

Toxicology Studies and Regulatory Information

Toxicology Study Results

Carbopol[®]* polymers, Pemulen[™]* polymeric emulsifiers, and Noveon[®]* polycarbophil have received extensive review and toxicological evaluation. Noveon[®] AA-1 polycarbophil meets the requirements of the U.S. Pharmacopeial monograph for polycarbophil. Lubrizol has also determined that Carbopol[®] 934 NF, 934P NF, 971P NF 974P NF and 71G NF polymers are GRAS (Generally Recognized As Safe) for use in dietary supplements.

Carbopol[®] products belong to a class of chemicals referred to as “carbomers”. The toxicity of carbomers has been summarized by the Cosmetic Ingredient Review Expert Panel in their assessment of the safety of the carbomers for cosmetic ingredients.¹ This assessment and subsequent toxicology testing have demonstrated a low toxicity and irritation potential.

As a result of the intensive testing and the properties offered by the polymers, they have gained wide acceptance in a variety of pharmaceutical, nutraceutical, cosmetic and detergent applications.

Carbopol[®] 934 NF and Carbopol[®] 934P NF Polymers

Acute Oral Toxicity

Numerous acute oral toxicity studies have been conducted on Carbopol[®] 934 polymer in rats, mice, Guinea pigs and dogs¹. These studies have shown that Carbopol[®] 934 polymer has a low acute toxicity. Depending on the animal species and the test design, LD₅₀ values have ranged from 2.5 g/kg to greater than 50 g/kg.

Eye Irritation

Studies with various salts of Carbopol[®] 934 polymer at pH ranges from 6.8 to 8.2 have shown the instillation of a 0.5% dispersion into the eyes of rabbits may result in mild eye irritation.¹

Instillation of large amounts of the various Carbopol[®] polymer salts or repeated instillation of small amounts may produce slight corneal injury.

Dispersions (pH 3) of Carbopol[®] polymer are eye irritants. Experience has shown that the dry powder inadvertently dusted into the eyes of workers caused only mild irritation when it was promptly removed by flushing the eyes with a 1% physiological saline solution. Water swells Carbopol[®] polymer into a gelatinous film which may be difficult to remove from the eye, therefore, the possibility of ocular damage may be greater than if a saline flush is used. Use of a 1% physiological saline solution to flush the eye is the treatment of choice. However, in the event that a 1% physiological saline solution is not readily available, the eye should be flushed with plenty of water.

Skin Irritation

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A number of studies have been conducted to evaluate the skin irritation potential of Carbopol® 934 polymer.¹ Two samples (A and B) of 100% carbomer 934 were tested for primary skin irritation using the Draize test.² 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.

Primary irritation scores for both test materials were determined to be 0.2, indicating minimal irritation. A skin moisturizer formulation containing 0.2% Carbomer 934 was also tested for primary skin irritation in 12 rabbits using the Draize method.² The animals were administered 0.5 g of the moisturizer under occlusive patches for 24 hours. Mild skin irritation with Primary Irritation Indices (PII) ranging from 0.5 to 0.9 (out of a maximum score of 8.0) was observed indicating a low irritation potential.

Tests of a 1.0% dispersion of Carbopol® 934 polymer also showed low irritancy potential. The skin irritation index in rabbits was 0.08.

Human Dermatologic Investigation

No evidence of skin irritation or sensitization was found during human skin patch testing of Carbopol® 934 polymer or its various salts.¹ There was no reaction of any kind to Carbopol® 934 polymer, even on the skin of subjects with histories of allergic reactions.

Acute I.V. Injection Toxicity

The acute effects of intravenous injection with Carbopol® 934 polymer were evaluated.¹ No mortality was associated with intravenous injection in three groups of three rabbits each of 1%, 2% or 3% dispersions of Carbopol® 934 polymer.

Subacute/Subchronic Oral Toxicity

Groups of rats were administered Carbomer 934 in the diet for 49 days at daily doses as high as 5.0 g/kg.¹ A significant reduction in body weight occurred only at the highest dose. No deaths were observed at any of the dose levels.

A 21-day feeding study was conducted with rats using dietary levels of either 0% or 5.0% Carbopol® 934P polymer.¹ Lower food consumption and body weight gain was observed in animals fed Carbopol® 934P polymer than in the controls. No abnormal reactions or deaths were observed during the study.

Feeding of Carbopol® 934 polymer at doses up to 5% (by weight) of the diet of rats for 90 days produced no effect on growth in animals consuming up to 1% of their diet as Carbopol® polymer.¹ Not surprisingly, animals consuming a diet composed of 5% Carbopol® 934 polymer did have a significantly lower growth rate. This growth suppression was most likely the result of non-nutritive, non-caloric bulk with Carbopol® polymer. When those animals previously receiving the 5% diet of Carbopol® polymer were given a normal diet for an additional 19 days, the growth suppression was partially reversed. There was no evidence of related adverse hematological or histopathological effects with Carbopol® 934 polymer.

The feeding of Carbopol® 934 polymer to dogs for 90 days at dietary levels as high as 5% was not associated with any compound related effects, except a slight growth suppression at the high dose.¹ This growth effect was most likely the result of the non-nutritive, non-caloric bulk of Carbopol® polymer.

Chronic Toxicity

Dietary levels of 0, 0.1, 0.5 and 5.0% Carbopol[®] polymer were fed to groups of male and female rats for six and one-half months¹. Growth, food consumption, behavior, hematology, blood chemistry, urinalysis, and histopathology were not effected by exposure. However, a non-statistically significant reduction in body weight and elevated gonad weights, gonad-to-body weight ratios, and gonad-to-brain weight ratios were observed at the high dose in females. Heart weight, heart-to-body weight ratios, and heart-to-brain weight ratios also were elevated in the 0.5 and 5.0% females while heart weights and heart-to-brain weight ratios were lowered in the 5.0% males. Liver-to-body weight ratios in the 0.1% females were elevated.

Six and one-half months administration of Carbopol[®] 934 polymer in gelatin capsules to beagle dogs at doses of 0, 0.1, 0.5 and 1.0 g/kg had no significant effect on body weight, food consumption, mortality, behavioral reactions, hematology, blood chemistry, urinalysis, or organ weight¹. Slight gastric irritation and pigment deposition within the Kupffer cells of the liver was observed in animals receiving 0.5 and 1.0 g/kg.

Chronic and Reproductive/Developmental Toxicity

Dogs were fed diets containing 0, 0.1, 0.5 or 1.0 g/kg for up to 32 months.^{1, 3} No effects on body or organ weights, blood count (CBC), hematocrit, alkali reserve, or gross or microscopic pathology was observed. Some of the dogs that received 0.1 g/kg for four and one-half months were mated successfully. No abnormalities were observed in the pups.

Carbopol[®] 940 NF Polymer

Acute Oral Toxicity

The highest dose capable of intragastric administration in the rat was equivalent to 625 mg/kg of dry Carbopol[®] 940 polymer administered as a 1% or 2.5% dispersion.¹ No deaths resulted. The LD₅₀ was greater than 625 mg/kg.

Eye Irritation

Instillation of 1 ml of a 1% dispersion of Carbopol[®] 940 polymer or some of its salts in the eyes of rabbits was minimally irritating.¹

Skin Irritation

The potential for a 1% dispersion of Carbopol[®] 940 polymer to cause skin irritation was evaluated using the Draize test.^{1, 2} The irritancy of this dispersion to rabbit skin was evaluated at 1, 24 and 48 hours. Based on the results of this test, the 1% dispersion was determined to be nonirritating with an irritation index of 0 (out of a maximum score of 8.0).

Human Dermatologic Investigation

No contact irritation or sensitization was observed during human skin patch testing of Carbopol[®] 940 polymer or its salts.¹

Carbopol[®] 941 NF Polymer

Acute Oral Toxicity

The rat oral LD₅₀ of Carbopol[®] 941 polymer exceeds 1 g/kg, which is the highest dose capable of intragastric administration to a rat.¹ No deaths were observed at this dose.

Eye Irritation

The instillation of 0.5 cc of a 1% dispersion of Carbopol[®] 941 polymer or a selection of some of its salts into the eyes of rabbits caused some immediate redness of the conjunctiva, but no irritation was observed at 1, 2 or 3 days post-instillation.¹

Skin Irritation

The potential for a 1% dispersion of Carbopol® 941 polymer to cause skin irritation was evaluated with rabbits at 1, 24 and 48 hours.¹ Based on the results of this test, the 1% dispersion of Carbopol® 941 polymer was determined to have a low irritation potential (0.04 out of a maximum score of 8.0).

Human Dermatologic Investigation

Human skin patch testing of Carbopol® 941 polymer and some of its salts produced no primary irritation, nor was there any evidence of sensitivity or allergic reaction in any subject.¹

Carbopol® 974P NF, Carbopol® 971P NF and Carbopol® 71G NF Polymers

Toxicology studies were conducted with Carbopol® 974P NF polymer. The toxicity data for Carbopol® 974P NF polymer can be used to assess the safety of Carbopol® 971P NF polymer and Carbopol® 71G NF polymers due to their nearly identical chemistry. The primary difference is that Carbopol® 971P NF polymer has a slightly lower crosslinker level than Carbopol® 974P NF polymer. Carbopol® 71G NF polymer is the granular form of Carbopol® 971P NF polymer which is obtained by roller compaction.

Acute Dermal Toxicity

The dermal toxicity was evaluated using a group of ten rabbits.⁴ A dose of 2.0 g/kg of Carbopol® 974P polymer, premoistened with a drop of tap water was applied to shaved skin. No effects were noted following the administration of the material. The acute dermal LD₅₀ for Carbopol® 974P polymer was determined to be greater than 2.0 g/kg.

Eye Irritation

The eye irritation potential of Carbopol® 974P polymer was evaluated.⁵ Ten (10) mg of the neat test material was administered to groups of six albino rabbits. The respective test material was instilled into the conjunctival sac of one eye of the test animals while the other eye served as control. The eyes were not washed after instillation.

The eyes were examined at 1, 2, 3 and 4 days following the instillation of the test material according to the method of Draize.² Because only one positive score (Grade 1 for corneal effects) was observed at 24 hours, Carbopol 974P polymer was not considered to be an eye irritant. All scores (Grade 1) for redness and chemosis were gone by day 4.

Human Dermatologic Investigation

Carbopol® 974P polymer was applied to the skin of 55 human volunteers in order to evaluate the skin irritation and sensitization potential of this product.⁶ A series of 12 applications (0.2 g) was conducted with each panelist during the primary/induction phase. On four consecutive days of weeks 1, 2, and 3, the patch containing the test material was applied to its designated site. The patches were removed and the contact sites were examined 24 hours after each application. Following a one week rest period (week 4), a challenge phase was conducted on week 5 with 4 applications of the test material on a virgin site of each volunteer.

Application of Carbopol® 974P polymer to the skin of humans did not cause any skin irritation or sensitization.

30-Day Subacute/Subchronic Oral Toxicity with Rats

The toxicity of Carbopol® 974P polymer, when fed daily in the diet to male and female Sprague-Dawley (CrI:CD® BR) rats for at least four weeks, was evaluated.⁷ The dose levels administered were 0, 6,250, 12,500, 25,000 and 50,000 ppm. In-life clinical observations, body weight, food consumption and clinical pathology (hematology and clinical chemistry) studies at the terminal sacrifice were performed to assess the temporally-related health status of the animals. No significant findings were observed which were considered to be the result of the exposure to the test material.

Postmortem gross examinations of protocol-specified tissues were performed to evaluate the potential toxicity of Carbopol[®] 974P polymer as the result of dietary exposure. No treatment-related toxicity was observed. The histopathological evaluation of the tissues of the Group 1 and Group 5 animals identified the liver as a potential target tissue for further analysis due to the occurrence of a marginal, albeit significant, increase in the severity of chronic active inflammation in the livers of the Group 5 (50,000 ppm) females.

The observation of increased severity of chronic active inflammation in the Group 4 and Group 5 females does not provide strong evidence of Carbopol[®] 974P polymer liver-induced or potentiated toxicity, because of the absence of corresponding clinical observations, clinical pathology or gross pathology, and because of the occurrence of chronic active inflammation in all animals. Based on the absence of any significant toxic effects from Carbopol[®] 974P polymer, the high dose level recommended for the 13-week study is 50,000 ppm.

90-Day Subacute/Subchronic Oral Toxicity with Rats

A study was designed to characterize the potential subchronic toxicity of Carbopol[®] 974P polymer, when administered to male and female Sprague-Dawley (CrI:CD[®] BR) rats in the diet at levels of 0, 12,500, 25,000 and 50,000 ppm (groups 1-4 respectively) for at least 13 weeks.⁸ Body weights and food consumption were obtained weekly. Cageside observations were performed daily and complete physical examinations were performed weekly. Blood and urine were collected at week 13 for evaluation by routine hematologic and biochemical methods and urinalysis. After 13 weeks of study, all animals were sacrificed and necropsied. Protocol-specified tissues were collected, preserved and examined microscopically for all animals in the control (untreated) and high-dose groups.

All animals survived until termination. Clinical observations noted during the study included, but were not limited to, alopecia, sores, and chromodacryorrhea. These signs occurred sporadically at a low frequency and are not considered related to treatment.

High-dose (group 4) males and females exhibited significantly decreased total body weight gains (weeks 1-3) when compared to controls. Only the high-dose males exhibited a significant decrease in absolute body weights at weeks 5, 9 and 14. Food consumption at weeks 4, 8, 13 and total (weeks 1-13) food consumption values were similar in all groups.

With respect to clinical pathology, an influence by the test material was suspected in the mild decreases observed in erythrocyte count and total protein, albumin and globulin concentrations in the high-dose males. Urinalysis values were comparable between control and treated groups.

Findings observed at necropsy were few and did not occur in a dose-related pattern. Microscopic evaluation revealed commonly seen lesions and findings, which were observed in the control and test rats at a similar frequency and severity. There were no compound-related histomorphologic lesions in any of the representative sections of tissues.

Overall, these findings indicate that Carbopol[®] 974P polymer at 50,000 ppm in the diet produces mild, albeit significant biological effects, as reflected by the decreased body weight gains. The effect of Carbopol[®] 974P polymer appears to be slightly greater in the 50,000 ppm male group, with the occurrence of significant decreases in the absolute body weights and mild changes in the clinical pathology parameters. While the mechanism(s) by which Carbopol[®] 974P polymer exerts the noted biological effects cannot be determined by the results of the study, the observed findings are consistent with a nutritional deficit. No biological effects were associated with Carbopol[®] 974P polymer at dietary levels of 12,500 and 25,000 ppm.

90-Day Subacute/Subchronic Oral Toxicity with Dogs

This study was designed to evaluate the toxicity of Carbopol[®] 974P polymer when fed daily to purebred beagle dogs for at least 13 weeks.⁹ A total of 32 (16 male and 16 female) purebred beagle dogs were assigned to 4 treatment groups, with each group having 4 dogs of each sex. Group 1 served as the vehicle (diet) control, whereas Groups 2, 3 and 4 received diet containing the test material at levels of 12,500, 25,000 and 50,000 ppm respectively.

All dogs were observed twice daily for mortality and moribundity. Cageside observations were conducted once daily for evidence of a toxic or pharmacological effect. Body weights were measured weekly, at which time thorough physical examinations were conducted. Ophthalmoscopic examinations were performed on all animals prior to treatment and on the control and high-dose dogs during week 14. During week 13, blood samples were collected for clinical pathology determinations. After at least 13 weeks of treatment, all dogs were food-fasted, weighed, anesthetized with thiopental sodium, exsanguinated and necropsies were performed. Protocol-specified tissues were collected, weighed (if appropriate), preserved, processed and examined microscopically.

All animals survived until the scheduled sacrifice. There were no clinical observations which could be attributed to exposure to the test material. Mean body weight, body weight change and total food consumption values for the treated animals were comparable to control values throughout the study. Ophthalmoscopic examination noted no visible lesions in the control and high-dose animals at week 14. There were no treatment-related hematology, clinical chemistry, gross pathology or histopathology findings. Organ weights were comparable among all treatment groups.

In summary, this study provides no indications of toxicity when dogs are exposed to dietary Carbopol[®] 974P polymer concentrations less than or equal to □50,000 ppm for approximately 13 weeks.

Carbopol[®] 980 NF and Carbopol[®] 981 NF Polymers

The following studies were conducted with Carbopol[®] 980 polymer and are believed to also characterize the toxicity of Carbopol[®] 981 polymer because the two polymers are nearly identical with respect to their chemistry. The primary difference is that Carbopol[®] 981 polymer has a slightly lower crosslinker level.

Eye Irritation

The irritation potential of Carbopol[®] 980 polymer was evaluated.¹⁰ A standard amount, 0.015 g (or 0.1 ml equivalent) of the test material was administered to groups of six albino rabbits. The respective test material was instilled into the conjunctival sac of one eye of the test animals while the other eye served as a control. The eyes were not washed after instillation. A similar procedure was followed on an additional three animals, with the exception that saline rinse was used.

In the no-rinse group, Carbopol[®] 980 polymer produced minimal conjunctivitis in 6 of 6 test animals at 24 hours. Redness and swelling persisted to the study termination (7 days) in 4 of 6 rabbits. Similar responses were seen in the rinse group.

Carbopol[®] 980 polymer was not considered to be an eye irritant according to FHSA evaluation criteria.

Skin Irritation

The skin irritation potential of Carbopol[®] 980 polymer was evaluated in rabbits in accordance with FHSA regulations.¹¹ Each of six rabbits received a 0.5 g dose of Carbopol[®] 980 polymer as a dermal application to both an intact and abraded test site. The dose was held in contact with the skin under a semi-occlusive binder for an exposure period of 24 hours. Following the exposure period, the binder was removed, and the remaining test article was wiped from the skin using gauze and distilled water.

The test sites were subsequently examined and scored for dermal irritation for up to three days following patch removal.

Although slight, well-defined erythema (redness of the skin) was noted at 25 hours, all responses had subsided by the 72-hour observation. No edema (swelling) was noted at any test site.

Under the test conditions, Carbopol[®] 980 polymer would be considered only very slightly irritating to rabbit skin. The calculated Primary Irritation Index for Carbopol[®] 980 polymer is 0.58 out of a possible 8.0.

Human Dermatological Investigation

Carbopol[®] 980 polymer was impregnated in a 1"x1" square piece of surgical gauze and moistened with 0.2 ml of distilled water just prior to application to the skin of 54 human volunteers.¹²

In order to evaluate the skin irritation and sensitization potential of this product, a series of 12 applications was conducted with each panelist during the primary/induction phase. On four consecutive days of weeks 1, 2, and 3, the patch containing the test material was applied to its designated site. The patches were removed and the contact sites were examined 24 hours after each application. Following a one week rest period (week 4), a challenge phase was conducted in week 5 with 4 applications of the test material on a virgin site of each volunteer.

Carbopol[®] 980 polymer produced no visible effects in 41 subjects out of 54 during the primary irritation/activation period. Faint or moderate reddening of the skin occurred on one occasion in 10 subjects, 2 times on one subject, and 4 times on another subject. These effects would put Carbopol[®] 980 polymer into the category of a weak skin irritant. Two subjects out of 53 who took part in the challenge phase displayed solitary episodes of faint or moderate reddening. Therefore, the investigators concluded that those subjects did not have a sensitizing reaction. Their overall assessment was that the results furnish no basis for contraindicating skin contact with Carbopol[®] 980 polymer under similar or less stringent conditions than the testing conditions used.

Carbopol[®] 1342 NF Polymer

Acute Oral Toxicity

The acute oral toxicity of Carbopol[®] 1342 polymer was evaluated in rats.¹³ Ten animals were force fed 5,000 mg/kg of the test substance. No mortality or other abnormalities were observed.

Eye Irritation

The eye irritation potential of both "neat" and 1% neutralized and unneutralized dispersions of Carbopol[®] 1342 polymer was evaluated.^{14, 15, 16} The latter dilute dispersions were tested because they are more reflective of end-use levels and therefore are a better indicator of irritation potential in commercial applications.

A standard amount, 0.1 g (or 0.1 ml of the dilute dispersions) of each test material was administered to groups of six albino rabbits. The respective test material was instilled into the conjunctival sac of one eye of the test animals while the other eye served as control. The eyes were not washed after instillation.

The eyes were examined at 1, 2, 3 and 4 and 7 days following the instillation of the test material according to the method of Draize².

For the undiluted Carbopol[®] 1342 polymer sample, minimal positive scores were observed in the cornea, iris and conjunctiva. However, none of these positive responses persisted beyond day 3. Based on these results, undiluted Carbopol[®] 1342 polymer was classified as a moderate eye irritant.

In eye irritation studies, the neutralized and unneutralized 1% dispersions of Carbopol[®] 1342 polymer were not primary ocular irritants, and they produced no eye irritation scores.

Skin Irritation

Carbopol[®] 1342 polymer was applied to the abraded and unabraded skin of rabbits. (0.5 g/abraded or unabraded site).¹⁷ The treated areas were covered with gauze and an impervious material. The bandages were removed and the sites were evaluated at 24 and 72 hours. No irritation was observed. The primary irritation index was 0.0 out of a maximum of 8.0.

Human Dermatologic Investigation

Carbopol[®] 1342 polymer was applied to the skin of 52 human volunteers^a in order to evaluate the skin irritation and sensitization potential of this product.¹⁸ A series of 12 applications (0.2 g) was conducted with each panelist during the primary/induction phase. On four consecutive days of weeks 1, 2, and 3, the patch containing the test material was applied to its designated site. The patches were removed and the contact sites were examined 24 hours after each application. A challenge phase was conducted in week 4, with 4 applications of the test material on a virgin site of each volunteer.

Application of Carbopol[®] 1342 polymer to the skin of humans did not cause any skin irritation or sensitization. It was concluded that this product should be well tolerated and that the hazard of sensitization is exceedingly small.

Carbopol[®] ETD Polymers

The toxicology studies summarized below were performed on 2 lots of experimental polymers with chemical compositions representative of the Carbopol[®] ETD polymer family. Therefore, the toxicology data included is expected to be valid for the commercial grades of Carbopol[®] ETD polymers.

Eye Irritation

The eye irritation potential of Carbopol[®] ETD polymer was evaluated undiluted and as a 1% dispersion (neutralized to pH 6.9 – 7.0) according to international OECD guidelines.^{19, 20, 21, 22} A standard amount of the test material (0.1 ml or the weight equivalent, 0.04 g) was administered to groups of three albino rabbits. The respective test material was instilled into the conjunctival sac of one eye of the test animals while the other eye served as a control. The eyes were not washed after instillation.

Under the test conditions, Carbopol[®] ETD polymers (undiluted) produced slight to moderate corneal irritation, and conjunctival irritation which cleared by the study termination (day 7). Only slight iridal and conjunctival irritation was noted with the 1% dispersion and all irritation was found to clear by 72 hours.

Skin Irritation

The skin irritation potential of Carbopol[®] ETD polymers was evaluated undiluted and as a 1% neutralized dispersion in rabbits according to international OECD guidelines.^{23, 24, 25, 26} The test materials (0.5 g of dry polymer of 0.5 ml of 1% dispersion) was applied to the intact skin on the backs of three animals. The dose was held in contact with the skin under a semi-occlusive binder for an exposure period of 4 hours. Following the exposure period, the binder was removed and the remaining test article was wiped from the skin using tap water and paper towels. The test sites were subsequently examined and scored for dermal irritation for up to seven days following patch removal.

Although very slight erythema (redness of the skin) and edema (swelling) were noted with the undiluted lots, all responses had subsided by the day-7 observation. Very slight erythema also was noted with one lot of the 1% test dispersion. However, even with this lot, the observation was limited to one of the three animals and was only seen at the 4-hour observation.

Under the test conditions, Carbopol[®] ETD polymers would be considered a slight irritant to rabbit skin when undiluted (Primary Irritation Index 0.9-1.5; highest score possible is 8.0), and a non-irritant to very slight irritant when tested as a 1% dispersion (PII 0.0-0.1).

^a Number of subjects remaining through the challenge phase

Human Dermatological Investigation

Two lots of dry experimental Carbopol® ETD polymers were impregnated separately into 20m X 20m X 1" surgical gauze pads which were moistened with distilled water just prior to application to the skin of two panels of 98 human volunteers^a in order to evaluate its skin irritation and sensitization potential.^{27, 28} A series of 12 applications was conducted with each panelist during the primary/induction phase. On four consecutive days of weeks 1, 2 and 3, the patches were removed and the contact sites were examined 24 hours after each application. Following a one-week rest period (week 4), a challenge phase was conducted on week 5 with 4 applications of the test material on a virgin site of each volunteer.

Neither lot of Carbopol® ETD polymer produced any product-related effects in any of the subjects during the primary irritation/activation or challenge period.

The investigator concluded that the results furnish no basis for contraindicating skin contact with Carbopol® ETD polymers under similar or less stringent conditions than the testing conditions used.

Pemulen™ TR-1 NF and Pemulen™ TR-2 NF Polymeric Emulsifiers

The following tests were performed on Pemulen™ TR-1, a copolymer polymerized in an ethyl acetate/cyclohexane cosolvent system. Pemulen™ TR-2 polymer is chemically similar to Pemulen™ TR-1 polymer. Therefore, the toxicological data for Pemulen™ TR-1 polymer are expected to apply to Pemulen™ TR-2 polymer.

Eye Irritation

The potential eye irritation potential of Pemulen™ TR-1 polymeric emulsifier was evaluated in New Zealand White rabbits.²⁹ Each of nine animals received a 0.021 g dose (0.1 ml equivalent) of the test article (i.e. neat powder) in the conjunctival sac of the right eye. The contralateral eye of each animal remained untreated and served as a control. At 30 seconds postinstillation, both eyes of three rabbits were rinsed with 50 ml of physiological saline (rinse group); no rinsing procedure was utilized on the six remaining rabbits (no-rinse group). Test and control eyes were examined for signs of irritation for up to 72 hours following dosing.

In the no-rinse group, exposure to the test article produced significant ocular irritation in 3 out of 6 test eyes. Corneal opacity was observed in 3 of 6 eyes, and iritis was observed in 1 of 6 eyes at the 24 hour scoring interval, but had resolved completely by 72 hours. Minimal conjunctivitis (conjunctival redness and swelling) was observed in 6 of 6 test eyes at 24 hours post-dose, but was completely resolved by test termination (72 hours).

In the rinse group, exposure to the test article produced generally milder responses than that noted in the no-rinse group. Iritis was observed in 1 of 3 eyes at 24 hours and diminished completely by 48 hours. Conjunctivitis was observed in 3 of 3 eyes at 24 hours and diminished by test termination in 2 of 3 eyes.

Based on the no-rinse test data, Pemulen™ TR-1 polymeric emulsifier is considered to be a borderline irritant to the ocular tissue of the rabbit according to the FHSA evaluation criteria.

Skin Irritation

The potential for Pemulen™ TR-1 polymeric emulsifier to cause skin irritation was evaluated in rabbits.³⁰ A dose of 0.5 g was applied to both abraded and intact sites, covered with gauze and an impervious wrap and evaluated after 24 and 72 hours. Slight irritation was observed (0.42 PII out of a possible 8.0).

^a Number of subjects remaining through the challenge phase

Human Dermatologic Investigation

The skin irritation and/or sensitizing potential of Pemulen™ TR-1 polymeric emulsifier was evaluated by the intensified version of the Shelanski and Shelanski Human Repeated Insult Patch test.³¹

Pemulen™ TR-1 polymeric emulsifier was impregnated into strips of surgical gauze which were then put into 1" x 1" squares. For each application, a patching device containing one of these squares on its webril pad was moistened and positioned directly on a designated site of the back of each subject with the gauze square in contact with the skin.

Pemulen™ TR-1 polymeric emulsifier produced no visible effects in 43 of 54 subjects during the primary irritation/activation test period. Faint or moderate erythema (reddening) occurred once in 9 subjects, and twice in 2 subjects. These effects would put Pemulen™ polymers in the category of very weak skin irritants.

Three of 53 subjects had solitary episodes of faint erythema during the challenge phase. The absence of responses significantly different than those obtained during the initial test phase indicates that Pemulen™ TR-1 polymeric emulsifiers do not possess a skin-sensitizing potential which can attain clinical status under the test conditions.

It was concluded that the results of this test furnish no basis for contraindicating skin contact with Pemulen™ TR-1 polymeric emulsifier under similar or less stringent conditions than those used in this test.

Effect on Aquatic Life

The aquatic toxicity of Carbopol® polymers was evaluated using Bluegill Sunfish (*Lepomis macrochirus* and *Daphnia magna*).³³

Carbopol® polymers were found to exhibit a relatively low to moderate degree of aquatic toxicity to both Bluegill and Daphnia. The death of the fish was believed to be caused by exhaustion rather than oxygen starvation. The exhaustion is the result of the high viscosity of the dispersion in which the aquatic series was tested. The LC₅₀ was a function of the thickening efficiency of the particular polymer which, in turn, is a function of molecular weight.

Bluegill Sunfish		
Carbopol® Polymer	LC ₅₀ (48 hrs.)	LC ₅₀ (96 hrs.)
934	1,120 mg/l	1,020 mg/l
940	660 mg/l	580 mg/l
Daphnia Magna		
934	216 mg/l	168 mg/l
940	210 mg/l	174 mg/l

Residual Solvent Levels

Lubrizol has made tremendous efforts to reduce the levels of residuals in the products and to introduce new products polymerized in safer solvents. Today, the polymers have low levels of ethyl acetate, and or cyclohexane, a solvent used extensively in the food industry. Additionally, a solvent mixture of ethyl acetate and cyclohexane is used and is referred to as "cosolvent."

Ethyl acetate, found naturally in such foods as yeast and sugar cane, is GRAS (Generally Recognized As Safe) as a direct food additive (21 CFR 182.60 and used as a secondary direct food additive to decaffeinated coffee (21 CFR 173.228). In addition to food uses, ethyl acetate is used as a pharmaceutical aid (flavor), NF 26. The oral LD₅₀ of ethyl acetate is reported to be 5600 mg/kg in the rat.

The LC₅₀ is approximately 200 mg/kg for the rat. Metabolic studies in the rat have revealed a "no observed effect level" (NOEL) of 2000 ppm. Metabolically, ethyl acetate is converted to ethyl alcohol and acetic acid.

One report found that intraperitoneal injection of ethyl acetate did not induce primary lung tumors in mice. An Ames test with and without metabolic activation, performed by Litton Bionetics for Lubrizol showed no mutagenic activity for ethyl acetate.

The American Conference of Governmental Industrial Hygienists (ACGIH) set a TLV for ethyl acetate of 400 ppm based mainly on its irritative properties.

Results of a comprehensive literature search on cyclohexane reveal it to be relatively nontoxic. Cyclohexane is acceptable for use as an indirect food additive (21 CFR 175.105 and 176.200).

The oral LD₅₀ in rats for cyclohexane is reported to be 29.82 g/kg; in the mouse 1.39 g/kg. The dermal LD₅₀ in rabbits is reported to be greater than 180.2 g/kg.

Like many alicyclic hydrocarbons, cyclohexane is a central nervous system depressant and can cause narcosis in high concentrations. However, in one study, no changes were found in the tissues of rabbits exposed to 434 ppm (1.49 mg/L) 6 hr/day x 26 weeks, while minor microscopic changes in liver and kidney tissues were reported in rabbits exposed to 786 ppm (2.7 mg/L 6 hrs/day x 50 days).

No deleterious effects were noted during or after exposure of a monkey by inhalation to 1243 ppm for 6 hr/day x 50 days. The tissues were normal in microscopic examination.

The traditional Carbopol[®] polymers (Carbopol[®] 934 NF, 934P NF, 940 NF, 941 NF and 1342 NF polymers) contain residual benzene, a suspected leukemia agent. For regulations on residual benzene, see OSHA Chapter XVII, Part 1910, Federal Register, Volume 43, No. 124 (6-27-78).

Material safety data sheets are available upon request for the various grades of Carbopol[®] polymers, Pemulen[™] polymeric emulsifiers and Noveon[®] polycarbophil.

Biotreatability of Carbopol[®] Polymers

The environmental fate of chemicals is increasingly becoming a concern of consumers and responsible chemical producers and formulators. The following aspects are important considerations regarding the biotreatability of Carbopol[®] polymers.

Biodegradability of Carbopol[®] Polymers

Biological oxygen demand tests were performed on a number of Carbopol[®] crosslinked polyacrylic acid polymers.³⁴ In each case the results were the same: the biological oxygen demand (BOD) was zero. In essence, the same characteristics which give these polymers excellent shelf life in severe environments also prevent them from degrading in a wastewater treatment facility.

Inhibition of Bacteria by Carbopol[®] Polymers

During the above BOD testing, the effect of Carbopol[®] crosslinked polyacrylic acid polymers on bacteria was examined. In the concentrations tested (0.85, 1.7, 8.5, 17 and 42 mg/l), this work found none of the polymers to be inhibitory to the bacteria typically found in a wastewater treatment facility. Thus, while these polymers are not degraded, they neither harm the bacteria nor render it less effective.

Removal of Carbopol® Polymers in a Wastewater Treatment Facility

If Carbopol® polymers are not degraded in a typical wastewater treatment facility, they must be removed in some fashion or else they would pass through to the environment. Tests were performed (Dr. Brian Arbuckle, University of Akron, April 16, 1992) to determine if the polymers would be removed during typical wastewater treatment by sorption onto the biomass. (When the term sorption is used, it usually means either a physical adsorption or absorption on the solid. It is also possible that material could be trapped in the biological floc and therefore be removed by that mechanism. Sorption will be used here to indicate removal, not necessarily the mechanism.)

The tests were performed at significantly higher concentrations of polymer than would be expected in real life (two to three orders of magnitude greater). This was done so the polymer could be detected analytically, but also results in a more severe test than would be expected in an actual municipal wastewater treatment situation. A standard U.S. EPA Synthetic Waste Recipe was used and mixing times representative of typical municipal treatment facilities were employed.

Conclusions

The previous tests show that within experimental test sensitivity, Carbopol® polymers are completely sorbed or trapped onto the biomass at polymer concentrations up to 16 ppm. Thus, instead of passing through to lakes and streams, these polymers are removed with the biomass and disposed or incinerated.

Based on the previous testing, it can be said that Carbopol® crosslinked polyacrylic acid polymers:

- Are not biodegradable,
- Do not inhibit waste treatment bacteria, and
- Do not pass through typical wastewater treatment to the environment, but are instead removed with the biomass.

Food Contact Regulations – 21 CFR

<u>Product</u>	<u>21 CFR Clearances</u>
Carbopol® 71G NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴ ; Hand Sanitizer ⁵
Carbopol® 934 NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴
Carbopol® 934P NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴
Carbopol® 940 NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴
Carbopol® 941 NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴
Carbopol® 971P NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴ ; Hand Sanitizer ⁵
Carbopol® 974P NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴ ; Hand Sanitizer ⁵
Carbopol® 980 NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴ ; Hand Sanitizer ⁵
Carbopol® 981 NF polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴ ; Hand Sanitizer ⁵
Carbopol® 1342 NF polymer	No clearance.
Carbopol® 5984 EP polymer	173.310 ¹ ; 173.340 ² ; 175.105; 175.300; 175.320; 176.170 ³ ; 176.180; 176.200 ² ; 177.1210; 177.2260 ⁴ ; Hand Sanitizer ⁵
Carbopol® ETD 2020 NF polymer	Hand Sanitizer ⁵
Carbopol® Ultrez 10 NF polymer	Hand Sanitizer ⁵
Pemulen™ TR-1 NF polymer	No clearance.
Pemulen™ TR-2 NF polymer	No clearance.

Limitations:

¹ As the sodium salt of Carbopol® polymer (sodium polyacrylate).

² As the sodium salt of Carbopol® polymer (polyacrylic acid, sodium salt) for use as a stabilizer and thickener in defoaming agents containing dimethylpolysiloxane in an amount usually required to accomplish the intended effect.

³ As the sodium salt of Carbopol® polymer (sodium polyacrylate) for use only: 1) as a thickening agent of natural rubber latex coating, provided it is used at a level not to exceed 2 percent by weight of coating solids, or 2) as a pigment dispersant in coatings at a level not to exceed 0.25 percent by weight of pigments.

⁴ Carbopol® polymer in combination with polyvinylalcohol.

⁵ Not to exceed 0.5% in hand sanitizer formulations. Reference: <http://www.cfsan.fda.gov/~dms/opa-fcn.html>

Pesticide Clearance: 40 CFR 180.960 Polymer Exemptions from the Requirement of a Tolerance*

- Carbopol® 934 NF Polymer
- Carbopol® 940 NF Polymer
- Carbopol® 941 NF Polymer
- Carbopol® 974P NF Polymer
- Carbopol® 980 NF Polymer
- Carbopol® 1342 NF Polymer
- Carbopol® ETD 2020 NF Polymer
- Carbopol® Ultrez 10 NF Polymer
- Pemulen™ TR-1 NF Polymer
- Pemulen™ TR-2 NF Polymer

*Note: EPA transferred all polymers listed in 40 CFR 180.1001 to 40 CFR 180.960 effective September 2002.

Food Supplement Regulations – Nutritional Tablets

GRAS Status of Carbopol® Polymers in Nutritional Tablets

Lubrizol has made a self determination that Carbopol® 934P NF, Carbopol® 971P NF, Carbopol® 974P NF and Carbopol® 71G NF polymers may be used in nutritional tablet applications because they are generally recognized as safe (GRAS) within the meaning of such terms under the Food, Drug and Cosmetic (FD&C) Act. Our opinion is based on the following information:

- Toxicology studies, summaries of which have been published, support the safety of Carbopol® 934P NF, 971P NF and 974P NF polymers at the estimated dietary exposure that may result from the intended use in nutritional tablets.
- Widely available, published information indicates a low order of toxicity for the class of compounds (polyacrylates) in which Carbopol® 934P NF, Carbopol® 971P NF and Carbopol® 974P NF polymers are included.
- FDA approved Carbopol® 934P NF and Carbopol® 974P NF polymers for use in oral solid dosage forms.
- Carbopol® 934P NF polymer has a history of safe use in magnesium lactate and vitamin B6 tablets in Europe.

Statutory and Regulatory Background

Under the FD&C Act as amended by the Dietary Supplement and Health Education Act of 1994, all excipients, such as Carbopol® polymers, used in the manufacture of dietary supplements (such as vitamin tablets) are regulated as food additives. As a result, they must be subject to an applicable food additive regulation, be GRAS or be prior sanctioned. Carbopol® 934P NF, 971P NF and 974P NF polymers have not been approved under any food additive regulation, nor are they prior sanctioned for use as food additives. No food additive petition requesting coverage under a food additive regulation has been filed with FDA, nor has any GRAS affirmative petition (GRASP) ever been filed seeking FDA approval for the use of Carbopol® polymers in dietary supplement applications. However, Lubrizol has, with the assistance of its FDA legal counsel, made a self-determination that Carbopol® 934P NF, Carbopol® 971P NF and Carbopol® 974P NF polymers should qualify as GRAS and may, therefore, be used in dietary supplement applications, such as vitamin tablets.

FDA Status of Carbopol® 934P NF, Carbopol® 971P NF, Carbopol® 71G NF and Carbopol® 974P NF Polymers

We have assumed that use of Carbopol® polymers will occur at levels between 5 and 30 percent of tablet mass, with a typical use of 20 percent. We have also assumed an average weight for the vitamin tablet of 500 milligrams. We have also assumed that the average person consuming the vitamin tablet weighs 60 kilograms. Based on these assumptions, the estimated daily intake of Carbopol® polymers present in a nutritional tablet at the 20% level would be 1.7 mg/kg-body weight per day. In light of this result, it is our opinion that Carbopol® 934P NF, 971P NF 71G NF and 974P NF polymers are properly considered GRAS for their intended use in the nutritional tablets.

Lubrizol has conducted extensive toxicological studies, including sub-chronic and chronic oral toxicity testing, acute oral and dermal toxicity studies as well as skin and eye irritation studies on Carbopol® 934P NF, Carbopol® 971P NF and Carbopol® 974P NF polymers to assure their safety. All of these studies have indicated that there is no significant health concern arising from the use of Carbopol® polymers in applications such as nutritional tablets, given the assumed usage levels.

Other carbomer products (linear polyacrylates and crosslinked polyacrylates) have demonstrated a very low order of toxicity when tested. A search of publicly-available literature also indicates that polyacrylates, in general, have a low order of toxicity by the oral route. Further, a very low order of toxicity is expected for a material, such as Carbopol® 934P NF, 971P NF or 974P NF polymer, that is not absorbed in the course of its use, but is rather subsequently passed through the user to a large (greater than 96%) extent.

U.S. FDA has approved the use of various Carbopol® polymers, including Carbopol® 934P NF polymer and Carbopol® 974P NF polymers, in oral dosage forms. Regulatory approvals have been obtained for certain drugs used for long term treatment of chronic diseases such as cardiovascular drugs containing Carbopol® 974P NF polymer. These cardiovascular medicines may be taken over a long-term period and would, therefore, expose the user of the drug to long-term exposure to Carbopol® 974P NF polymer.

Heavy Metals

No heavy metals are utilized as catalysts or as part of the manufacturing process for Carbopol® polymers. Please refer to the product specification sheets for further details regarding heavy metal content.

Ozone Depleting Substances (ODS)

According to the definitions provided in the final ruling published as 40 CFR part 82, Carbopol®, Noveon® and Pemulen™ polymers do not contain, and are not manufactured with ozone depleting chemicals.

ISO 9000 Registration

The Carbopol® polymer manufacturing locations worldwide have achieved ISO 9001 registration. ISO 9000 is a system for establishing, documenting and maintaining a system for ensuring the quality of the results of a manufacturing process.

American Chemistry Council (ACC)



Lubrizol is a member of the ACC. As a member, Lubrizol has firmly adopted the Responsible Care® Initiative. This initiative is the most ambitious and comprehensive environmental improvement effort ever attempted by an American industry.

Responsible Care commits all members to two critical elements:

- To continually improve performance in the areas of health, safety and environmental quality
- To work with the local communities to elicit and respond to the public concerns about products and operations.

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