alkaline hydroxides or with amines, they dissolve in water, alcohol, and glycerin.[5] Molecular weights for Carbomers-934, -940, and -941 range from approximately 500,000 to 4,000,000.[9]

The Carbomer polymers are hygroscopic in nature. Because of their ability to absorb and retain water, these polymers swell to many times their original volume. Such swollen particles remain discrete in various mucilaginous or colloidal dispersions. Although swelling is inherently caused by their hydrophilic nature, "maximum volume swell" does not occur in water until the polymers are converted to partial organic or inorganic salts. The increased volume is stable at all pH levels and increases as neutralization increases. Maximum volume occurs at 50–90% neutralization, with a neutralization of 75% normally occurring at pH 7.0.[4]

The finely divided, free-flowing Carbomer powders readily disperse in water to yield a low viscosity acid solution. When neutralized, the solution is transformed into a clear, stable gel. In acidic aqueous media (pH 3.5–4.0), the Carbomers yield dispersions of low to moderate viscosity. Between pH 5.0 and 10.0, the polymers reach their optimal viscosity when they set into an emollient gel. At pH levels above 10, the gel structure collapses and viscosity drops.[10] Carbomer dispersions show increased viscosity with increasing concentration of the polymer. Viscosity may be decreased by adding NaCl to the dispersion.[11]

Cahen et al.[10] reported that " . . . Carboxy vinyl polymer . . . does not form a gel in the acid medium of the stomach, whereas in alkaline medium, gel formation gradually occurs."

Chemical and physical properties of the Carbomers are presented in Table 1.[1,5,7,10,12] Additional data relating to the chemical and physical properties of these polymers are reported elsewhere in the literature.[13-29]

Reactivity

Carbomer-934, -940, and -941 gels undergo oxidative degradation when they are exposed to sunlight. The reaction is known to be catalyzed by trace metals; however, no information on the degradation products has been reported. UV absorbers can be incorporated into Carbomer gels to prevent metal-catalyzed depolymerization which in turn can cause loss of viscosity and emulsion stability.[30-32]

Carbomers may react with amines to form thick and stable emulsions of oils in water.[3]

TABLE 1. Chemical and Physical Properties.[a]

Properties	*Carbomer-910*	*Carbomer-934*	*Carbomer-934P*	*Carbomer-940*	*Carbomer-941*	*Carbomer-962*	*Carbomer (unspec.)*
Loss on Drying (Maximum) (%)	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Viscosity (0.5% aqueous) (CPS)		30,500–39,000	29,400–39,400	40,000–60,000	4,000 min.–11,000 max.		
Viscosity of Neutralized Solution at 25°C: (CPS)							
a. 0.2% Solution		2,000–5,450		15,000–30,000	2,500–6,400		
b. 0.5% Solution		26,500–39,500		45,000–70,000	5,400–11,400		10,000
c. 1.0% Solution							30,000
Clarity of Neutralized Solution				80.0% min.			
Specific Gravity							1.41
pH of 0.5% Solution at 25°C							2.7–3.3
pH of a 1% Water Solution							3.0
Equivalent Weight							71–80
Viscosity of Neutralized Solution containing 2.50 g Carbomer in 500 ml of Water (CPS)							not less than 30,000 and not more than 40,000
Equilibrium Moisture Content at Room Temperature and 50 percent Relative Humidity							8.0%
Bulk Density (lbs./cubic foot)							13
Moisture Content (%)							2.0 max.
Carbon (%)							47.0–50.8
Hydrogen (%)							5.0–6.2
Residue on Ignition (%)							0.1

[a]Data from Refs. 1, 5, 7, 10, and 12.

Methods of Manufacture and Impurities

The Carbomer polymers are manufactured by reflux polymerization of acrylic acid in an inert solvent in the presence of a catalyst; in doing this, a closed system, free of oxygen and water, is used.[9] Details of the manufacturing process are proprietary information.[7]

Impurities for each of the Carbomers are presented in Table 2.[7] The Panel calls attention to the presence of benzene as an impurity in Carbomers and recommends that every effort be made to reduce it to the lowest possible value. Benzene is a known toxic agent and human epidemiological evidence strongly suggests that it is a leukemogenic agent as well.[33-39]

PURPOSE AND FREQUENCY OF USE IN COSMETICS

The Carbomer polymers are supplied as free-flowing powders, but in cosmetic preparations they are frequently used in their neutralized form—that is, as a gel. (In a few preparations, such as aerosol formulations and shaving creams, they are used in the unneutralized form.) The Carbomers are normally used in cosmetics between a pH of 6.0 and 9.0.[9]

The Carbomers are used as thickening, suspending, dispersing, and emulsifying agents.[3,4,9,12,32,33] They are widely used to provide emulsion stability[4,28,29] and rheologic control.[4]

FDA product formulation data are presented in Table 3. These data show that the various Carbomers may be used up to a concentration of 50 percent.[41] However, one industry source reports that in cosmetics, Carbomers are normally used at concentrations below 1.0%. When Carbomers are used in unneutralized form, however, their concentration may be as high as 2.0%.[9]

TABLE 2. Impurities.[a]

Ingredient	Impurities	Typical values
Carbomers-910, -934, -940 and -941	Water	<0.5%
	Benzene	1,800 ppm (5,000 ppm max.)
	Propionic Acid	1,200 ppm
	Acetic Acid	600 ppm
	Acrylic Acid	80 ppm
	Heavy Metals	10 ppm maximum
	Iron	1 ppm
	Arsenic	<1 ppm
	Lead	<0.3 ppm
Carbomer-934P	Same as above except for:	
	Benzene	<100 ppm (100 ppm max.)
Carbomer-962	Water	<0.5%
	Benzene	1,300 ppm (4,000 ppm max.)
	Propionic Acid	1,000 ppm
	Acetic Acid	500 ppm
	Acrylic Acid	60 ppm
	Heavy Metals	10 ppm maximum
	Iron	1 ppm
	Arsenic	<1 ppm
	Lead	<0.3 ppm

[a]Data from Ref. 7.

TABLE 3. Product Formulation Data.[a]

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Carbomer-934		
Lotions, oils, powders, and creams	>0.1–1	4
	≤0.1	1
Other bath preparations	>10–25	1
	>1–5	2
	>0.1–1	2
Eyeliner	>0.1–1	5
Eyeshadow	>0.1–1	20
Mascara	≤0.1	1
Perfumes	>0.1–1	9
Sachets	>0.1–1	10
	≤0.1	1
Other fragrance preparations	>0.1–1	5
Hair conditioners	>0.1–1	3
Permanent waves	>0.1–1	1
Shampoos (noncoloring)	≤0.1	1
Tonics, dressing, and other hair grooming aids	>1–5	1
	>0.1–1	7
Wave sets	>0.1–1	1
Other hair preparations	>1–5	1
	>0.1–1	3
Hair dyes and colors (all types requiring caution statement and patch test)	>0.1–1	1
Other hair coloring preparations	>0.1–1	1
Blushers (all types)	>1–5	4
	>0.1–1	10
Foundations	>1–5	1
	>0.1–1	12
Makeup bases	>0.1–1	2
	≤0.1	2
Rouges	>10–25	1
	>0.1–1	5
Makeup fixatives	≤0.1	1
Other makeup preparations	>0.1–1	2
Cuticle softeners	>0.1–1	3
Dentifrices (aerosol, liquid, pastes, and powders)	>0.1–1	1
Bath soaps and detergents	>0.1–1	1
Deodorants (underarm)	>0.1–1	1
	≤0.1	1
Other personal cleanliness products	>0.1–1	1
Aftershave lotions	>0.1–1	8
Beard softeners	>0.1–1	1
Shaving cream (aerosol, brushless, and lather)	>0.1–1	4
Other shaving preparations	>0.1–1	2
	≤0.1	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1–5	2
	>0.1–1	29
	≤0.1	9
Face, body, and hand (excluding shaving preparations)	>1–5	2
	>0.1–1	68
	≤0.1	18

TABLE 3. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Moisturizing	>1–5	3
	>0.1–1	123
	≤0.1	21
Night	>1–5	1
	>0.1–1	16
	≤0.1	3
Paste masks (mud packs)	≤0.1	7
Wrinkle smoothing (removers)	>0.1–1	4
Other skin care preparations	>1–5	1
	>0.1–1	7
	≤0.1	2
Suntan gels, creams, and liquids	>1–5	1
	>0.1–1	14
	≤0.1	1
	Total	477
Carbomer-934P		
Other bath preparations	>0.1–1	1
Moisturizing	>0.1–1	2
Night	>0.1–1	1
	Total	4
Carbomer-940		
Eyeliner	≤0.1	1
Eyeshadow	>0.1–1	2
Eye makeup remover	>0.1–1	1
Mascara	>0.1–1	1
Other eye makeup preparations	>0.1–1	1
Colognes and toilet waters	>1–5	4
	>0.1–1	12
Perfumes	>0.1–1	1
Sachets	>0.1–1	4
Other fragrance preparations	>1–5	6
	>0.1–1	14
	≤0.1	1
Hair conditioners	>1–5	1
	>0.1–1	4
Tonics, dressing, and other hair grooming aids	>1–5	3
	>0.1–1	15
	≤0.1	2
Wave sets	>1–5	2
	>0.1–1	37
	≤0.1	2
Other hair preparations	>0.1–1	3
Blushers (all types)	>1–5	3
	>0.1–1	27
Foundations	>0.1–1	6
Leg and body paints	>1–5	1
Makeup bases	>0.1–1	1
Rouges	>0.1–1	9
Other makeup preparations	>1–5	4
	>0.1–1	8
Cuticle softeners	>0.1–1	1
	≤0.1	1
Other personal cleanliness products	>0.1–1	1

TABLE 3. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Aftershave lotions	>1–5	1
	>0.1–1	8
Cleansing (cold creams,	>1–5	3
cleansing lotions, liquids,	>0.1–1	18
and pads)	≤0.1	7
Face, body, and hand	>1–5	1
(excluding shaving	>0.1–1	31
preparations)	≤0.1	10
Foot powders and sprays	>0.1–1	1
Moisturizing	>10–25	1
	>1–5	1
	>0.1–1	37
	≤0.1	7
Night	>1–5	2
	>0.1–1	23
Paste masks (mud packs)	>0.1–1	8
	≤0.1	2
Skin fresheners	>0.1–1	6
	≤0.1	3
Wrinkle smoothing (removers)	>0.1–1	1
Other skin care preparations	>0.1–1	18
	≤0.1	1
Suntan gels, creams, and	>1–5	1
liquids	>0.1–1	7
Indoor tanning preparations	>0.1–1	2
Other suntan preparations	>0.1–1	3
	Total	382
Carbomer-941		
Bubble baths	>0.1–1	2
	≤0.1	1
Other bath preparations	>0.1–1	1
Eyeshadow	≤0.1	1
Eye lotion	>0.1–1	1
Eye makeup remover	≤0.1	1
Colognes and toilet waters	>0.1–1	8
Perfumes	>1–5	1
	>0.1–1	2
	≤0.1	1
Sachets	>5–10	2
	>0.1–1	10
Other fragrance	>1–5	1
preparations	>0.1–1	12
	≤0.1	8
Hair conditioners	>0.1–1	1
Tonics, dressing, and other	>0.1–1	2
hair grooming aids	≤0.1	1
Wave sets	>0.1–1	1
Other hair preparations	>0.1–1	4
Blushers (all types)	>0.1–1	1
	≤0.1	1
Lipsticks	>0.1–1	1
Makeup bases	>0.1–1	1
	≤0.1	1
Other makeup preparations	>0.1–1	3
Cuticle softeners	>0.1–1	3

TABLE 3. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Nail creams and lotions	≤0.1	1
Other manicuring preparations	>25-50	1
Aftershave lotions	>0.1-1	5
	≤0.1	3
Other shaving preparation products	>0.1-1	2
	≤0.1	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>0.1-1	13
	≤0.1	11
Face, body, and hand (excluding shaving preparations)	>1-5	1
	>0.1-1	23
	≤0.1	20
Moisturizing	>0.1-1	31
	≤0.1	20
Night	≤0.1	3
Skin fresheners	>0.1-1	3
	≤0.1	3
Other skin preparations	>10-25	1
	>0.1-1	4
	≤0.1	1
Suntan gels, creams, and liquids	>0.1-1	1
	≤0.1	1
	Total	221

[a]Data from Ref. 41.

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations (21 CFR 720.4). Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Carbomers can be applied to or come in contact with skin, eyes, mucous membranes, respiratory epithelium, hair, and nails; small amounts are likely to be ingested from dentifrices (Carbomer-934) and lipsticks (Carbomer-941). Product formulations containing one or more of these ingredients may be used from once a week up to several times per day. Many of the products may be expected to remain in contact with the body for as little as a few minutes to as much as a few days. Over the course of several years, each product could be applied hundreds of times.[41]

Non-cosmetic Uses

Pharmaceutical Uses: Carbomer polymers are used in pharmaceutical products as thickening,[3,12,42,43] suspending,[3,5,12,43-47] dispersing,[3] and emulsifying

agents.[3,5,12] They are also used to control the release of medicaments from time-release tablets or from entrapped systems,[48-52] as bulking agents in laxatives,[12] and as bases or vehicles for jellies, ointments, and pastes.[53-57] Spermicidal jellies and ointments formulated in a Carbomer-934 base are particularly effective on human sperm in vitro,[58] and are nonirritating to the vaginal mucosa of rats.[59] Various jellies formulated with Carbomer-934 and -940 are nonirritating to the rabbit eye and skin.[56] Carbomer-934 is currently used in oral pharmaceutical preparations under an over-the-counter label.[12]

Chemical and Industrial Specialities: Carbomers are used in wallpaper removers, waxes, polishes, paints, waterproof and oilproof coatings, emulsion-based lubricants, and printing inks. In latexes, tape adhesives, and solvents Carbomers function as thickeners. In creosote, tars, and asphalts they are used as emulsifiers. They are also employed in suspensions of glass fibers, graphite, powdered metals, and in forming gels with hydrocarbons.[3,12,43]

Additional data relating to the noncosmetic use of the Carbomer polymers are reported elsewhere in the literature.[60-66]

BIOLOGICAL PROPERTIES

General Effects

Carbomer as a Bulk Laxative in Animals: Carbomer-934 was reported by Cahen et al.[10] to have a significant laxative effect on rats, guinea pigs, and dogs. The nature of its laxative activity was essentially different from that of cathartics or saline purgatives and more comparable to the activity of bulk laxatives. In contrast to other hydrophilic laxatives like methylcellulose, Carbomer-934 exhibited a swelling action 20 times its bulk in intestinal fluid and no action in gastric juice. The minimum effective dose for laxative activity in rats was 0.4 g/kg; the laxative effect of this disappeared after 72 hours.

Effect of Carbomer on the Growth and Metabolic Activities of *Aspergillus Niger:* Addition of 0.3% (w/v) Carbomer-934 to fermentation media "enhanced the metabolic activities" of *Aspergillus niger*. Increases in cellular growth, potassium transport, amylase production, and respiration rate were observed; more specifically, the last of these was increased by as much as 200%.[67,68] However, the addition of 0.3% (w/v) Carbomer-934 to growth media did not alter the respiratory quotient or the overall enzyme system for respiration.[69]

Effect of Carbomer on Viral Reverse Transcriptase: De Clercq and Claes[70] reported that Carbomer-934 has a stimulatory effect on the activity of RNA-dependent DNA polymerase (reverse transcriptase) in the Moloney strain of Murine Leukemia Virus (M-MuLV). The addition of Carbomer-934 to a standard in-vitro RNA-dependent DNA polymerase assay mixture containing the M-MuLV virus resulted in a significant increase in both the rate and extent of DNA synthesis. The stimulatory effect was found to be dose-dependent; a "maximum response" was obtained at a concentration of 160 μg Carbomer-934/ml saline.

Bloemers and Van der Horst[71] showed that Carbomer-934 had an inhibitory effect on reverse transcriptase activity in both Rauscher Murine Leukemia Virus (R-MuLV) and Avian Myoblastosis Virus (AMV). When synthetic

poly(A)* templates were used, 50 to 500 μg Carbomer-934/ml saline was strongly inhibitory to R-MuLV reverse transcriptase activity. Employing both synthetic poly(A) and poly(C)† templates, investigators observed strong inhibition of AMV enzyme activity at concentrations of 100–300 μg/ml. The endogenous activity of R-MuLV reverse transcriptase was slightly stimulated at 1 and 5 μg/ml, but concentrations ranging from 5 to 100 μg/ml were inhibitory. According to the authors, "The observed competitive inhibition seems a logical result, because a negatively charged polymer-like Carbopol could be expected to mimic nucleic acids and, thus, to interfere with the binding of the template to the enzyme."[71]

Kumar[72] confirmed Bloemers and Van der Horst's work[71] regarding Carbomer-934's inhibition of reverse transcriptase. Further, he also showed that it was possible to use these inhibitory activities to differentiate viral reverse transcriptase from such closely related enzymes as mammalian r-DNA polymerase.

Effect of Carbomer on the Resistance of Mice to Viral Infection: De Clercq and Luczak[6] reported that intraperitoneal administration of Carbomer-934 imparts to mice a resistance to vaccinia and herpes simplex (Type 1) viral infections. When Carbomer-934 was injected intraperitoneally into mice at a dose of 80 mg/kg four days before intravenous vaccinia virus challenge, the number of pox lesions was significantly reduced relative to the number of such lesions in the controls. However, when Carbomer-934 was injected intramuscularly at a dose of 80 mg/kg four days before vaccinia virus innoculation, the polymer was not effective in reducing pox lesions. An intraperitoneal dose of 100 mg/kg (0.8 mg/mouse) one or four days before intranasal herpes simplex (Type 1) virus challenge significantly reduced mortality caused by viral encephalitis. An intramuscular dose of 100 mg/kg one or four days before virus innoculation, however, failed to confer any significant protection. When female mice were injected intraperitoneally with the polymer at 100 mg/kg (2 mg/mouse), a low titer interferon response was generated. The investigators postulated that the antiviral effects that Carbomer-934 did manifest were brought about by activation of peritoneal macrophages and/or interferon production. Since Carbomer-934 was only effective against viral infection when it was injected intraperitoneally (vs. intramuscularly), the possibility that this compound acted by directly inactivating the virus was dismissed.

Animal Toxicology

General Studies

Acute toxicity: oral

Acute oral studies with rats, guinea pigs, mice, and dogs showed that Carbomers-910, -934, -940, and -941, have low toxicity when ingested. Results of these studies are presented in Table 4.[10,73-80]

Acute toxicity: inhalation

Carbomer-910: Three groups of albino rats (five males and females/group) were exposed to Carbomer-910 dust for four hours at chamber concentrations of

*poly(A) = poly(adenyl acid)
†poly(C) = poly(cytidylic acid)

TABLE 4. Acute Oral Toxicity.[a]

Carbomer	*Concentration (%)*	*Dose and/or amounts administered (g/kg)*	*No. and type of animal*	*No. of animals per dose level*	*Observations and/or comments*	*LD50 (g/kg)*	*Ref.*
-910	30 w/v susp. in corn oil	4.556, 6.834, 10.250, 15.380	16 albino rats	4	Hypoactivity at all dose levels; diarrhea, labored breathing, muscular weakness, rhinitis at 10.250 and 15.380 g/kg. Two out of 4 and 4/4 rats died at 10.250 and 15.380 g/kg, respectively. Gross necropsy of 6 that died revealed pale livers, kidneys and spleens; test material present in stomach and blood noted in GI tract. Body weight gains of 10 survivors w/in normal limits.	10.250 ± 1.203	81
-934	20 in aq. susp.	5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0	80 albino rats	10	All animals survived 14-day observation period in good health.	>40 > 8 (ingred.)	74
-934	20 in aq. susp.	50	10 albino rats	10	All animals survived w/out showing evidence of pharmacological disturbance.	>50 >10 (ingred.)	75
-934 Sample A	25 w/v susp. in corn oil	4.556, 6.834, 10.250	12 albino rats	4	At 10.250 g/kg, 2/4 rats died; all other animals survived w/no pathologic alterations noted. Necropsy of 2 that died revealed hemorrhages in GI tract. Reactions at 10.250 g/kg included hypoactivity, labored breathing, muscular weakness, hemorrhagic rhinitis.	10.250	76

TABLE 4. (Continued.)

Carbomer	Concentration (%)	Dose and/or amounts administered (g/kg)	No. and type of animal	No. of animals per dose level	Observations and/or comments	LD50 (g/kg)	Ref.
-934 Sample B	25 w/v susp. in corn oil	4.556, 6.834, 10.250	12 albino rats	4	At 10.250 g/kg, 4/4 rats died; all other animals survived w/no pathologic alterations noted. Necropsy of 4 that died revealed hemorrhages in GI tract, hardened test material noted in stomach. Reactions at 10.250 g/kg included hypoactivity, labored breathing, muscular weakness, ataxia, prostration, tremors.	8.370	76
-934	7.5 in aq. sol'n	–	230 rats	–		4.1	10
-934	–	–	rats	–		4.3	77
-934	0.20 in formulation	30 of form.	10 rats	10	No deaths or toxic signs reported for the skin moisturizer formulation as tested.	>30 (form.) >.06 (ingred.)	78
-934	0.20 in formulation	25 of form.	10 rats	–	No deaths or toxic signs reported for the skin moisturizer formulation as tested.	>25 (form.) >.05 (ingred.)	78

-934	20 in aq. susp.	5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0	80 albino guinea pigs	10	All animals survived 14-day observation period in good health.	>40 >10 (ingred.)	74
-934	20 in aq. susp.	50	10 albino guinea pigs	10	All animals survived w/out showing evidence of pharmacological disturbance.	>50 >10 (ingred.)	75
-934	7.5 in aq. sol'n	–	124 guinea pigs	–	–	2.5	10
-934	–	–	guinea pigs	–	–	2.5	77
-934	10.0 in aq. sol'n	–	266 albino mice	–	–	4.55	77
-934	–	–	mice	–	–	4.6	77
-934	–	2.24, 4.0, 4.8, 6.0, 8.0, respectively; mixed w/food in ratio 1:10.	16 dogs	2, 5, 2, 5, 2, respectively	Anorexia, vomiting observed 6–24 hrs following Carbomer administration; no relationship between dose and effect noted. No fatalities observed even at highest dose.	–	10
-940	1.0 or 2.5 in aq. sol'n	0.625 max. dose	10 albino rats	–	No deaths.	>0.625	79
-941	1.0 or 2.0 in aq. susp.	0.1, 0.5, 1.0	10 albino rats	10	No deaths during 14-day observation period.	>1.0	80

[a]Data from Refs. 10 and 74–81.

1.01, 1.82, or 5.86 mg/l air.[81] Analysis of the Carbomer particles revealed that 83.4% were 10 microns or less in diameter; particles less than 10 microns were considered respirable. One male and one female rat from the low-dose group, three males and two females from the middle-dose group, and all rats from the high-dose group died during the 14-day observation period. The average two-week body weight gains of all animals were within normal limits. Moreover, "No gross tissue changes attributable to the effects of the test material were observed at necropsy of any of the rats that survived to termination of the study. Gross tissue changes found at necropsy of rats that died during the experiment were considered normal postmortem alterations." Under conditions of this test, the acute LC50 was determined to be 1.71 mg/l air.[81]

Acute toxicity: dermal

Carbomer-910: Carbomer-910 was applied to the skin of four albino rats, two with abraded skin and two with intact skin, at a dose of 3.0 g/kg. The test material was premoistened with water and then held in place for 24 hours by an impervious wrapping. At the end of this period, the wrapping and the residual test material were removed and the animals observed thereafter for 14 days. "No unusual behavioral or systemic reactions" or signs of skin irritation were observed. Under these test conditions, the dermal LD50 was determined to be >3.0 g/kg.[73]

Carbomer-934: A skin moisturizer containing 0.20% Carbomer-934 was tested for acute dermal toxicity in eight albino rabbits (4M, 4F) weighing 2.3 to 2.8 kg. A single 10 g/kg was topically applied to abraded and intact skin. No treatment-related deaths or toxic signs were reported. The acute dermal LD50 and MLD of the skin moisturizer formulation were considered to be >10 g/kg.[78]

Acute toxicity: intravenous administration

Carbomer-934: Three groups of albino rabbits (3 animals/group) were given intravenous injections of either 1%, 2%, or 3% Carbomer-934 in aqueous solution at doses of 5 ml/kg; no deaths resulted.[74]

Skin irritation

Carbomer-910: Using the procedures of the Federal Hazardous Substances Act (FHSA), investigators evaluated the skin irritation potential of 100% Carbomer-910 in six albino rabbits. The test material, 0.5 g moistened with 0.5 ml water, was applied to abraded and intact skin under an impervious wrapping for 24 hours. Erythema was observed at all test sites (abraded and intact) at 24 hours, but by the end of 72 hours this was reduced to barely perceptible erythema at three sites (two abraded and one intact). Slight edema was noted in three rabbits on both abraded and intact skin at 24 hours, but not at 72 hours. A score of 1.3 out of a possible 8.0 was assigned to the polymer. The investigators concluded that Carbomer-910 is not an "irritant" as defined in the FHSA.[81]

Carbomer-934: By means of the Draize procedure,[82] two samples (A and B) of 100% Carbomer-934 were tested for primary skin irritation. Each test sample of 0.5 g was premoistened with water and applied for 24 hours under an impervious wrapping to the abraded and intact skin of six albino rabbits. Three of six animals tested with Sample A showed barely perceptible erythema of the abraded skin at 24 hours, whereas, two of six animals showed the same response on intact skin. Of the six rabbits tested with Sample B, two showed barely perceptible erythema

on both abraded and intact skin at 24 hours. All the tested animals were negative for edema at 24 hours and for edema and erythema at 72 hours. Primary irritation scores for both test materials were 0.2, indicating minimal irritation.[83]

By means of the Draize method, a skin moisturizer formulation containing 0.2% Carbomer-934 was tested for primary skin irritation in 12 rabbits. The animals were exposed to 0.5 g of the moisturizer under occlusive patches for 24 hours. The formulation elicited mild skin irritation with Primary Irritation Indices (PIIs) ranging from 0.5 to 0.9 out of a possible score of 8.0.[78]

Eye irritation

In studies conducted on rabbits, Carbomers-910, -934, -934P, -941, and/or their salts caused zero to moderate eye irritation at concentrations of 0.20%–100%. Results of the various tests are summarized in Table 5, while details of the individual studies are presented in the discussion that follows.[73,78,79,83-91] Since Carbomers are hydroscopic gel-forming polymers, one would expect them to draw water from the eye tissue in such a way as to result in some irritation.[4]

Carbomer-910: Through the use of the FHSA procedures, the eye irritation potential of 100% Carbomer-910 resin was evaluated in six rabbits. At one hour, Carbomer-910 formed a thick gel in the eyes, so that a valid evaluation of the cornea was precluded. Corneal injury was noted in the eyes of two animals at 24 hours and in one at 48 hours. Irritation was noted in the iris of each animal at one hour, of two animals at 24 hours, and of one at 48 hours. Although irritation of the conjunctiva was observed in each animal at 1, 24, and 48 hours, this had cleared by 72 hours. At the one-hour reading, the highest score obtained was 17 out of 110 points. On the basis of these results, Carbomer-910 was classified as an eye "irritant" as defined in the FHSA.[81]

Carbomer-934: Using a modified Draize procedure, investigators tested each of two samples (A and B) of 100% Carbomer-934 resin for eye irritation in six rabbits. Both samples formed a gelatinous film over the cornea, so that no valid one-hour readings of corneal injury could be made. At 24 hours, three rabbits manifested corneal injury caused by Sample A while one animal displayed corneal injury caused by Sample B. Corneal injury persisted through the 14-day observation period in two animals tested with Sample A, while no injury was apparent at the 3-, 7-, or 14-day readings of rabbits tested with Sample B. Sample A produced slight to moderate irritation in the iris and conjunctiva of each animal at one hour and in five of six animals at 24 hours; at 72 hours, no irritation was observed. By 24 hours, sample B had caused slight to moderate irritation in the iris of three animals and moderate irritation in the conjunctiva of two animals; no evidence of irritation was noted at 72 hours. Sample A was considered to be "moderately irritating," insofar as it elicited a score of 15.7 points out of a possible 110. With a score of 7.0 points, Sample B was rated as "minimally irritating."[83]

The following salts at 0.5% in aqueous solution were each tested for eye irritation potential in six rabbits:

(1) Sodium salt of Carbomer-934: pH 7.0;
(2) Sodium salt of Carbomer-934: pH 8.0;
(3) Sodium dodecylamine salt of Carbomer-934: pH 6.8;
(4) Sodium dodecylamine salt of Carbomer-934: pH 7.0;
(5) Sodium dodecylamine salt of Carbomer-934: pH 8.2.

TABLE 5. Eye Irritation.[a]

Carbomer	Concentration (%)	No. of rabbits	Procedure	Conclusion	Ref.
1. *-910*	100	6	FHSA	"irritant"	73
2. *-934*					
Sample A	100	6	Draize	"moderately irritating"	83
Sample B	100	6	Draize	"minimally irritating"	84
3a. *-934*					
sodium salt: pH 7.0	0.5 in aq. sol'n	6	–	mild irritant	
sodium salt: pH 8.0	0.5 in aq. sol'n	6	–	mild irritant	
sodium dodecylamine salt: pH 6.8	0.5 in aq. sol'n	6	–	mild irritant	
sodium dodecylamine salt: pH 7.0	0.5 in aq. sol'n	6	–	mild irritant	
sodium dodecylamine salt: pH 8.2	0.5 in aq. sol'n	6	–	mild irritant	
b. sodium salt: pH 7.0	0.5 in aq. sol'n	1	–	mild irritant	84
sodium salt: pH 8.0	0.5 in aq. sol'n	1	–	mild irritant	
sodium dodecylamine salt: pH 6.8	0.5 in aq. sol'n	1	–	mild irritant	
sodium dodecylamine salt: pH 7.0	0.5 in aq. sol'n	1	–	mild irritant	
sodium dodecylamine salt: pH 8.2	0.5 in aq. sol'n	1	–	mild irritant	
4. *-934*					
sodium PEG-15-Cocamine	0.5 by wt in aq. gel	9	–	"... no ... detectable evidence of eye injury ..."	86
5. *-934*	2.0 in TEA	9	–	"... may possess very mild irritant properties"	87

6.	*-934 and -934P*					
	-934 neutralized w/TEA-pH 7.0	1.0 in gel	6	FHSA	". . . cannot be considered . . . a mild or severe eye irritation hazard"	88, 89
	-934 neutralized w/NaOH-pH 7.0	1.0 in gel	6	FHSA	". . . cannot be considered . . . a mild or severe eye irritation hazard"	
	-934 P neutralized w/NaOH-pH 7.0	1.0 in gel	6	FHSA	". . . cannot be considered . . . a mild or severe eye irritation hazard"	
	-934					
7a.	skin moisturizer formulation	0.20 in formulation	9	Draize modification	formulation "minimally irritating"	78, 90–91
b.	skin moisturizer formulation	0.20 in formulation	9	Draize modification	formulation "minimally irritating"	
8.	*-940*					
	-940	1.0 in aq. sol'n	6	Draize	minimally irritating	79
	monoisopropanolamine salt	0.4 and 1.0 in aq. sol'n, resp.	6 and 3, resp.	Draize	minimally irritating	
	sodium salt	0.4, and 1.0 in sol'n, resp.	6 and 3, resp.	Draize	minimally irritating	
9.	*-940*					
	di-(2-ethylhexyl)amine salt	1.0 in aq. susp.	10	–	". . . no . . . detectable evidence of eye injury . . ."	86
10.	*-941*					
	-941	1.0 in aq. susp.	4	–	Practically nonirritating	85
	sodium salt	1.0 in aq. susp.	4	–	Practically nonirritating	
	monoisopropylamine salt	1.0 in aq. susp.	4	–	Practically nonirritating	

[a]Data from Refs. 73, 78, 79, and 83–91.

Quantities varying from 0.01 to 1.0 ml were instilled into the eyes in a single application. Slight corneal injury and slight to severe hyperemia of the conjunctiva and sclera were frequently noted 24 hours after instillation; however, by 72 hours there was complete recovery in most of the eyes so affected. In a second test, each of the five Carbomer-934 salts (0.1 ml) was instilled into the eye of one rabbit every day for five days. Again, corneal injury and hyperemia of the conjunctiva and sclera were frequently observed, with most symptoms disappearing 72 hours after the final treatment. The investigators concluded that "Any of these compounds at 0.5% aqueous solutions, if accidentally introduced into the eyes of workmen, may produce mild irritation."[84]

An aqueous gel containing 0.5% by weight sodium-PEG-15 Cocamine salt of Carbomer-934 was instilled into the right eye of each of nine albino rabbits. Eyes were examined at one-half hour and 24 hours post-instillation. The results indicated that "in no instance was there any detectable evidence of eye injury . . . "[86]

A triethanolamine solution containing 2.0% Carbomer-934 was instilled into one eye of each of nine albino rabbits. Twenty-four hours later, seven animals showed corneal epithelial damage, while two animals showed no eye injury. Seventy-two hours after instillation, only one of the original seven affected eyes still manifested corneal damage. The investigators concluded that Carbomer-934 ". . . may possess very mild irritant properties"; however, they also stated that "Reservation may be placed on that conclusion in the absence of eye irritation testing with triethanolamine as a control."[87]

According to the method outlined in *Principles and Procedures for Evaluating the Toxicity of Household Substances,*[89] a 1.0% gel of each of the following materials (neutralized to pH 7.0) was tested for eye irritation potential in six albino rabbits:

(1) Carbomer-934: neutralized with triethanolamine (TEA);
(2) Carbomer-934: neutralized with sodium hydroxide (NaOH);
(3) Carbomer-934P: neutralized with sodium hydroxide (NaOH).

Carbomer-934 neutralized with TEA caused superficial corneal damage in one of six rabbits 24 hours after instillation; however, at the 48-hour reading, this eye had cleared, and it remained clear 72-hours post-instillation. At 48 hours, Carbomer-934 neutralized with NaOH caused conjunctivitis and slight dullness of the cornea in one of the six rabbits that were tested; at 72 hours these changes had disappeared. Carbomer-934P neutralized with NaOH produced no corneal damage. According to the investigators, "These tests must be considered negative since only one of the six rabbits tested by exposure to any test compound demonstrated any reaction. Accordingly, under the provisions . . . of the Hazardous Substances Labelling Act, these materials . . . cannot be considered as constituting a mild or severe eye irritation hazard."[88]

Through the use of a modified Draize procedure, a skin moisturizer containing 0.20% Carbomer-934 was tested for eye irritation potential in nine rabbits.[90] While six of the rabbit eyes remained unwashed, three of them were washed 30 seconds after instillation of the test material. Generally, irritation was characterized by mild conjunctivitis and mild irititis, though the level of irritation was lower in the washed eyes; all eyes were normal by 72 hours. According to the classification system of Kay and Calandra,[91] the moisturizer formulation was considered "minimally irritating."[78] In a second test, a new group of nine rabbits

displayed responses similar to those of the first when they were exposed to the same formulation and concentration.[78,90-91]

Carbomer-940: Aqueous solutions of Carbomer-940 (1.0%), the monoisopropanolamine salt of Carbomer-940 (0.4% and 1.0%), and the sodium salt of Carbomer-940 (0.4% and 1.0%) were tested for eye irritation potential in 24 rabbits. Approximately 1 ml of each test substance was introduced into the conjunctival sac; the eyes were then scored by the Draize method (max. score = 110). At the one-hour reading, minimal eye irritation was observed in all animals for all three test substances; the maximum score in any instance was 4.0. The incidence of irritation was reduced to half the animals at 24 hours (max. score = 2.0) and to one animal at 48 hours (score = 2.0). At 72 hours post-instillation, scores for each test material were 0. The investigators considered Carbomer-940 and its sodium and monoisopropanolamine salts to be at most minimally irritating.[79]

An aqueous suspension containing 1.0 percent by weight di-(2-ethylhexyl) amine salt of Carbomer-940 was instilled into the right eye of each of ten albino rabbits. Observations for eye irritation were made at one and 24 hours. "In no instance was there any detectable evidence of eye injury . . . ".[86]

Carbomer-941: Aqueous solutions containing 1.0% by weight Carbomer-941, sodium salt of Carbomer-941, or monoisopropylamine salt of Carbomer-941 were tested for eye irritation potential. Each test material was instilled into the right eye of each of four albino rabbits by a single application. Seven of the 12 animals that were tested reacted immediately showing redness of the conjunctiva; there was no reaction on the part of five rabbits. Of the seven rabbits showing immediate eye reactions, one rabbit showed irritation to the Carbomer-941 solution, two to the solution containing the sodium salt of Carbomer-941, and four to the solution containing the monoisopropylamine salt of Carbomer-941. No irritation was observed for any of the test materials on Days 1, 2, or 3 post-instillation.[85]

Subchronic toxicity

Carbomer-934: Five groups of rats (eight rats/group) were administered Carbomer-934 in the diet for 49 days at daily doses of either 0.055, 0.133, 0.3, 0.95, or 5.0 g/kg. Animals receiving 5.0 g/kg daily showed a significant reduction in body weight; however, when the Carbomer-934 was withdrawn from their diet on Day 30, their weights increased normally. No deaths occurred at any of the dose levels.[10]

Carbomer-934P: For 21 days, male and female albino rats were fed Carbomer-934P at dietary levels of either 0% (10 rats) or 5.0% (20 rats). Male rats consumed less food and gained less body weight than did controls. With regard to females, food consumption and weight gains were comparable to those of controls. No abnormal reactions or deaths occurred during the study.[92]

Four groups of rats (30 animals/group) were fed Carbomer-934P at dietary levels of either 0%, 0.2%, 1.0%, or 5.0% for 90 days. Rats to which doses of less than 5.0% were administered showed no ill effects, but the growth of those on 5.0% was stunted. No differences were observed between test and control animals with respect to hematology, blood chemistry, urinalyses, or gross pathology. In rats on the highest dose, absolute liver weights and liver to body and brain weight ratios were reduced; however, this reduction was not accompanied by gross or microscopic pathologic changes. Other organ-weight data revealed no significant differences between treated and untreated animals.[93]

Four groups of beagle dogs (eight animals/group) were fed Carbomer-934P at dietary levels of either 0%, 0.2%, 1.0%, or 5.0% for 90 days. No significant differences between treated and control animals were observed with respect to mortality, food consumption, behavior, chemistry, urinalyses, liver-function tests (for bromosulfophthalein retention), organ weights, organ-to-body and brain-weight ratios, gross pathology, or histopathology. Animals receiving less than 5.0% Carbomer-934P gained weight normally; however, those receiving 5.0% had retarded growth. Although erythrocyte counts, hemoglobin concentrations, and hematocrit values of the high-dose group were also lowered, the values remained within normal limits. Hematologic values of dogs receiving 0.2% and 1.0% were comparable to those of controls.[94]

Chronic toxicity

Carbomer-934: For five days a week over periods of up to 32 months (960 days), dogs received Carbomer-934, in the diets, at doses of either 0, 0.1, 0.5, or 1.0 g/kg. Gross and microscopic examination of tissues revealed no abnormalities. Body and organ weights were also normal. The blood of treated animals showed no deviation from that of controls with regard to complete blood count (CBC), hematocrit, or alkali reserve. Some of the dogs receiving 0.1 g/kg daily for four and one-half months were mated successfully, and the pups born to them were normal.[10]

Carbomer-934P: Carbomer-934P was fed at dietary levels of 0%, 0.1%, 0.5%, and 5.0% to groups of 50, 100, 100, and 100 albino rats, respectively, for six and one-half months. Whereas growth patterns of animals receiving concentrations less than 5.0% were normal, the rats which received 5.0% manifested reduced body weights. (This weight depression, however, was not statistically confirmed.) No significant differences were noted between treated and control animals with respect to food consumption, behavior, or mortality. Hematologic studies, blood chemistries, and urinalyses of the 5% group were also comparable to those of controls. Gonad weights, gonad-to-body weight ratios, and gonad-to-brain weight ratios of females in the 5.0% group were elevated, as were heart weights, heart-to-body weight ratios, and heart-to-brain weight ratios of females in the 0.50% and 5.0% groups. Heart weights and heart-to-brain weight ratios among males in the 5.0% group were lowered, while liver-to-body weight ratios of females receiving 0.1% were elevated. Organ weights and ratios of all other test animals were normal. Gross and microscopic pathological findings of all treated animals were comparable to those of controls.[95]

Beagle dogs were orally administered gelatin capsules containing Carbomer-934P for seven days a week over a period of six and one-half months (200 days). Doses of 0, 0.1, 0.5, and 1.0 g/kg were given to 6, 12, 12, and 12 dogs, respectively. No significant differences were observed between treated and control animals with respect to body weight, food consumption, mortality, behavior, hematology, blood chemistries, urinalyses, or organ weights. Most animals receiving 0.5 and 1.0 g/kg showed gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver. There were no other pathological findings.[96]

Clinical Assessment of Safety

Primary Skin Irritation and Sensitization Studies: Clinical studies with Carbomer-934 and its various salts showed that these polymers have low poten-

tial for skin irritation and sensitization at concentrations of 0.5%, 5.0%, 10.0%, and 100%. When tested at 1.0% concentration, Carbomers-940, -941, and their various salts also showed low potential for human skin irritation and sensitization. Further, clinical studies with formulations containing up to 0.25% Carbomer-934 demonstrated that the products have low potential for both skin irritation and sensitization. These tests are individually discussed below; results are summarized in Table 6.

Carbomer-934: Carbomer-934 was applied daily for five days to skin on the backs of 200 human subjects, half of them men and half women; the polymer was put on each subject in two different forms—as a dry resin and as a 10% aqueous solution under occlusive patches. After a three-week rest period, the material was reapplied to the backs of the same subjects for one 48-hour period. None of the test individuals exhibited any evidence of skin irritation or sensitization. The same lot of Carbomer-934 was applied as a dry resin under occlusive patches to the backs of 50 human subjects (25 males and 25 females) for a 24-hour period, every other day, for 15 applications (30 days). After a three-week rest period, the polymer was reapplied for one 48-hour period. No evidence of skin irritation or sensitization was observed.[74]

In a repeated insult patch test, Carbomer-934 was applied as a dry resin to skin on the backs of 50 human subjects (25 males and 25 females) for 24 hours, every other day, for 15 applications (30 days). After a three-week rest period, the polymer was reapplied to the backs for one 48-hour period. No evidence of skin irritation or sensitization was observed.[75]

In a repeated insult patch test, Carbomer-934 was applied as a dry resin and as a 10% (w/v) aqueous solution to skin on the backs of 50 human subjects (25 males and 25 females). Each test material was applied every other day for a total of 15 applications (30 days). Following a two-week rest period, all subjects were given a single challenge application. Forty-eight of the 50 subjects tested with the dry resin showed no irritation reaction (scores = 0), while two individuals scored single 1+ reactions. No reactions occurred in any subject as a result of the challenge application. Of the 50 subjects tested with 10% (w/v) Carbomer-934, 44 showed no irritation reaction, while six individuals showed at most only 1+ reactions. One of the 50 subjects showed a 1+ reaction as a result of the challenge application. In this study, the investigators concluded that Carbomer-934 demonstrated a low potential for primary skin irritation and sensitization.[97]

The following salts at 0.5% in aqueous solution were tested for human skin sensitization potential:

(1) Sodium salt of Carbomer-934: pH 8.0;
(2) Sodium dodecylamine salt of Carbomer-934: pH 6.8;
(3) Sodium dodecylamine salt of Carbomer-934: pH 7.0;
(4) Sodium dodecylamine salt of Carbomer-934: pH 8.2.

Sixty-five subjects (28 males and 37 females) ranging in age from five months to 86 years were selected for study; 50 of these subjects were white and 14 were black. After being applied in a single drop to the previously cleaned skin, each test material was covered with a patch. Every site was inspected daily, and a new drop of test solution was applied each day for 15 days. After a one-week rest, test substances were reapplied for a single 24-hour period. Daily inspections made through the 27th day revealed no reactions to any of the test materials.[101]

The sodium PEG-15 Cocamine salt of Carbomer-934 was tested for skin irrita-

TABLE 6. Human Skin Irritation and Sensitization Studies.[a]

Carbomer	*Conc. (%)*	*Method applied to skin*	*No. of subjects*	*Conclusion/Comments*	*Ref.*
-934	100 (dry resin)	Applied to skin daily for 5 days; occlusive patches; reapplied for 48 hrs. after 3-wk rest	200	No skin irritation or sensitization	74
-934	10 in aq. sol'n.	Applied to skin daily for 5 days; occlusive patches; reapplied for 48 hrs. after 3-wk rest	200	No skin irritation or sensitization	74
-934	100 (dry resin)	Applied to skin every other day for 30 days; occlusive patches; re-applied for 48 hrs. after 3-wk rest	50	No skin irritation or sensitization	74
-934	100 (dry resin)	Applied to skin every other day for 30 days; reapplied for 48 hrs. after 3-wk rest	50	No skin irritation or sensitization	75
-934	100 (dry resin)	Applied to skin every other day for 30 days; challenge after 2-wk rest	50	2/50 showed single 1+ reactions for skin irritation; no sensitization observed	97
-934	10 in aq. sol'n.	Applied to skin every other day for 30 days; challenge after 2-wk rest	50	6/50 showed at most only two 1+ reactions for skin irritation; 1/50 showed single 1+ reaction to challenge. In this study, the polymer demonstrated a low potential for primary skin irritation and sensitization.	97
-934 Sodium salt pH 8.0	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80

Sodium dodecyl-amine salt pH 6.8	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80
Sodium dodecyl-amine salt pH 7.0	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80
Sodium dodecyl-amine salt pH 8.2	0.5 in aq. sol'n.	Applied to skin daily for 15 days; reapplied for 24 hrs. after 1-wk rest	65	No reactions	80
-934					
Sodium PEG-15 Cocamine salt	0.5 in aq. gel	Applied to skin daily for 14 days; reapplied for 24 hrs. after 6 days rest	50	No visible reactions; however, 2/50 complained of itching. Investigators concluded that the polymer was neither a primary skin irritant nor a sensitizer.	86
-934					
Sample A	5 in aq. gel	Applied to skin every other day for total of 9 induction patches; reapplied for 24 hrs after 2-wk rest	50	2/50 demonstrated single 2.0± skin irritation reactions (max. score = 8.0); no sensitization observed. Investigators concluded that material was neither a primary skin irritant nor sensitizer.	98
Sample B	5 in aq. gel	Applied to skin every other day for total of 9 induction patches; reapplied for 24 hrs after 2-wk rest	50	4/50 demonstrated a total of five skin irritation reactions: 3 reactions were 1.0± and 2 reactions were 2.0± (max. score = 8.0): no sensitization observed. Investigators concluded that material was neither a primary skin irritant nor sensitizer.	98
-934	0.20 in skin moisturizer	Applied to skin daily for 10 days (Kligman and Wooding, 1967)	10	No instances of primary irritation observed	78
-934	0.20 in skin moisturizer	Applied to skin 3 times a day for 28 days	30	No instances of skin irritation or sensitization were observed; however, investigators concluded that formulation has a low potential for both skin irritation and sensitization.	78

TABLE 6. (Continued.)

Carbomer	*Conc. (%)*	*Method applied to skin*	*No. of subjects*	*Conclusion/Comments*	*Ref.*
-934	0.20 in perfumed skin moisturizer	Applied to skin 3 times a day for 28 days	50	1/50 demonstrated a minimal facial erythema on day 28. Investigators concluded that formulation has low potential for skin irritation and sensitization.	78
-934	0.25 in perfumed skin moisturizer	Applied to skin 3 times a day for 28 days	50	No observed reactions. Investigators concluded that formulation has a low potential for skin irritation and sensitization.	78
-934	0.20 in non-perfumed skin moisturizer	Applied to skin 3 times a day for 28 days	50	2/50 reacted with doubtful to minimal erythema. Investigators concluded that formulation has low potential for skin irritation and sensitization.	78
-934	0.15 in moisturizing lotion	Applied to skin every other day for 3 wks; challenge after 2-wk rest (Draize, 1959)	94	The formulation elicited "little or no primary irritation" and no sensitization.	99
-934	0.20 in non-perfumed skin moisturizer	Kligman Maximization Procedure (Kligman, 1966)	25	Most subjects showed slight erythema at challenge, but investigators attributed this to sodium lauryl sulfate. Investigators concluded that formulation was unlikely to present risk of contact sensitization. Repeat of test with a second group showed similar results.	78
-934	0.25 in skin moisturizer	Kligman modified Maximization Procedure (Kligman and Epstein, 1975)	25	No observed reactions. Investigators concluded that formulation was unlikely to present a risk of contact sensitization.	78
-940	1 in aq. gel	Applied to skin essentially every other day for 15 days; 24-hr challenge after 1-wk rest.	68	No skin irritation or sensitization.	81

Sodium salt	1 in aq. gel	Applied to skin essentially every other day for 15 days; 24-hr challenge after 1-wk rest.	68	No skin irritation or sensitization.	81
Monoisopropanolamine salt	1 in aq. gel	Applied to skin essentially every other day for 15 days; 24-hr challenge after 1-wk rest	68	No skin irritation or sensitization.	81
-941	1 in aq. sol'n.	Applied to skin daily for 15 days; occlusive patches; reapplied for 24 hrs following 1 wk rest.	58	No skin irritation or sensitization.	100
Sodium salt	1 in aq. sol'n.	Applied to skin daily for 15 days; occlusive patches; reapplied for 24 hrs following 1 wk rest.	58	No skin irritation or sensitization.	100
Monoisopropanolamine salt	1 in aq. sol'n.	Applied to skin daily for 15 days; occlusive patches; reapplied for 24 hrs following 1 wk rest.	58	No skin irritation or sensitization.	100

[a]Data from Refs. 74, 75, 78, 80, 81, 86, and 97–100.

tion and sensitization on 50 white human subjects, 38 of them males and 12 females, aged 20–79. An aqueous gel containing 0.5% of the test material was applied to the arm of each subject daily for 14 days. After a six-day rest, the investigators reapplied the test material for a single 24-hour period. The sites were examined on four subsequent days. There were no visible reactions to any of the applications; however, on days six through ten, two subjects complained of itching at the test sites. The investigators concluded that the test material was neither a primary skin irritant nor a sensitizer.[86]

In a repeated insult patch test, two samples (A and B) of 5.0% Carbomer-934 in deionized water were evaluated for their skin irritation and sensitization potential on 50 human subjects. The test population ranged in age from 18 to 47 and consisted of 29 males (28 whites and 1 black), and 21 females (19 whites and 2 Asians). Each test material was applied to the skin for 24 hours on Monday, Wednesday, and Thursday for a total of nine induction patches. After the ninth patch, a rest period of two weeks elapsed before a single 24-hour challenge patch was applied. Of the 50 subjects tested with Sample A, 48 showed no irritation, while two demonstrated single 2.0± reactions (max. score = 8.0). Thus, the overall incidence of irritation reaction during the nine induction patches on 50 subjects was 2/450 or 0.4 percent. Forty-six of the 50 subjects tested with Sample B showed no irritation, while four individuals demonstrated a total of five reactions. Of these five reactions on the skin of four reactors, three were 1.0± and two were 2.0± (max. score = 8.0). Thus, the overall incidence of irritation reaction during the nine induction patches on 50 subjects was 5/450 or 1.1%. In no subject was there evidence of skin sensitization to either sample. On the basis of the "incidence" and "severity" of the reactions to these repeated tests, the investigators concluded that the test materials were neither primary skin irritants nor sensitizers.[98]

The procedure of Kligman and Wooding[102] was used on 10 normal, adult subjects to test a skin moisturizer containing 0.20 percent Carbomer-934 for skin irritation potential. Approximately 0.3 ml of undiluted moisturizer was applied every day for 10 days under an occlusive patch. No instances of primary irritation were observed.[78]

In a safety-in-use study, a skin moisturizer containing 0.20% Carbomer-934 was tested on 30 adult women for its skin irritation and sensitization potential. Three times a day for 28 days, the undiluted product was applied to facial and periorbital areas. Examinations were conducted at 14 and 28 days for facial, periorbital, conjunctival, and mucous membrane irritation. Occlusive patches were applied pre- and post-treatment. No instances of skin irritation or sensitization were observed in any of the test subjects. The investigators concluded that the formulation has a low potential for skin irritation and sensitization "under conditions of normal intended use."[78]

In a second safety-in-use study, three groups of 50 adult women were tested with either a perfumed skin moisturizer which contained 0.20% or 0.25% Carbomer-934, or a nonperfumed variation of the moisturizer which contained 0.20% Carbomer-934. Three times a day for 28 days, the undiluted products were applied to facial and periorbital areas. Occlusive patches were applied pre- and post-treatment. No instances of mucous membrane, periorbital, or conjunctival inflammation were observed. There were no instances of facial erythema, except in one subject to whom the perfumed formulation containing 0.20% Carbomer-934 had been applied; this individual demonstrated a minimal facial

erythema on Day 28. Of the 150 subjects tested, only two on the nonperfumed formulation reacted to the post-study patches, one with minimal (1+) erythema at 24 and 48 hours, and one with doubtful (±) erythema at 24 hours. The investigators concluded that the formulations have low potential for irritation and sensitization "under conditions of normal intended use."[78]

By means of a modified version of the repeated insult test of Draize,[90] a moisturizing lotion containing 0.15% Carbomer-934 was tested for its skin irritation and sensitization potential. Of the 112 adult men and women selected for study, only 94 completed the program. The 18 panelists who left the evaluation protocol did so for causes unrelated to reactions to the test material. A patch containing 0.2 g of the lotion was applied to the back of each panelist for 24 hours on Monday, Wednesday, and Friday for three consecutive weeks. Duplicate challenge applications of the test material were made two weeks after the final serial applications, one patch to the original site and one to an adjacent site. The test sites were scored just prior to the patch applications on the second through the ninth visits and on the tenth visit. The challenge application sites were scored at 48 and 96 hours after application. The moisturizing lotion elicited "little or no primary irritation" and no sensitization.[99]

Using the Kligman Maximization Procedure,[103] investigators tested an undiluted, nonperfumed skin moisturizer containing 0.20% Carbomer-934 for its sensitization potential on 25 human subjects. At challenge, most subjects showed slight erythema, a phenomenon which the investigators attributed to sodium lauryl sulfate. Four cases of definite erythema (±) were observed at 48 hours, but only one was still evident at 72 hours. The investigators did not consider these four reactions to be the result of contact sensitization. On the basis of the maximization grading scale, the moisturizer formulation was rated the lowest grade (i.e., Grade 1, a weak potential sensitizer) and was considered "unlikely to present a risk of contact sensitization under conditions of normal intended use."[78] In a second test, a second group of 25 subjects displayed similar responses when they were exposed to the same formulation and concentration.[78,103]

Through the use of Kligman's modified Maximization Procedure,[104] an undiluted skin moisturizer containing 0.25% Carbomer-934 was tested for its sensitization potential on 25 human subjects. No reactions were observed in any of the test subjects. On the basis of the maximization grading scale, the moisturizer formulation was rated the lowest grade (i.e., Grade 1, a weak potential sensitizer) and was considered "unlikely to present a risk of contact sensitization under conditions of normal intended use."[78]

Carbomer-940: Aqueous gels containing 1.0% Carbomer-940, 1.0% sodium salt of Carbomer-940, and 1.0% monoisopropanolamine salt of Carbomer-940 were applied, under occlusive patches, to the skin of 68 subjects. The test population consisted of 36 men and 32 women ranging in age from 18 to 80; nine of the subjects were black and 59 were white. On Days 2, 3, 5, 7, 11, and 15, the patches were removed and new test material was reapplied. After a one-week rest period, the materials were reapplied for 24 hours. No skin irritation or sensitization was observed for any of the test materials.[81]

An aqueous suspension containing 1.0 percent by weight di-(2-ethylhexyl)-amine salt of Carbomer-940 was tested on 50 white subjects (38 men and 12 women) aged 20–79. The test material was applied daily to the arm for 14 days. Following a six-day rest period, the material was reapplied for 24 hours, and the sites examined on the four subsequent days. Two subjects complained of itching

at the test site on Days 6, 7, 8, 9, and 10; however, no visible evidence of irritation or sensitization could be detected.[86]

Carbomer-941: Aqueous solutions of 1.0% Carbomer-941, 1.0% sodium salt of Carbomer-941, and 1.0% monoisopropanolamine salt of Carbomer-941 were tested on 58 hospitalized subjects (32 men and 26 women) aged 18–78. A drop of each test material was applied daily, under occlusive patches, to the skin of the chest for a total of 15 applications. After a one-week rest period, the test materials were reapplied for one 24-hour period. (The study was discontinued on six subjects because they were discharged from the hospital.) No primary skin irritation or sensitization was observed in any subject for any of the test materials.[100]

Photo-Testing

Carbomer-934: A skin moisturizer containing 0.25% Carbomer-934 was tested for phototoxicity on ten normal adult subjects. The material was applied (5 $\mu l/cm^2$) undiluted under occlusive patches and after 6 and 24 hours of contact, the sites irradiated with a solar simulator. No instances of phototoxicity were observed. The investigators concluded that this formulation "is unlikely to present a risk of phototoxicity under conditions of normal intended use."[78]

Twenty-five normal, adult subjects were tested with a skin moisturizer containing 0.25% Carbomer-934 for photo-contact allergenicity. During the induction period, the material was applied (5 $\mu l/cm^2$) under occlusive patches for 24 hours and then irradiated with a solar simulator; this procedure was repeated twice a week until there was a total of six exposures for each subject. A challenge was performed ten days after the last induction exposure. No instances of photo-contact allergenicity were observed. The investigators concluded that the formulation has "a low potential for photo-contact allergenicity under conditions of normal intended use."[78]

Miscellaneous Studies

Carbomer-934: Carbomer-934 was clinically tested as a bulk laxative over a period of several months. Hospitalized patients given tablets of the polymer showed no deleterious effects.[12]

SUMMARY

The Carbomers are synthetic, high molecular weight, nonlinear polymers of acrylic acid, cross-linked with a polyalkenyl polyether. These polymers are hygroscopic and, when exposed to sunlight, they undergo oxidative degradation. Reported impurities for the Carbomer resins include water, benzene, propionic acid, acetic acid, acrylic acid, heavy metals, iron, arsenic, and lead. The Panel calls attention to the presence of benzene as an impurity in Carbomers and recommends that every effort be made to reduce it to the lowest possible value.

Although supplied as free flowing powders, the Carbomer polymers are frequently used in cosmetic preparations as gels. They function as thickening, suspending, dispersing, and emulsifying agents, and they are also used to provide emulsion stability and rheologic control. Concentrations in cosmetic formulations are reported to vary between $\leq 0.1\%$ and 50%, with most formulations containing concentrations below 1.0%. Products incorporating these polymers are applied to or come in contact with skin, eyes, mucous membranes,

respiratory epithelium, hair and nails; small amounts of Carbomers are likely to be ingested in dentifrices and lipsticks.

Acute oral studies with rats, guinea pigs, mice, and dogs showed that Carbomers-910, -934, -940, and -941 have low toxicities when ingested. The inhalation LC50 of Carbomer-910 in albino rats was 1.71 mg/l. The dermal LD50 of rats exposed to Carbomer-910 was > 3.0 g/kg. No mortalities occurred in rabbits injected intravenously with 1%, 2%, or 3% Carbomer-934 in aqueous solution at a dose of 5 ml/kg. Rabbits showed minimal skin irritation when tested with 100% Carbomer-910 or -934, and zero to moderate eye irritation when tested with Carbomers-910, -934, -934P, -940, -941, and/or their various salts at concentrations of 0.20–100%.

Subchronic feeding of rats with doses up to 5.0 g/kg/day Carbomer-934 (49 days) and of rats and dogs with up to 5.0% Carbomer-934P in the diet (21 and/or 90 days) resulted in lower than normal body weights. In rats fed Carbomer-934P at dietary levels of 5.0% for 90 days, absolute liver weights and liver to body and brain weight ratios were reduced, but no pathological changes were observed.

When dogs were chronically fed up to 1.0 g/kg/day Carbomer-934 (32 months) or -934P (six and one-half months), and when rats chronically received less than 5.0% Carbomer-934P in their diet (six and one-half months), there was no significant effect on body weight, food consumption, mortality, behavior, or blood chemistries. Hematology, gross pathology, histology, and urinalyses of treated animals were comparable to those of controls. Rats fed Carbomer-934P at dietary levels of 0.1%, 0.5%, or 5.0% for six and one-half months exhibited various organ weight changes. Dogs fed 0.5 or 1.0 g/kg/day Carbomer-934P for six and one-half months manifested gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver.

Clinical studies with Carbomer-934 and its various salts showed that these polymers have low potential for skin irritation and sensitization at concentrations of 0.5%, 5.0%, 10.0%, and 100%. When tested on humans at 1.0% concentration, Carbomers-940, -941, and their various salts also demonstrated low potential for skin irritation and sensitization. Further, formulations containing up to 0.25% Carbomer-934 demonstrated low potential for human skin irritation, sensitization, phototoxicity, and photo-contact allergenicity.

The following data were not available for Carbomers-910, -934, -934P, -940, -941, or -962: (1) exact structural composition; (2) details of manufacturing process; (3) analytical methods; (4) potential interactions with other ingredients; (5) absorption; (6) metabolism; (7) excretion; (8) teratogenesis; (9) mutagenesis; and (10) carcinogenesis.

Clinical data for assessing the skin irritation and sensitization potential of Carbomer-940 and -941 were limited to studies in which concentrations of only 1.0% were tested. Clinical data for assessing phototoxicity and photo-contact allergenicity were limited to formulation studies in which concentrations of only 0.25% Carbomer-934 were tested. No clinical studies were reported for Carbomers-910, -934P, or -962.

CONCLUSION

On the basis of the available information presented in this report, and as the information is qualified in the summary, the Panel concludes that the Carbomers are safe as cosmetic ingredients in the present practices of use and concentration.

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