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Final Report on the Safety Assessment of Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer

ABSTRACT

Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are polymers consisting of the partial ethyl ester and butyl ester, respectively, of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride. These esters are used in cosmetic formulations as film formers and hair fixatives. Ethyl Ester and Butyl Ester of PVM/MA Copolymer had oral LD_{50}s for rats of >25.6 g/kg. Butyl Ester of PVM/MA Copolymer was not toxic in a short-term oral toxicity study. Neither ester was toxic in subchronic inhalation animal studies and were neither ocular or dermal primary irritants. Neither was a skin irritant, sensitizer, or photosensitizer when assayed in human volunteers. Butyl Ester of PVM/MA Copolymer was not mutagenic in a mouse forward mutation assay with or without metabolic activation, and was inactive in an unscheduled DNA Synthesis assay. This ingredient was weakly active in the *in vitro* transformation of Balb/3T3 cells assay. On the basis of the animal and clinical data presented in this report, it is concluded that Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are safe in a neutralized form as cosmetic ingredients in the present practices of use.

INTRODUCTION

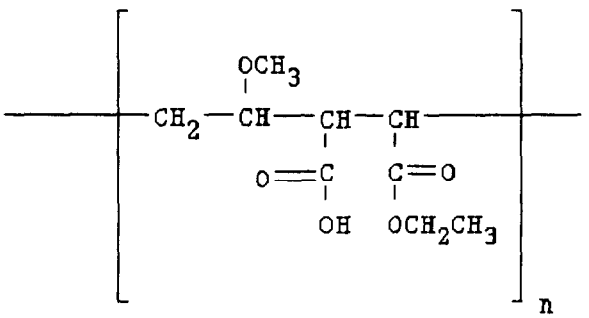
ETHYL ESTER OF PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are polymers consisting of the partial ethyl ester or butyl ester, respectively, of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride (Nikitakis, 1988). The base polymer is a true interpolymer, with a 1:1 molar ratio of vinyl methyl ether to maleic anhydride and an alternating sequence of these two monomer units (Petter, 1982).

CHEMISTRY

Definition and Structure

Ethyl Ester of PVM/MA Copolymer

Ethyl Ester of PVM/MA Copolymer (CAS nos. 25087-06-3 (GAF, 1991); 50935-57-7; 54578-90-4 (Estrin et al., 1982)) is a polymer consisting of the partial ethyl ester of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride that generally conforms to the following formula (Estrin et al., 1982):

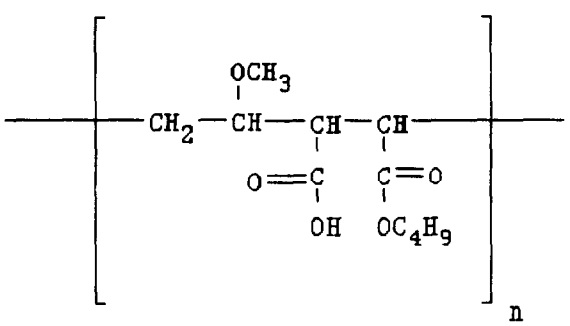


Ethyl Ester of PVM/MA Copolymer has free carboxyl groups with an equal number of adjacent ester groups along the chain (GAF, 1991).

Ethyl Ester of PVM/MA Copolymer is also known as Vinyl Methyl Ether/Ethyl Maleate Copolymer; Vinyl Methyl Ether/Monoethyl Ester of Maleic Acid Ester (CTFA, 1983); 2-Butenedioic Acid, Polymer with Methoxyethene, Ethyl Ester (Estrin et al., 1982); 2-Butenedioic Acid (z), Monoethyl Ester, Polymer with Methoxyethene (GAF, 1991); Gantrez ES 225 (Estrin et al., 1982; Petter, 1982; GAF, 1991); and Gantrez SP-215 (GAF, 1991).

Butyl Ester of PVM/MA Copolymer

Butyl Ester of PVM/MA Copolymer [CAS Nos. 25119-68-0 (GAF, 1991); 54018-18-7; 54578-91-5 (Estrin et al., 1982)] is a polymer consisting of the partial butyl ester of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride that generally conforms to the following formula (Estrin et al., 1982):



Butyl Ester of PVM/MA Copolymer also has free carboxyl groups with an equal number of adjacent ester groups along the chain (GAF, 1991).

Butyl Ester of PVM/MA Copolymer is also known as Vinyl Methyl Ether/Butyl

Maleate Copolymer (CTFA, 1983); 2-Butenedioic Acid, Polymer with Methoxyethene, Monobutyl Ester; Methoxyethene, Polymer with 2-Butenedioic Acid, Monobutyl Ester (Estrin et al., 1982); 2-Butenedioic Acid (z), Monobutyl Ester, Polymer with Methoxyethene (GAF, 1991); Gantrez ES 425 (Estrin et al., 1982; Petter, 1982; GAF, 1991); and Gantrez ES 435 (Estrin et al., 1982).

Physical and Chemical Properties

Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are supplied as ethanol solutions that are clear viscous liquids with concentrations of 50 ± 2% (Petter, 1982; GAF, 1991). Ethyl Ester and Butyl Ester of PVM/MA Copolymer are soluble in a variety of solvents; the degree of solubility can be modified by the type and degree of neutralization with a variety of bases. The physical and chemical properties of Ethyl Ester and Butyl Ester of PVM/MA Copolymer are summarized in Table 1.

Impurities

The amount of residual methyl vinyl ether in Ethyl and Butyl Esters of PVM/MA Copolymer has not been determined (ISP, 1991). Methyl vinyl ether is a gas at room temperature (boiling point, 6–7°C) and it is therefore expected that very little remains in the polymers. The oral and dermal LD_{50}s for methyl vinyl ether in rats were 4.9 g/kg and >2 ml/kg, respectively, and the inhalation LC_{50} was >64,000 ppm. Methyl vinyl ether was neither a dermal nor an ocular irritant, and it was not mutagenic in the Ames assay.

Manufacture and Production

Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are manufactured by the catalytic polymerization of a solution of maleic anhydride with methyl vinyl ether followed by hydrolysis of the anhydride using ethanol or butanol to yield either the ethyl or butyl half ester, respectively, of the PVM/MA Copolymer (GAF, 1991). For cosmetic use, the free carboxyl groups are neutralized.

Analytical Methods

Both Ethyl Ester and Butyl Ester of PVM/MA Copolymer can be identified by adding newly purified resorcin and sulfuric acid to the ingredient, heating it, cooling the solution, and then adding water to dissolve the residue. Sodium hydroxide TS is added to the solution, which is then observed under ultraviolet (UV) light at 366 nm. The solution generates a green–blue fluorescence (Yakuji Nippo Ltd., 1988).

USE

Cosmetic

Both Ethyl Ester and Butyl Ester of PVM/MA Copolymer function in cosmetics as film formers and hair fixatives (Nikitakis, 1988).

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES

Properties of both esters		*Reference*
Physical form	Clear viscous liquid	Petter, 1982; GAF, 1991
Activity (% solids)	50 ± 2% (in ethanol)	Petter, 1982; GAF, 1991
Solubility	Miscible with alcohols, esters, ketones, and glycol esters; insoluble in hexane and carbon tetrachloride; in the unneutralized form, the resin is insoluble in water or acid solution, but soluble in alkali; neutralized, the resin is water-soluble.	Petter, 1982
	Soluble in alcohols, ketons, esters and glycol esters	GAF, 1991
Purity	<10 ppm heavy metals <2 ppm arsenic	Yakuji Nippo Ltd., 1988
Residue on ignition	<1.0%	Yakuji Nippo Ltd., 1988
Ethyl ester of PVM/MA copolymer		
Mean molecular weight	46,200	ISP, 1991
Acid number (100% solids)	275–300	Petter, 1982
Specific gravity (as supplied)	0.983	Petter, 1982
Density (lb/gal) (as supplied)	8.18	Petter, 1982
Solubility	also soluble in diethyl ether and toluene	Petter, 1982
Butyl ester of PVM/MA copolymer		
Mean molecular weight	52,700	ISP, 1991
Acid number (100% solids)	235–265	Petter, 1982
Specific gravity (as supplied)	0.977	Petter, 1982
Density (lb/gal) (as supplied)	8.13	Petter, 1982

The combined chemical and tradename product formulation data that were submitted to the Food and Drug Administration (FDA) for Ethyl Ester of PVM/MA Copolymer indicated that it was used in a total of 160 cosmetic product formulations (FDA, 1991, 1992). Ethyl Ester of PVM/MA Copolymer was used in hair sprays, tonics, dressings, and other hair grooming aids, other hair preparations, and mascaras. The greatest reported use of Ethyl Ester of PVM/MA Copolymer was in hair sprays (74 formulations).

The combined chemical and tradename product formulation data submitted to the FDA for Butyl Ester of PVM/MA Copolymer indicated that it was used in a total of 67 cosmetic product formulations (FDA, 1991, 1992). Butyl Ester of PVM/MA Copolymer was used in hair sprays, wave sets, and other noncoloring hair preparations. The greatest reported uses of Butyl Ester of PVM/MA Copolymer were in hair sprays and other noncoloring hair preparations (23 and 25 formulations, respectively).

Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, 1984 product formulation data submitted

to the FDA indicated that Ethyl Ester of PVM/MA Copolymer was used at a concentration of ≤10% in hair sprays, and tonics, dressings, and other hair grooming aids and at ≤25% in other hair preparations. In 1984, Ethyl Ester of PVM/MA Copolymer was not reported to be used in mascaras (FDA, 1984).

The product formulation data submitted to the FDA in 1984 for Butyl Ester of PVM/MA Copolymer indicated that it was used at a concentration of ≤25% in hair sprays and other noncoloring hair preparations and at ≤10% in wave sets (FDA, 1984).

Product formulation data for Ethyl Ester and Butyl Ester of PVM/MA Copolymer are given in Table 2.

In aerosol products, both Ethyl and Butyl Ester of PVM/MA Copolymer give relatively the same particle size, which is dependent on the formulation (CTFA, 1992). Aerosols are formulated to minimize the amount of respirable particulate (<10 μm). Information provided to CTFA on two different aerosol products indicated particle size to be in the range of 6–83 μm with a mean of 36 μm for one product and in the range 6–110 μm with a mean of 42 μm for the other product.

International

Ethyl and Butyl Esters of PVM/MA copolymer are listed in the Japanese Cosmetic Ingredient Dictionary, Volume IV (Nikko Chemicals Co., 1992). As solutions, both ingredients are included in the Comprehensive Licensing Standards of Cosmetics by Category, Volume III. Both Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are listed in a Japanese Ministry of Health and Welfare (MHW) informal list of traditional cosmetic ingredients (CTFA, 1983).

TABLE 2. PRODUCT FORMULATION DATA*

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*
Ethyl ester of PVM/MA copolymer		
Hair sprays (aerosol fixatives)	323	74
Tonics, dressings, and other hair grooming aids	548	39
Other hair preparations (noncoloring)	418	39
Mascara	247	3
No. of uses under tradename		5
Total		160
Butyl ester of PVM/MA copolymer		
Hair sprays (aerosol fixatives)	323	23
Wave sets	160	6
Other hair preparations (noncoloring)	418	25
No. of uses under tradename		13
Total		67

*CIR requests that the cosmetic industry provide current formulation data on each product category.

Source: FDA, 1992.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Five groups of five albino Sherman-Wistar rats, sex not specified, were used to determine the oral LD_{50} of Ethyl Ester of PVM/MA Copolymer (Industrial Biology Laboratories, Inc., 1965a) and five groups of five albino Sherman-Wistar rats, gender not specified, were used to determine the oral LD_{50} of Butyl Ester of PVM/MA Copolymer (Industrial Biology Laboratories, Inc., 1965b). The test articles, evaporated to dryness and suspended in corn oil, were administered to fasted rats using a syringe and stomach tube. The dosages tested ranged from 1.6 to 25.6 g/kg. All groups were observed for 2 weeks after dosing. The oral LD_{50} of both Ethyl Ester and Butyl Ester of PVM/MA Copolymer was >25.6 g/kg.

Butyl Ester of PVM/MA Copolymer had an oral LD_{50} of >10 g/kg in rats (gender and strain not specified) and >2 g/kg in dogs (gender and strain not specified) (Lappas and McKeehan, 1965).

Short-Term Toxicity

Oral

A group of six female Holtzman rats was fed diet containing 25% Butyl Ester of PVM/MA Copolymer daily for 10 days (Nessel et al., 1964). A group of six female Holtzman rats was fed a similar diet, with lactose replacing Butyl Ester of PVM/MA Copolymer, and used as a control group. Physical observations were made and the animals were weighed prior to receiving each dose. All animals were killed on day 10 and their livers were removed. There were no significant differences in either the wet or dry liver weights or liver to body weight ratios between the treated and control groups. No gross physical changes were observed in the test animals.

Subchronic Toxicity

Inhalation

Ethyl Ester of PVM/MA Copolymer

Four groups of Sprague-Dawley rats, 15 males and 15 females per group, were used in an inhalation study to assess the toxicity of Ethyl Ester of PVM/MA Copolymer (FDRL, 1980a). The rats were placed in inhalation chambers for 4 h plus equilibration, if necessary, 5 days/week for 13 weeks, for a total of 65 exposures. To ensure uniformity of exposure, the rats in each group were repositioned in their chambers by cage unit daily.

The pressurized aerosol containers were positioned in line with, and within 5 cm of, the chamber such that the aerosol mixed with the room air entering the chamber. Exposure concentrations were adjusted and set by the rate and duration at which the aerosol containers were activated. For the low-, mid-, and high-dosage groups, the containers were actuated 0.2 sec of every 60 sec, 0.3 sec of every 30 sec, and 0.5 sec of every 30 sec, respectively. The rats in the control group were exposed to ambient air only. Particle size determinations were conducted weekly on all chambers throughout most of the study using a Casella Cascade Impactor.

The mean chamber concentrations of solids based on 65 determinations as measured by gravimetric analysis over the entire study were 0.017 ± 0.035, 0.531 ± 0.206, 2.17 ± 0.656, and 6.59 ± 1.522 μg/L for the control, low-, mid-, and high-dosage groups, respectively. These values for the low-, mid-, and high-dosage groups were 3.7, 15.1, and 45.8 times the concentration (0.144 μg/L) determined in an aerosol study using humans. The control group value was negligible and represented background dust.

Determination of the particle size distribution of the aerosol reported the geometric mean (50% size) to be ~20, 3.2, 3.4, and 1.6 μm for the control, low-, mid-, and high-dosage groups, respectively. The difference in particle size for the high-dosage group compared to the low- and mid-dosage groups was probably due to the mechanics of delivery of the aerosol to the chamber and was acceptable. The amount of the aerosol <10 μm (considered respirable) was ~38, 71, 73, and 88% for the control, low-, mid-, and high-dose groups, respectively. The control group values were not considered meaningful since the background values were so low.

Body weights and 24 h feed consumption were determined immediately prior to dose initiation; weekly measurements were made during the study. All rats were observed before and after dosing for signs of toxicity or moribundity, and all animals were observed on nontreatment days. Blood and urine samples were taken from eight nontest rats/gender at study initiation and from eight randomly selected rats/gender/group during week 6 of the study and at study termination. After 13 weeks of dosing, all animals were killed for necropsy, and a microscopic examination was performed on selected tissues.

There were no significant differences in mean body weights between the treated and control groups neither during the study nor at study termination. At various times during the study, feed consumption was significantly decreased for all test groups, males and females, when compared to control values. This did not appear to be dose-related.

With the exception of two mid-dosage females, pharmacotoxic observations were similar for all test and control animals. The two mid-dosage animals had alopecia starting at wk 7 or 11 and continuing until study termination. This lesion was not observed in the other dosage groups.

At week 6, females of all test groups had significantly increased erythrocyte counts, females of the low-dosage group had a significantly increased total leukocyte count, and females of the low- and high-dosage groups had decreased blood glucose values compared to the controls. No significant differences in either these or other values were observed at study termination.

At necropsy, the absolute heart weights of females of the low- and mid-dosage groups and the absolute kidney weights of females of the low-dosage group were decreased compared to the controls. However, there were no significant differences observed in any of the organ-to-body weight ratios for either these groups or any other group. Upon microscopic examination, the lungs of animals of the mid- and high-dosage groups had "scattered small foci of foamy cells" (alveolar macrophages). Ethyl Ester of PVM/MA Copolymer did not produce any obvious signs of toxicity.

Butyl Ester of PVM/MA Copolymer

Groups of Sprague-Dawley rats were used in an inhalation study to assess the toxicity of Butyl Ester of PVM/MA Copolymer (FDRL, 1980b). The control, low-dosage, and mid-dosage groups consisted of 15 males and 15 females per group and the

high-dosage group consisted of 30 males and 30 females. All rats were placed in inhalation chambers for 4 h plus equilibration, if necessary, 5 days/week for 13 week, resulting in 65 exposures to the test material; the rats used in the clinical studies after 6 weeks of dosing received 64 exposures. The rats in each group were repositioned in the chambers on a daily basis to ensure uniformity of exposure.

The theoretical exposures for rats in the low-, mid-, and high-dosage groups were 0.44, 0.74, and 1.36 μg/L (uncorrected for background) of test material, respectively, as measured by gravimetric analysis. The control rats were exposed to ambient air only.

The pressurized aerosol containers were positioned in line with, and within 5 cm of, the chamber such that the aerosol mixed with the room air entering the chamber. Exposure concentrations were adjusted and set by the rate and duration at which the aerosol containers were activated. The containers were actuated according to the following schedule: 0.2 sec on and 600 sec off during weeks 1–13 for the low-dosage group, 0.2 sec on and 99.9 sec off initially and during weeks 10–13 and 0.1 and 0.2 sec on and 99.9 sec off Monday–Wednesday and Thursday–Friday, respectively, during weeks 1–9 for the mid-dosage group, and 0.2 sec on and 43.8 sec off during weeks 1–9 and 0.2 sec on and 40.0 sec off during weeks 10–13 for the high-dosage group. Particle size determinations were conducted weekly on all chambers throughout most of the study using a Casella Cascade Impactor.

The actual mean chamber concentrations of solids based on 65 determinations as measured by gravimetric analysis over the entire study were 0.027 ± 0.007, 0.442 ± 0.086, 0.736 ± 0.067, and 1.362 ± 0.084 μg/L (uncorrected for background) for the control, low-, mid-, and high-dose groups, respectively. The actual mean chamber concentrations corresponded to factors of 0, 30, 49, and 91 times the estimated theoretical human exposure (as determined in an aerosol study using humans). The control group value was negligible and represented background dust.

The particle size distribution of the aerosol reported as the geometric mean (50% size) was 7.0, 3.4, 2.2, and 1.4 μm for the control, low-, mid-, and high-dose groups, respectively. The amount of the aerosol < 10 μm (considered respirable) was 66, 72, 73, and 82% for the control, low-, mid-, and high-dose groups, respectively. The control group values were not considered meaningful since the background values were so low.

Body weights and feed consumption were determined weekly. All rats were observed daily for signs of toxicity; checks for mortality were made twice daily. Blood and urine samples were taken from 8 nontest rats/gender at study initiation; at weeks 6 and 13 of the study, blood and urine samples were taken from eight randomly selected rats/gender/group. After 13 weeks of dosing, all control, low-, and mid-dosage animals, and 15 male and 15 female high-dosage animals, were killed for necropsy. The remaining high-dosage animals were allowed to recover for 4 weeks and then killed for necropsy. A microscopic examination was performed on selected tissues.

At various times during the study, mean body weights of males of the mid-dosage group were significantly decreased compared to control values. Also at various times throughout the study, feed consumption was significantly decreased for males and females of the mid- and high-dosage groups or significantly increased for males of the high-dosage group and females of all dosage groups when compared to control values.

Pharmacotoxic observations were similar for all test and control animals.

The results of clinical chemistry, hematology, and urinalysis were similar for treated and control animals. The only difference observed was a significantly increased urine albumin value for females of the high-dosage group at week 6.

After 13 weeks of dosing, absolute lung weights were significantly decreased for males of the mid-dosage group and lung-to-body weight ratios were significantly decreased for females in all three dosage groups compared to control values. No significant microscopic observations were made. There were no significant observations for animals of the high-dosage recovery group. No toxicological effects were produced by Butyl Ester of PVM/MA Copolymer.

Ocular Irritation

Two groups of albino rabbits, six per group, were used to determine the ocular irritation index of Ethyl ester of PVM/MA Copolymer (Industrial Biology Laboratories, Inc., 1965c) and Butyl Ester of PVM/MA Copolymer (Industrial Biology Laboratories, Inc., 1965d). Both ingredients were tested as a 5% w/v solution in distilled water; the pH was adjusted to 6.1 or 6.7 using aminoethyl propanediol (AMPD) for Ethyl Ester and Butyl Ester of PVM/MA Copolymer, respectively. A volume of 0.1 ml of test solution was applied to the conjunctival sac of the right eye of each rabbit; the eyes were not rinsed. The left eye served as the control. The eyes were examined for ocular lesions 24, 48, and 72 h after application of the test material and scored according to the methods of Draize (Draize, 1959). Neither Ethyl Ester of PVM/MA Copolymer nor Butyl Ester of PVM/MA Copolymer was an ocular irritant.

Dermal Irritation

Two groups of albino rabbits, six per group, were used to determine the primary dermal irritation of Ethyl Ester of PVM/MA Copolymer (Industrial Biology Laboratories, Inc., 1965e) and Butyl Ester of PVM/MA Copolymer (Industrial Biology Laboratories, Inc., 1965f). Both ingredients were tested as a 5% w/v solution in distilled water; the pH was adjusted to 6.1 or 6.7 using AMPD for Ethyl Ester and Butyl Ester of PVM/MA Copolymer, respectively. The procedure used was that described under section 191.11 of the Final Order, Enforcement Regulations, Federal Register (1961). Ethyl and Butyl Esters of PVM/MA Copolymer were not primary irritants as defined by the Federal Hazardous Substances Labeling Act.

Mutagenicity

Butyl Ester of PVM/MA Copolymer

A mouse lymphoma mutation assay was performed on Butyl Ester of PVM/MA Copolymer to determine the ability of the test material to induce forward mutations in the L5178Y TK+/− mouse lymphoma cell line (Litton Bionetics, Inc., 1981a). Dimethylsulfoxide (DMSO) was used as the solvent. The test material was soluble in the culture medium at concentrations of $\leq$125 nl/ml; precipitate formed at concentrations $\geq$250 nl/ml. In a preliminary cytotoxicity assay, 24 h cell growth was only slightly reduced by a concentration of 1000 nl/ml Butyl Ester of PVM/MA Copolymer.

Butyl Ester of PVM/MA Copolymer was assayed at concentrations of 15.6–2000 nl/ml with metabolic activation and at concentrations of 500–2,000 nl/ml without metabolic activation. Three trials were performed with and one without metabolic activation. Negative controls, solvent and untreated media, and positive controls, dimethylnitrosamine (DMN) with activation and ethylmethane sulfate (EMS) without activation, were used.

Without metabolic activation, mutant frequency remained comparable to the negative control values at all concentrations. A range of toxicities from weak to moderate was observed; however, the degree of toxicity did not increase as a function of increased concentration. At a concentration of 2,000 nl/ml, relative growth was decreased to 35.4%.

In the first acceptable trial with metabolic activation, mutant frequency was not increased as compared to the controls for all dosages except the 2,000 nl/ml dosage. For the concentration range of 15.6–2,000 nl/ml, weak to moderate toxicity was observed.

The second trial used duplicate treatments of 2,000 nl/ml to evaluate the mutant frequency results obtained in the first trial. In one experiment, the concentration was too toxic and mutant analysis could not be performed. In the second experiment with 2,000 nl/ml, moderate to high toxicity was observed, but mutant frequency did not vary significantly from the negative control values. (Therefore, the increase observed in trial 1 could not be confirmed.) At the other concentrations used, the mutant frequency was similar to that observed for the negative controls.

Butyl Ester of PVM/MA Copolymer was not mutagenic with or without metabolic activation in the mouse lymphoma forward mutation assay.

An *in vitro* transformation of Balb/3T3 cells assay was performed using Butyl Ester of PVM/MA Copolymer in order to evaluate its carcinogenic potential (Litton Bionetics, Inc., 1980). Butyl Ester of PVM/MA Copolymer was completely insoluble in culture medium at a concentration of 1.0 mg/ml; therefore, DMSO was used as the solvent.

A preliminary cytotoxicity test using concentrations of 0.06 μg/ml–1.0 mg/ml resulted in survival rates of 71–85%. A second preliminary cytotoxicity test used concentrations of 0.313–10.0 mg/ml. The survival rates were 46.5–90.5% for the concentrations of 0.313–2.5 mg/ml; no survivors were observed at 5.0 or 10.0 mg/ml.

The transformation assay used concentrations of 0.313–5.0 mg/ml Butyl Ester of PVM/MA Copolymer. A negative control, solvent, a historical negative control, and a positive control, 3-methylcholanthrene (MCA), were used. The results obtained with the negative control differed significantly from the historical control value; therefore, experimental results were evaluated independently.

Butyl Ester of PVM/MA Copolymer produced absolute and dosage-related increases in the number of transformed foci at all concentrations; these increases were statistically significant at concentrations of 2.5 and 5.0 mg/ml. Butyl Ester of PVM/MA Copolymer was weakly active in the *in vitro* transformation of Balb/3T3 cells assay.

An unscheduled DNA synthesis (UDS) assay using primary rat hepatocytes was performed on Butyl Ester of PVM/MA Copolymer (Litton Bionetics, Inc., 1981b). DMSO was used as the solvent. Butyl Ester of PVM/MA Copolymer was assayed at concentrations of 9.77–5,000 μg/ml. A negative control, solvent, and a positive control, 2-acetyl aminofluorene (2-AFF), were used. Freshly isolated cells were exposed to [^{3}H]thymidine in addition to the test material to improve the results.

An exposure of 625–5,000 μg/ml Butyl Ester of PVM/MA Copolymer produced rounded and loosely attached cells. Although these cells were still viable, they were not considered surviving cells. There were no survivors at concentrations of 2,500 and 5,000 μg/ml and a very low number of survivors at concentrations of 625 and 1,250 μg/ml were used. As concentrations decreased, survival rate increased. An analysis of nuclear labeling was performed at all concentrations. Butyl Ester of PVM/MA Copolymer did not produce a significant amount of UDS in primary rat hepatocytes and was inactive in the assay.

CLINICAL ASSESSMENT OF SAFETY

Irritation/Sensitization

Ethyl Ester and Butyl Ester of PVM/MA Copolymer were applied to subjects simultaneously to evaluate the human irritation and sensitization potentials of the test articles (ToxiGenics, 1981). A repeated insult patch test (RIPT) was performed using the Draize-Shelanski method (Draize, 1955; Shelanski and Shelanski, 1953). The test materials were applied as supplied (50 ± 2%) using semiocclusive patches. The patches were prepared by applying approximately 0.15 ml of test material to the patch and allowing it to volatilize for a minimum of 10–15 min. Of the initial 170 subjects, 150 completed the study.

Patches were applied to the scapular area of the back on Mondays, Wednesdays, and Thursdays for 3 weeks for a total of 9 induction applications. (Some patches had to be applied on different days of the week for some subjects.) The patches were removed and the sites evaluated for irritation 24 h after application. After the ninth patch, there was a nontreatment period of at least 10 days. A challenge patch was then applied to a site adjacent to the induction site. The patch was removed after 24 h; both sites were graded upon patch removal and 48 and 72 h after the challenge application.

During the induction phase of the study, 0.21% of the applications induced skin irritation reactions that were regarded as "singular, transient occurrences of a slight nature." Ethyl Ester and Butyl Ester of PVM/MA Copolymer were not irritants nor sensitizers.

Photoallergenicity and Contact Allergenicity

Ethyl Ester of PVM/MA Copolymer

The photoallergenic and contact allergenic potentials of Ethyl Ester of PVM/MA Copolymer were evaluated (FDRL, 1982). The test material was applied as supplied (50 ± 2%) using semiocclusive patches. The patches were prepared by applying approximately 0.2 ml of the test material to the patch and allowing it to volatilize for 15 min. Of the 35 subjects at study initiation, 31 completed the study.

Patches were applied to the inner aspect of the forearm on Mondays, Wednesdays, and Thursdays until 10 doses were received. For half of the subjects, the inner aspect of the right arm was irradiated; for the other half, it was the inner aspect of the left arm. The opposite arm served as the control (non-irradiated) site. The irradiated sites were exposed to ultraviolet A (UVA) radiation for 15 min at a distance of 10 cm from the source, resulting in a dosage of 4400 $\mu W/cm^2$. To avoid irradiation of a test site on 2 consecutive days, Thursdays' patches were applied to an adjacent site, which was irradiated on Friday; the first site was considered the original site at challenge. The application sites that were not irradiated were covered with black adhesive tape to prevent UV exposure.

After a 10–13 day nontreatment period, a challenge patch was applied to an untreated site adjacent to the original site. After 24 h, the patches were removed and the test sites were graded for irritation. The challenge site was then irradiated and examined 24 and 48 h after irradiation.

Only slight transient reactions were observed during the study. Ethyl Ester of PVM/MA Copolymer did not induce either a photoallergenic or contact allergenic response in human subjects.

Aerosol Study

Ethyl Ester of PVM/MA Copolymer

A panel of 20 women was used to determine the amount of respirable Ethyl Ester of PVM/MA Copolymer resulting from the use of two hair spray formulations, one in an aerosol can and the other in a pump spray; this study was not an inhalation study (FDRL, 1979). The test sprays contained 0.02% fluorescein. A reference air sample was taken using an open face filter prior to testing. The panelists were fitted with a wig, safety glasses, filter mask, and laboratory coat and instructed to use the first hair spray in a normal manner. Using open face filters and a cyclone sampler, a total of five different test air samples were taken over 15 min. (The open face filters sampled all airborne material, regardless of particle size, while the cyclone sampler only collected particles ≤ 10 μm). The same procedure was repeated for the second sample.

The concentrations of Ethyl Ester of PVM/MA Copolymer, determined from the amount of fluorescein collected, were 0.100 and 0.064 μg/L for the aerosol and pump spray, respectively (for the cyclone filter after 15 min), and 0.281 and 0.191 μg/L for the aerosol and pump spray, respectively (for the open face filter after 15 min). The amounts of Ethyl Ester of PVM/MA Copolymer collected by the open face filters decreased from 0.823 and 0.610 μg/L during the 0–3 min period to 0.013 and 0.045 μg/L during the 11–14 min period for the aerosol and pump spray, respectively. The amount of respirable Ethyl Ester of PVM/MA Copolymer was 39.8 ± 3.3% for the aerosol and 37.5 ± 4.3% for the pump spray. The aerosol and pump spray contained approximately 6% and 10% Ethyl Ester of PVM/MA Copolymer, respectively; however, the percentages of respirable material produced by both were essentially the same, indicating that the panel used more of the aerosol formulation than the pump spray formulation during normal use.

SUMMARY

Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are polymers consisting of the partial ethyl ester and butyl ester, respectively, of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride. They both have free carboxyl groups with an equal number of adjacent ester groups along the chain. The free carboxyl groups are neutralized for cosmetic use.

Both esters are supplied as clear viscous ethanol solutions with concentrations of 50 ± 2% and are soluble in a variety of solvents. The mean molecular weights for Ethyl and Butyl Ester of PVM/MA Copolymers are 46,200 and 52,700, respectively. The amount of residual vinyl methyl ether remaining in the esters has not been determined, but very little is expected to remain in the polymers.

Ethyl and Butyl Esters of PVM/MA Copolymer function as film formers and hair fixatives in cosmetics. In 1991/1992, Ethyl Ester of PVM/MA Copolymer was used in 160 cosmetic formulations and Butyl Ester of PVM/MA Copolymer was used in 67 cosmetic formulations. In aerosol products, both esters give relatively the same particle size. The mean particle size for two formulations ranges from 36 to 42 μm, which is greater than the size that is considered respirable.

Ethyl Ester and Butyl Ester of PVM/MA Copolymer were relatively harmless to rats according to the terminology of Hodge and Sterner (1949), with both compounds having an oral LD_{50} for rats of >25.6 g/kg. For dogs, Butyl Ester of PVM/MA Copolymer

had an LD_{50} of >2 g/kg. Butyl Ester of PVM/MA Copolymer was not toxic in a short-term oral toxicity study. Ethyl Ester and Butyl Ester of PVM/MA Copolymer were not toxic in subchronic inhalation studies. Ethyl and Butyl Esters of PVM/MA Copolymer were neither ocular nor primary dermal irritants.

Butyl Ester of PVM/MA Copolymer was not mutagenic in a mouse forward mutation assay with or without metabolic activation, was weakly active in the in vitro transformation of Balb/3T3 cells assay, and was inactive in a UDS assay.

Ethyl and Butyl Esters of PVM/MA Copolymer were neither irritants nor sensitizers in an RIPT using human subjects. Ethyl Ester of PVM/MA Copolymer did not produce a photoallergenic or contact allergenic response in humans.

DISCUSSION

The Expert Panel recognizes that the amount of the ingredient that can be respired is an important factor and, therefore, examined this issue. Data submitted to the Panel indicate that the average particle size of Ethyl and Butyl Esters of PVM/MA Copolymer is larger than the size that is considered respirable (i.e., 10 μm). In the subchronic inhalation animal studies presented in this report, the particle size of the test material was smaller than the particle size normally used in cosmetic formulation; therefore, a greater amount of material was respired by the animals as compared to usual human use.

CONCLUSION

On the basis of the animal and clinical data presented in this report, the CIR Expert Panel concludes that Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer are safe in neutralized form as cosmetic ingredients in the present practice of use.

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