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# Final Report of the Amended Safety Assessment of PVM/MA Copolymer and Its Related Salts and Esters as Used in Cosmetics

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**Abstract**

Polyvinyl methyl ether/maleic acid (PVM/MA) copolymer, and its related salts and esters, are used in cosmetics, mainly as binders, film formers, and hair fixatives. Animal and human data relevant to the use of these ingredients in cosmetic products were reviewed by the CIR Expert Panel. The Panel concluded that these ingredients are safe for use in cosmetic products.

**Keywords**

cosmetics, polyvinyl methyl ether/maleic acid, PVM/MA copolymer, safety

## Introduction

A safety assessment of the ethyl ester and butyl ester of polyvinyl methyl ether/maleic anhydride or polyvinyl methyl ether/maleic acid (collectively referred to as PVM/MA) copolymers was published in 1993 with the conclusion from the Cosmetic Ingredient Review (CIR) Expert Panel that these chemicals "are safe in neutralized form as cosmetic ingredients in the present practice of use."[1]

The Expert Panel determined that the available data in the original safety assessment on ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer are sufficient to support the safety of calcium/sodium PVM/MA copolymer, potassium ethyl ester of PVM/MA copolymer, sodium ethyl ester of PVM/MA copolymer, potassium butyl ester of PVM/MA copolymer, Sodium butyl ester of PVM/MA copolymer, isopropyl ester of PVM/MA copolymer, and PVM/MA copolymer. These ingredients consist of the parent copolymer, PVM/MA copolymer, and additional simple esters and salts of this ingredient.

## Chemistry

### *Definition and Structure*

The definitions and structures of the salts and esters of the PVM/MA copolymer ingredients presented in this report are listed in Table 1. Technical and trade names[2] for these ingredients, according to Gottschalck and Bailey, are listed in Table 2.

### *Physical and Chemical Properties*

Butyl ester and ethyl ester of PVM/MA copolymer consist of the partial butyl ester or ethyl ester, respectively, of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride.[3] 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 2 monomer units.[4] Butyl ester and ethyl ester of PVM/MA copolymer have free carboxyl groups with an equal number of adjacent ester groups along the chain.[5]

Monoesters of PVM/MA copolymer contain a hydrophobic ester group that decreases the penetration of water into the polymer and a solubilizing carboxylic group.[6]

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%.[4,5] 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.

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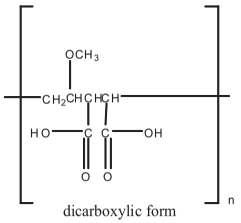
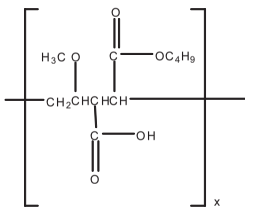
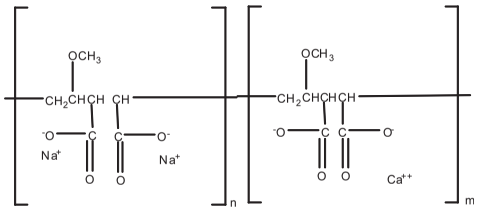
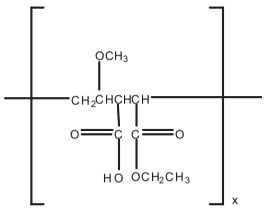
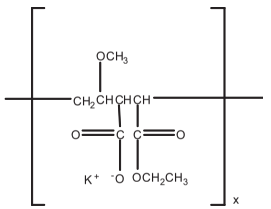
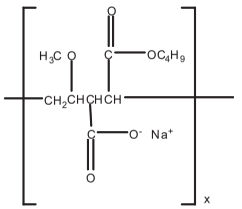
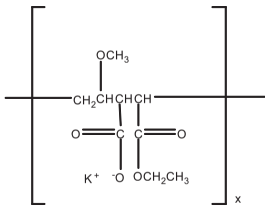
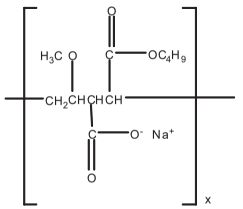
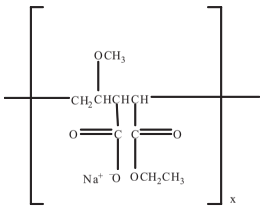
**Table 1.** Definitions, Structures, and Functions for PVM/MA Copolymer and Its Salts and Esters[2,11,a]

| Ingredient | Definition | Structure | Function | Reviewed? |
|---|---|---|---|---|
| PVM/MA copolymer (CAS No. 9011-16-9; 25153-40-6; 25249-64-3) | A copolymer of methyl vinyl ether and maleic anhydride or maleic acid. |  dicarboxylic form | Binder; emulsion stabilizer; film former; hair fixative; suspending agent-nonsurfactant | No |
| Butyl ester of PVM/MA copolymer (CAS No. 25119-68-0; 53200-28-5; 54018-18-7) | A polymer consisting of the partial butyl ester of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride |  | Binder; film former; hair fixative | 1993 JACT 12(3) |
| Calcium/sodium PVM/MA copolymer (CAS No. 62386-95-2) | A mixed calcium and sodium salt of PVM/MA copolymer |  | Film former; hair fixative | No |
| Ethyl ester of PVM/MA copolymer (CAS No. 25087-06-3; 50935-57-4; 67724-93-0) | A polymer consisting of the partial ethyl ester of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride. |  | Binder; film former; hair fixative | 1993 JACT 12(3) |
| Isopropyl ester of PVM/MA copolymer (CAS No. 54077-45-1; 54578-88-0) | A polymer consisting of the partial isopropyl ester of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride. |  | Binder; emulsion stabilizer; film former; hair fixative; suspending agent-nonsurfactant | No |

*(continued)*

**Table 1.** (continued)

| Ingredient | Definition | Structure | Function | Reviewed? |
|---|---|---|---|---|
| Potassium butyl ester of PVM/MA copolymer (CAS No. not found) | The potassium salt of butyl ester of PVM/MA copolymer. |  | Binder; film former; hair fixative | No |
| Potassium ethyl ester of PVM/MA copolymer (CAS No. not found) | The potassium salt of ethyl ester of PVM/MA copolymer |  | Binder; film former; hair fixative | No |
| Sodium butyl ester of PVM/MA copolymer (CAS No. not found) | The sodium salt of butyl ester of PVM/MA copolymer |  | Binder; film former; hair fixative | No |
| Sodium ethyl ester of PVM/MA copolymer (CAS No. not found) | The sodium salt of ethyl ester of PVM/MA copolymer |  | Binder; film former; hair fixative | No |

[a] In cases where the structure was not available or not correct, the structures were prepared by CIR.

**Table 2.** Technical and Trade Names for PVM/MA Copolymers and Its Salts and Esters[2]

| Technical/Other Names | Trade Names |
|---|---|
| PVM/MA Copolymer | |
| 2-Butanedioic Acid (2Z)-, polymer with methoxyethene | Gantrez AN-119 |
| 2,5-Furandione, Polymer with Methoxyethene | Gantrez AN-139 |
| Methyl Vinyl Ether/Maleic Anhydride Copolymer | Gantrez AN-149 |
| | Gantrez AN-169 |
| | Gantrez S-95 |
| | Gantrez S-97 |
| | Luviform FA 139 |
| Butyl ester of PVM/MA copolymer | |
| 2-Butenedioic Acid, polymer with methoxyethene, monobutyl ester | Gantrez A-425 |
| 2,5-Furandione, polymer and methoxyethene, 1-methylethyl ester | Gantrez ES 425 |
| Methoxyethene, polymer with 2-butenedioic acid, monobutyl ester | Gantrez ES 435 |
| Vinyl methyl ether.butyl maleate copolymer solution | Gantrez V-425 |
| Calcium/sodium PVM/MA copolymer | |
| None found | Gantrez MS-955 |
| Ethyl ester of PVM/MA copolymer | |
| 2-Butanedioic acid, polymer with methoxyethene, ethyl ester | Gantrez ES 225 |
| 2,5-Furandione, polymer and methoxyethene, ethyl ester | Gantrez SP-215 |
| Vinyl methyl ether.ethyl maleate copolymer solution | Gantrez V-215 |
| | Gantrez V-225 |
| | Omnirez 2000 |
| Isopropyl ester of PVM/MA copolymer | |
| 2-Butenedioic acid, polymer with methoxyethene, 1-methylethyl ester | Gantrez ES 335-I |
| Potassium butyl ester of PVM/MA copolymer | |
| None found | None found |
| Potassium ethyl ester of PVM/MA copolymer | |
| None found | None found |
| Sodium butyl ester of PVM/MA copolymer | |
| None found | None found |
| Sodium ethyl ester of PVM/MA copolymer | |
| None found | None found |

The physical and chemical properties of PVM/MA copolymer and its salts and esters are summarized in Table 3.

### Impurities

The amount of residual methyl vinyl ether in ethyl and butyl esters of PVM/MA copolymer has not been determined.[7] Methyl vinyl ether is a gas at room temperature (boiling point, 6°C-7°C), and it is therefore expected that very little remains in the polymers. See Table 3 for additional impurity information on specific copolymers.

### Manufacture and Production

PVM/MA copolymers are all derived from similar chemistry.[8] Methyl vinyl ether and maleic anhydride are reacted to form the copolymer of methyl vinyl ether and maleic anhydride. This copolymer can then be hydrolyzed to create the copolymer of methyl vinyl ether and maleic acid (the dicarboxylic form).

Ethyl ester of PVM/MA copolymer, butyl Ester of PVM/MA copolymer, and isopropyl 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, n-butanol, or isopropyl alcohol to yield monoethyl, monobutyl, or monoisopropyl ester, respectively, of the PVM/MA copolymer.[5,8] For cosmetic use, the free carboxyl groups are neutralized with a choice of bases, although 2-amino-2-methylpropanol is common.[5]

Calcium/sodium PVM/MA copolymer is formed by adding a mixture of calcium and sodium bases to the dicarboxylic form of the PVM/MA copolymer.[8]

### 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 (1M) is added to the solution, which is then observed under ultraviolet (UV) light at 366 nm. The solution generates a green-blue fluorescence.[9]

## Use

### Cosmetic

The available product formulation data for the PVM/MA copolymer ingredients are presented in Table 4. At the time of the original safety assessment (1993), ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer were used in a total of 160 and 67 cosmetic products, respectively, at use concentrations of ≦25% for both ingredients.[1] Current Voluntary Cosmetic Registration Program (VCRP) data indicate that ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer are used in 42 and 28 cosmetic products, respectively.[11] A survey of current use concentrations conducted by the Personal Care Products Council reported a range from 0.002% to 30% for ethyl ester of PVM/MA copolymer and 0.002% to 14% for butyl ester of PVM/MA copolymer.[12] The total uses for the related ingredients were reported for PVM/MA copolymer (80 uses) and calcium/sodium PVM/MA copolymer (1 use).[11] The Council reported use concentration ranges from 0.0006% to 13% for PVM/MA copolymer. Use concentration data were not available for calcium/sodium PVM/MA copolymer. Use frequency and concentration data were not available for the remaining salts and esters.

PVM/MA copolymer and its salts and esters are used in hair sprays, and effects on the lungs that may be induced by aerosolized products containing this ingredient are of concern.

**Table 3.** Physical and Chemical Properties of PVM/MA Copolymer and Its Salts and Esters

| Property | Description | Reference |
|---|---|---|
| PVM/MA copolymer (Maleic anhydride derivation) | | |
| Physical form | Free flowing powder | 8 |
| % Active | 98 min | 8 |
| % Water | 0.75 max | 8 |
| Solubility | Soluble in a variety of solvents; insoluble in aliphatic, aromatic, and halogenated hydrocarbons | 8 |
| Acid number (mg KOH/g sample) | 695 | 8 |
| Molar mass (absolute weight, SEC/LALLS) | 130 000-2 500 000 | 8 |
| Specific Gravity @ 25°C, 5% solids | 1.018-1.016 | 8 |
| Bulk density (lbs/ft$^2$) | 20.0-21.8 | 8 |
| Residual maleic anhydride ppm | Negative | 8 |
| Toluene (%) | < 2 | 8 |
| Benzene (ppm) | < 5 | 8 |
| PVM/MA copolymer (maleic acid derivation) | | |
| Physical form | White to off-white free flowing powder; slightly hazy viscous liquid in solution | 8 |
| % Active | 94 min; 12.0-14.4 in solution | 8 |
| % Water | 6 max; 85.6-88.0 in solution | 8 |
| Solubility | Soluble in water, alcohol, and a variety of solvents; insoluble in acetone, methyl ethyl ketone, and ethyl acetate. | 8 |
| Acid number (mg KOH/g sample) | 592-601 | 8 |
| Molar mass (absolute weight, SEC/LALLS) | 74 000-1 200 000; 1 500 000 in solution | 8 |
| Specific gravity @ 25°C, 5% solids | 1.0152-1.058; 1.0455 in solution | 8 |
| Bulk density (g/mL) | 0.57-0.71 | 8 |
| Residual maleic anhydride ppm | Negative | 8 |
| Benzene (ppm) | <40 ppb | 8 |
| Heavy metals ppm (as lead) | Not detected | 8 |
| Calcium/sodium PVM/MA copolymer | | |
| Physical form | White/off-white powder | 8 |
| % Active | 85-94 | 8 |
| % Water | 6.0-15.0 | 8 |
| Molar mass (absolute weight, SEC/LALLS) | 1 060 000 | 8 |
| Specific gravity @ 30°C, 30% solid–saqueous | 1.061 | 8 |
| Bulk density (g/mL) | 0.6-0.75 | 8 |
| Benzene (ppm) | <40 ppb | 8 |
| Heavy metals ppm (as lead) | Not detected | 8 |
| Ethyl ester and butyl ester of PVM/MA copolymer | | |
| Physical form | Clear viscous liquid | 4,5 |
| Activity (% solids) | 50% $\pm$ 2% (in ethanol) | 4,5 |
| 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; in neutralized form, the resin is water-soluble. Soluble in alcohols, ketones, esters, and glycol esters | 4,5 |
| Purity | <10 ppm heavy metals; < 2 ppm arsenic | 9 |
| Residue on ignition | <1.0% | 9 |
| Ethyl ester PVM/MA copolymer | | |
| Physical form | Viscous liquid | 8 |
| % Active | 48.0-52.0 | 8 |
| Molar mass (relative weight to polystyrene standards) | 80 000-150 000 | 8 |
| Mean molecular weight | 46 200 | 7 |
| Acid number | 275-300 (100% solids); 265-300 (mg KOH/g sample) | 4,8 |
| Specific gravity | 0.983 (as supplied, at 25°C C) | 4,8 |
| Water (%) | 0.5 max | 8 |
| Acetone (%) | 0.4 max | 8 |
| Density (lb/gal) (as supplied) | 8.18 | 4 |

*(continued)*

**Table 3.** (continued)

| Property | Description | Reference |
|---|---|---|
| Solubility | Soluble in diethyl ether, toluene, and SD alcohol 40-B. | 4,8 |
| t-Butanol denatonium benzoate | <0.1%, 6-10 ppm | 8 |
| Heavy metals ppm (as lead) | Not detected | 8 |
| Butyl ester PVM/MA copolymer | | |
| Physical form | Slightly yellow clear viscous liquid in ethanol; viscous liquid in isopropanol | 8 |
| % Active | 48.0-52.0 in ethanol and in isopropanol | 8 |
| Solvent | SD Alcohol 40-B (when in ethanol); isopropanol (when in isopropanol) | 8 |
| Molar mass (relative weight to polystyrene standards) | 78 000–150 000 in ethanol; 110 000-140 000 in isopropanol | 8 |
| Mean molecular weight | 52 700 | 7 |
| Acid number | 235-265 (100% solids); 235-275 (mg KOH/g sample, in ethanol); 245-280 (mg KOH/g sample, in isopropanol) | 4,8 |
| Specific gravity (as supplied) | 0.977 (as supplied); 0.977 in ethanol @ 25°C; 0.962 in isopropanol @ 25°C | 4,8 |
| Water (%) | 0.5 to 0.7 max in ethanol; 0.5 max in isopropanol | 8 |
| Acetone (%) | 0.5 max in ethanol | 8 |
| Density (lb/gal, as supplied) | 8.13 | 4 |
| t-Butanol denatonium benzoate | <0.1%, 6-10 ppm in ethanol | 8 |
| Heavy metals ppm (as lead) | Not detected | 8 |
| Isopropyl ester of PVM/MA Copolymer (in isopropanol) | | |
| Physical form | Viscous liquid | 8 |
| % Active | 48.0-52.0 | 8 |
| Solvent | Isopropanol | 8 |
| Acid number (mg KOH/g sample) | 250-280 | 8 |
| Molar mass (relative weight to polystyrene standards) | 110 000-140 000 | 8 |
| Specific gravity @ 25°C | 0.957 | 8 |
| Water (%) | 0.5 max | 8 |

A panel of 20 women was used to determine the amount of respirable ethyl ester of PVM/MA copolymer resulting from the use of 2 hair spray formulations, one in an aerosol can and the other in a pump spray; this study was not an inhalation study.[13] 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 5 different test air samples were taken over 15 minutes. The open-face filters sampled all airborne material, regardless of particle size, while the cyclone sampler only collected particles ≦10 μm. The concentrations of ethyl ester of PVM/MA copolymer were 0.100 and 0.064 μg/L for the aerosol and pump spray, respectively, for the cyclone filter after 15 minutes, and 0.281 and 0.191 μg/L for the aerosol and pump spray, respectively, for the open-face filter after 15 minutes.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.[14] In general, the smaller the particle, the further into the respiratory tree the particle will deposit and the greater the impact on the respiratory system.[15]

Anhydrous hair spray particle diameters of 60 to 80 μm have been reported, and pump hair sprays have particle diameters of ≥80 μm.[16] The mean particle diameter is around 38 μm in a typical aerosol spray.[17] In practice, aerosols should have at least 99% of particle diameters in the 10 to 110 μm range. This means that most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

Jachowicz and Yao studied the properties of hair spray resins, including ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer, on several hair types.[18] Properties of hair treated with a fixative are affected by the concentration and molecular weight of a polymer, with stiffness ratios increasing with the increase of both these parameters. Higher degrees of neutralization usually increase the moisture sensitivity of a polymer, with decreased stiffness retention at high humidity.

PVM/MA copolymer and its salts and esters are not included among the substances listed as prohibited, restricted, or provisionally allowed in the use of cosmetic products marketed in Japan.[19,20] In addition, these ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[21]

## Noncosmetic

According to *Hawley's Condensed Chemical Dictionary*, PVM/MA copolymer is used as a protective colloid, dispersing agent, thickener, binder, adhesive and "size in coatings,"

**Table 4.** Historical and Current Cosmetic Product Uses and Concentrations for Ethyl Ester of PVM/MA Copolymer, Butyl Ester of PVM/MA Copolymer, PVM/MA Copolymer, and Calcium/Sodium PVM/MA Copolymer

| Product Category | 1992 Uses[1] | 2009 Uses[10] | 1984 Concentrations[1] (%) | 2008 Concentrations[10] (%) |
|---|---|---|---|---|
| Ethyl ester of PVM/MA copolymer | | | | |
| Eye makeup | | | | |
| Mascara | 3 (247) | 1 (463) | – | – |
| Noncoloring hair care products | | | | |
| Sprays/aerosol fixatives | 74 (323) | 11 (371) | ≦10 | 5-13 |
| Tonics, dressings, etc | 39 (548) | 13 (1097) | ≦10 | 3-30 |
| Wave sets | – | 4 (50) | – | – |
| Other | 39 (418) | 13 (716) | ≦25 | - |
| Hair coloring products | | | | |
| Color sprays | – | – (8) | – | 0.002 |
| Makeup | | | | |
| Lipstick | – | – (1912) | – | 2 |
| Nail care products | | | | |
| Basecoats and undercoats | – | – (62) | – | 14 |
| Skin care products | | | | |
| Foot powders and sprays | – | – (48) | – | 15 |
| Uses under tradename[1] | 5 | NA | NA | NA |
| Total uses/ranges for Ethyl Ester of PVM/MA Copolymer | 160 | 43 | ≦25 | 0.002-30 |
| Butyl ester of PVM/MA copolymer | | | | |
| Noncoloring hair care products | | | | |
| Sprays/aerosol fixatives | 23 (323) | 21 (371) | È25 | 2-14 |
| Tonics, dressings, etc | – | 2 (1097) | – | 3-4 |
| Wave sets | 6 (160) | – (50) | ≦10 | – |
| Other | 25 (418) | 5 (716) | ≦25 | - |
| Hair coloring products | | | | |
| Color sprays | – | – (8) | – | 0.002 |
| Uses under tradename[1] | 13 | NA | NA | NA |
| Total uses/ranges for butyl ester of PVM/MA copolymer | 67 | 28 | ≦25 | 0.002-14 |
| PVM/MA copolymer | | | | |
| Bath products | | | | |
| Soaps and detergents | NA | 2 (1329) | NA | – |
| Eye makeup | | | | |
| Eye shadow | NA | 1 (1196) | NA | 0.01 |
| Eye makeup remover | NA | 1 (131) | NA | – |
| Other | NA | 3 (288) | NA | – |
| Fragrance products | | | | |
| Perfumes | NA | – (569) | NA | 3 |
| Noncoloring hair care products | | | | |
| Tonics, dressings, etc | NA | 2 (1097) | NA | – |
| Other | NA | 2 (716) | NA | – |
| Makeup | | | | |
| Foundations | NA | 1 (635) | NA | – |
| Lipstick | NA | 1 (1912) | NA | 0.2 |
| Oral hygiene products | | | | |
| Dentifrices | NA | – (59) | NA | 0.2 |
| Mouthwashes and breath freshener sprays | NA | – (85) | NA | 0.5 |
| Shaving products | | | | |
| Other | NA | 5 (107) | NA | 0.0007[2] |
| Skin care products | | | | |
| Face and neck creams, lotions, powder, and sprays | NA | 3 (1195) | NA | 0.01-0.04 |
| Body and hand creams, lotions, powder, and sprays | NA | 23 (1513) | NA | 0.0006-0.02 |
| Foot powders and sprays | NA | – (48) | NA | 0.01 |
| Moisturizers | NA | 24 (2039) | NA | – |
| Night creams, lotions, powder, and sprays | NA | 2 (343) | NA | – |
| Paste masks (mud packs) | NA | 2 (418) | NA | 0.006 |
| Other | NA | 6 (1244) | NA | 0.01-13[3] |

*(continued)*

**Table 4.** (continued)

| Product Category | 1992 Uses[1] | 2009 Uses[10] | 1984 Concentrations[1] (%) | 2008 Concentrations[10] (%) |
|---|---|---|---|---|
| Suntan products | | | | |
| Suntan gels, creams, and liquids | NA | – (156) | NA | 0.03 |
| Indoor tanning preparations | NA | 1 (200) | NA | – |
| Other | NA | 1 (62) | NA | – |
| Total uses/ranges for PVM/MA copolymer | NA | 80 | NA | 0.0006-13 |
| Calcium/sodium PVM/MA copolymer | | | | |
| Personal hygiene products | | | | |
| Other | NA | 1 (514) | NA | – |
| Total uses/ranges for calcium/sodium PVM/MA copolymer | NA | 1 | NA | – |

detergents, paper, textiles, leather, latex, rust preventative, and foam stabilizer.[22]

Isopropyl ester of PVM/MA copolymer may have potential use in ophthalmic matrices for drug release in place of eye drops.[6,23] These matrices are put in contact with the conjunctiva for noncorneal drug absorption.

PVM/MA copolymer is included in the Code of Federal Regulations (CFR) at 21 CFR §175.105 and 21 CFR §175.125 for its approved use in indirect food contact applications as adhesives and pressure-sensitive adhesives.[24,25] It is also included in 21 CFR §872.3500 for its use in dental devices.[26] Calcium/sodium PVM/MA copolymer is included in 21 CFR §872.3490 for its use in dental devices (dental adhesives).[27] PVM/MA copolymer and its butyl ester are listed on the Food and Drug Administration (FDA) inactive database for uses in a dental paste and a topical solution at 30%, respectively.[28]

## Absorption, Distribution, Metabolism, and Excretion

No studies concerning the absorption, distribution, metabolism, or excretion of PVM/MA copolymer or its salts or esters were found in the published literature.

## Animal Toxicology

### *Acute Oral Toxicity*

Butyl and ethyl esters of PVM/MA copolymer. Five groups of 5 albino Sherman-Wistar rats, sex not specified, were used to determine the oral $LD_{50}$ of ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer.[29,30] 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).[31]

### *Short-Term Oral Toxicity*

Butyl ester of PVM/MA copolymer. A group of 6 female Holtzman rats was fed a diet containing 25% butyl ester of PVM/MA copolymer daily for 10 days.[32] A group of 6 female Holtzman rats were 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 Inhalation Toxicity*

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.[33] The rats were placed in inhalation chambers for 4 hours plus equilibration, if necessary, 5 days/week for 13 weeks, for a total of 65 exposures.

The mean chamber concentrations of solids based on 65 determinations as measured by gravimetric analysis over the entire study were $0.017 \pm 0.035$, $0.531 \pm 0.206$, $2.17 \pm 0.656$, and $6.59 \pm 1.522$ 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 approximately 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 approximately 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-hour 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 8 nontest rats/gender at study initiation and from 8 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, both males and females, when compared to control values. This did not appear to be dose related.

With the exception of 2 mid-dosage females, pharmacotoxic observations were similar for all test and control animals. The 2 mid-dosage animals had alopecia starting at week 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.[34] 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. The study was conducted in the same manner as for the ethyl ester of PVM/MA copolymer described above.

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.

At various times during the study, mean body weights of males of the mid-dosage group were significantly decreased compared to control values. At various times throughout the study, feed consumption was significantly decreased in males and females of the mid- and high-dosage groups or significantly increased in males of the high-dosage group and in 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 in males of the mid-dosage group and the lung-to-body-weight ratios were significantly decreased in females in all 3 dosage groups compared to control values. No significant microscopic findings were noted. 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.

## Chronic Toxicity

No chronic toxicity studies of PVM/MA copolymer, its salts, or esters were found.

## Ocular Irritation

Butyl and ethyl esters of PVM/MA copolymer. Two groups of albino rabbits, 6 per group, were used to determine the ocular irritation index of ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer.[35,36] Both ingredients were tested as a 5% weight/volume (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 hours after application of the test material and scored according to the Draize method. Neither ethyl ester of PVM/MA copolymer nor butyl ester of PVM/MA copolymer was an ocular irritant.

Isopropyl ester of PVM/MA copolymer. Finne et al investigated the use of ophthalmic matrices for drug release.[23] The matrices consisted of isopropyl ester of PVM/MA copolymer (50% isopropanol solution of the polymer), 0.12 mmol timolol maleate, and 2.11 mmol of sodium acetate and were 5 mm in diameter and 0.59 $\pm$ 0.02 mm thick. The matrices were applied to the lower conjunctival sac of pigmented rabbits (both sexes; 1.9-2.8 kg; number not reported). The inserts did not cause any observable irritation to the rabbit eye.

### Dermal Irritation

Ethyl and butyl esters of PVM/MA copolymer. Two groups of albino rabbits, 6 per group, were used to determine the primary dermal irritation of ethyl ester of PVM/MA copolymer and butyl ester of PVM/MA copolymer.[37,38] 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. Ethyl and butyl esters of PVM/MA copolymer were not primary irritants as defined by the Federal Hazardous Substances Labeling Act.

## Reproductive and Developmental Effects

No studies concerning the reproductive and development effect of PVM/MA copolymer, its salts or esters were found in the existing published literature.

### Genotoxicity

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.[39] Dimethylsulfoxide (DMSO) was used as the solvent. The test material was soluble in the culture medium at concentrations of $\leqq$125 nL/mL; precipitate formed at concentrations 2250 nL/mL. In a preliminary cytotoxicity assay, 24-hour 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 to 2000 nL/mL with metabolic activation and at concentrations of 500 to 2000 nL/mL without metabolic activation. Three trials were performed with and 1 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 2000 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 2000 nL/mL dosage. For the concentration range of 15.6 to 2000 nL/mL, weak-to-moderate toxicity was observed.

The second trial used duplicate treatments of 2000 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 2000 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.[40] 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 to 1.0 mg/mL resulted in survival rates of 71% to 85%. A second preliminary cytotoxicity test used concentrations of 0.313 to 10.0 mg/mL. The survival rates were 46.5% to 90.5% for the concentrations of 0.313 to 2.5 mg/mL; no survivors were observed at 5.0 or 10.0 mg/mL.

The transformation assay used concentrations of 0.313 to 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.[41] Dimethylsulfoxide was used as the solvent. Butyl ester of PVM/MA copolymer was assayed at concentrations of 9.77 to 5000 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 to 5000 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 2500 and 5000 μg/mL and a very low number of survivors at concentrations of 625 and 1250 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.

## Carcinogenicity

No carcinogenicity studies of PVM/MA copolymer, its salts or esters were found in the existing published literature.

## Clinical Assessment of Safety

### *Irritation/Sensitization*

Ethyl and butyl esters of PVM/MA copolymer. Ethyl ester and butyl ester of PVM/MA copolymer were applied to participants simultaneously to evaluate the human irritation and sensitization potentials of the test articles.[42] A repeated insult patch test (RIPT) was performed using the Draize-Shelanski method. 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 to 15 minutes. Of the initial 170 participants, 150 completed the study.

Patches were applied to the scapular area of the back 3 times a week for 3 weeks for a total of 9 induction applications. The sites were evaluated for irritation 24 hours 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 for 24 hours. Both sites were graded upon patch removal and 48 and 72 hours 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 neither 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.[43] 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 minutes. Of the 35 participants 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 participants, 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 (nonirradiated) site. The irradiated sites were exposed to ultraviolet A (UVA) radiation for 15 minutes 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- to 13-day nontreatment period, a challenge patch was applied to an untreated site adjacent to the original site. After 24 hours, the patches were removed and the test sites were graded for irritation. The challenge site was then irradiated and examined 24 and 48 hours after irradiation.

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

### *Oral Health*

Numerous clinical studies on the efficacy of dentifrices containing PVM/MA copolymer for several dental health parameters were discovered in the published literature. No adverse effects from exposure to PVM/MA copolymer were reported in any of these studies. Table 5 contains a brief overview of these studies.

## Summary

PVM/MA copolymer is the polymer of vinyl methyl ether and either maleic anhydride or maleic acid. Butyl ester of PVM/MA copolymer, ethyl ester of PVM/MA copolymer, and isopropyl ester of PVM/MA copolymer are polymers consisting of the partial butyl ester, ethyl ester, or isopropyl ester, respectively, of the polycarboxylic resin formed from vinyl methyl ether and maleic anhydride. These esters 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.The salts of these polymers are formed by adding the salt bases to the dicarboxylic form of the PVM/MA copolymer or the esters of PVM/MA copolymer.

The butyl and ethyl esters are supplied as clear viscous ethanol solutions with concentrations of 50% ± 2% and are soluble in a variety of solvents. 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. PVM/MA copolymer and its salts and esters mainly function as film formers and hair fixatives in cosmetics. In 2007/2008, PVM/MA copolymer, butyl ester of PVM/MA copolymer, ethyl ester of PVM/MA copolymer, and calcium/sodium PVM/MA copolymer were used in 43, 36, 43, and 1 cosmetic formulations, respectively.

No uses or concentrations were reported for the remaining salts and esters of PVM/MA copolymer discussed in this report.

**Table 5.** Summary of Clinical Studies of Dentifrices Containing PVM/MA Copolymer.

| Test Dentifrice/Dentifrices Active Ingredients | Control Dentifrice/Dentifrices Active Ingredients | Methods | Results | Reference |
|---|---|---|---|---|
| 1.5% PVM/MA copolymer, 1.3% pyrophosphate, and 0.243% sodium fluoride/silica base in one dentifrice; 2% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride/ silica base in another dentifrice; and 0.3% triclosan, 0.75% zinc citrate, and 1.14% sodium monofluorophosphate in a third. | 0.243% sodium fluoride in silica base | Study of the anticalculus efficacy of 3 dentifrices in 143 participants with an 8-week pretest phase and 12-week test phase. | No adverse effects on the oral soft and hard tissues. Statistically significant reduction in supragingival calculus formation observed in all 3 test dentifrices when compared to control. No statistically significant difference in the efficacy was observed among the 3 dentifrices. | [45] |
| 2% PVM/MA copolymer, 0.3% triclosan, and 0.331% sodium fluoride/silica base | 0.331% sodium fluoride/silica base | 3-year study of the anticaries efficacy of a dentifrice in 1296 participants. | No adverse effects on oral hard or soft tissues. Anticaries efficacy of test dentifrice was "at least as good as" the control dentifrice. | [46] |
| PVM/MA copolymer (concentration not reported), tetrasodium pyrophosphate, sodium tripolyphosphate, and 0.243% sodium fluoride/silica base | PVM/MA copolymer, tetrasodium pyrophosphate, and 0.243% sodium fluoride/ silica base | 12-week study of the anticalculus efficacy of a new tartar control dentifrice in 73 participants. | No adverse effects on oral hard or soft tissues. Test dentifrice was more efficacious in controlling the development of supragingival calculus formation than control. | [47] |
| PVM/MA Copolymer (concentration not reported), tetrasodium pyrophosphate, sodium tripolyphosphate, and 0.243% sodium fluoride/silica base | 0.243% sodium fluoride/silica base | 6-week study of tooth whitening efficacy of a calculus-inhibiting dentifrice in 79 participants. | No side effects on oral hard or soft tissues were observed. Test dentifrice group exhibited statistically significant reductions of over 40% with extrinsic tooth stain area and intensity relative to control. | [48] |
| PVM/MA Copolymer, triclosan, zinc, and pyrophosphate (concentrations not reported) | Dentifrices containing triclosan + PVM/MA Copolymer; triclosan + zinc; and one that did not contain any of the test active ingredients | 84 day, 4-phase study of the effect of 3 dentifrices on supragingival plaque and gingivitis in 25 participants. | No adverse effects reported. Test dentifrice was able to reduce baseline plaque, gingivitis, and bleeding index scores when compared to controls. | [49] |
| 2% PVM/MA copolymer, 0.3% triclosan, 0.243% sodium fluoride/silica base | 0.243% sodium fluoride/silica base | 6-month study of the effect of a liquid dentifrice on supragingival plaque and gingivitis in 119 participants. | No adverse effects on oral hard or soft tissues. Test dentifrice significantly reduced plaque and gingivitis when compared to control. | [50] |
| 2% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride/silica base with 10% of silica as high cleaning grade | 0.243% sodium fluoride/silica base | 8-week study of supragingival anticalculus efficacy of an anticalculus dentifrice in 63 participants. | No adverse effects on oral hard or soft tissues. Test dentifrice was effective in the control of the formation of supragingival calculus. | [51] |
| 3% PVM/MA copolymer, 0.2% triclosan, and 0.243% sodium fluoride/high cleansing base | One control contained 7.0% sodium hexametaphosphate and 0.243% sodium fluoride/ silica base, the other contained 0.243% sodium fluoride/silica base. | 6-week study of tooth-whitening efficacy of a tooth-whitening dentifrice in 123 participants. | No side effects on oral hard or soft tissues. Test dentifrice had statistically significant reductions in extrinsic tooth stain area and intensity relative to the control dentifrices. | [52] |

*(continued)*

**Table 5.** (continued)

| Test Dentifrice/Dentifrices Active Ingredients | Control Dentifrice/Dentifrices Active Ingredients | Methods | Results | Reference |
|---|---|---|---|---|
| 2% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride | 0.243% sodium fluoride | 3-week study of the effectiveness of a dentifrice on the management of oral malodor in 81 participants. | Test dentifrice was an effective control of oral malodor for up to 12 hours. | [53] |
| 2% PVM/MA copolymer, 0.24% sodium monofluorophosphate, and 0.3% triclosan | 0.76% sodium monofluorophosphate and 0.1% sodium fluoride | 10-week study of the effect of test dentifrice on plaque and gingival bleeding in 34 female, nonsmoking participants. | One participant developed a benign migratory glossitis on the tongue. No other adverse effects were observed in the remaining participants. Odds ratio of bleeding on probing was 30% less in test dentifrice compared to control. No effects on plaque levels and calculus were observed. | [54] |
| 2.0% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride in 17% dual silica base | 2.0% PVM/MA Copolymer, 0.3% triclosan, 0.243% sodium fluoride in 10% high-cleaning silica base (positive control) and 0.243% sodium fluoride in regular silica base (negative control) | Two single-blind, 3-treatment, crossover studies to evaluate antiplaque efficacy of the test dentifrice in 17 and 16 participants, respectively, over a 24-hour period. | No adverse effects reported or observed during any part of the study. The test dentifrice was comparable to the positive control in controlling dental plaque and was significantly better at controlling dental plaque over the negative control. | [55] |
| 2.0% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride in 17% dual silica base | 0.243% sodium fluoride in silica base | Two 6-week double-blind studies of the extrinsic stain prevention and stain removal efficacy of a new dentifrice in 114 and 119 participants, respectively. | No adverse effects on the oral soft and hard tissues. Test dentifrice exhibited significantly lower levels of extrinsic tooth stain area and intensity when compared to control. | [56] |
| 2.0% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride in 17% dual silica base | 0.243% sodium fluoride in silica base | 6-month double-blind study to assess the efficacy of test dentifrice to control established supragingival plaque and gingivitis in 94 participants. | No adverse effects on the oral soft and hard tissues. Test dentifrice had significantly lower whole-mouth plaque and gingival index scores, significant reductions in plaque and gingival index scores proximally, and significant reductions in plaque and gingival severity index scores when compared to control. | [57] |
| 2.0% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride in 17% dual silica base | 0.243% sodium fluoride in silica base | Single-evening double-blind study to assess the efficacy of test dentifrice to control overnight oral malodor and plaque microflora in 81 participants. | No adverse effects on the oral soft and hard tissues. A single-evening use of test dentifrice provided statistically significant lower levels of oral malodor and plaque microflora when compared to control. | [58] |
| 2.0% PVM/MA copolymer, 0.3% triclosan, and 0.243% sodium fluoride in 17% dual silica base | 0.243% sodium fluoride in silica base | 12-week double-blind study to assess the efficacy of test dentifrice to reduce supragingival calculus formation in 77 participants. | No adverse effects on the oral soft and hard tissues. Test dentifrice had significantly greater control of supragingival calculus formation when compared to control. | [59] |

The mean particle size for 2 formulations ranges from 36 to 42 μm, which is greater than the size that is considered respirable.

No studies concerning the absorption, distribution, metabolism, elimination, or other general biology of PVM/MA copolymer or its salts or esters were found in the existing published literature.

Ethyl ester and butyl ester of PVM/MA copolymer were relatively harmless to rats according to the terminology of Hodge and Sterner, with both compounds having an oral $LD_{50}$ for rats of >25.6 g/kg.[44] 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 participants. Ethyl ester of PVM/MA copolymer did not produce a photoallergenic or contact allergenic response in humans. PVM/MA copolymer did not produce any adverse effects in clinical studies of the ingredient in dentifrices.

## Discussion

While very few toxicity studies were identified specifically in the published literature for the additional salts and esters that were added to this safety assessment, there is no reason to expect the parent copolymer or its salts and esters to differ in toxicity from butyl ester of PVM/MA copolymer and ethyl ester PVM/MA copolymer. The salts and esters of the expanded group of PVM/MA copolymer ingredients are expected to have similar toxicological profiles as the butyl and ethyl esters. In solution, the salts are expected to dissociate in any product formulation independent of whether the salt is calcium, sodium, or potassium. The esters likely will break down into their component parts, none of which present any safety issues. The PVM/MA copolymer-derived esters that have been added to this safety assessment, that is isopropyl ester of PVM/MA copolymer, do not raise any significant toxicity concerns. Accordingly, the available data for butyl ester of PVM/MA copolymer and ethyl ester of PVM/MA copolymer are considered supportive of the safety of the expanded group of derivatives as used in cosmetics. Therefore, the Expert Panel determined that the toxicity data on butyl ester of PVM/MA copolymer and ethyl ester of PVM/MA copolymer could be extrapolated to include calcium/sodium PVM/MA copolymer, potassium ethyl ester of PVM/MA copolymer, sodium ethyl ester of PVM/MA copolymer, potassium butyl ester of PVM/MA copolymer, sodium butyl ester of PVM/MA copolymer, isopropyl ester of PVM/MA copolymer, and PVM/MA copolymer.

The Expert Panel recognizes that use concentration data are not available for all ingredients in this group and that some ingredients in this group are not in current use. The Panel considers that the use concentrations for the ingredients that are in use are not likely to be different from the use concentration for butyl ester of PVM/MA copolymer and ethyl ester of PVM/MA copolymer.

The Expert Panel noted the absence of reproductive and developmental toxicity and carcinogenicity data. Because these ingredients are very large molecular weight structures, the Panel considered that they would not be easily absorbed into the skin. While hydrolysis products may form as a result of any oral intake, the resulting compounds separately are considered safe. In addition, there are no structural alerts for toxic activity of these compounds.

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 (ie, ≦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. In the absence of inhalation toxicity data for the remaining PVM/MA copolymer ingredients, the Panel determined that PVM/MA copolymer and its salts and esters can be used safely in hair sprays, because the particle sizes of the ingredients are not respirable. The Panel reasoned that the particle size of aerosol hair sprays (−38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes (≦10 μm).

## Amended Conclusion

The CIR Expert Panel concludes that PVM/MA copolymer, butyl ester of PVM/MA copolymer, calcium/sodium PVM/MA copolymer, ethyl ester of PVM/MA copolymer, isopropyl ester of PVM/MA copolymer, potassium butyl ester of PVM/MA copolymer, potassium ethyl ester of PVM/MA copolymer, sodium butyl ester of PVM/MA copolymer, and sodium ethyl ester of PVM/MA copolymer are safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment (note 1).

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### Author's Note

The 2009 Cosmetic Ingredient Review Expert Panel members are Chairman, Wilma F. Bergfeld, MD, FACP; Donald V. Belsito, MD; Ronald A. Hill, PhD; Curtis D. Klaassen, PhD; Daniel C. Liebler, PhD; James G. Marks Jr, MD, Ronald C. Shank, PhD; Thomas J. Slaga, PhD; and Paul W. Snyder, DVM, PhD. The CIR Director

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## Notes

1. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.
2. Unpublished data are available for review: Director, Cosmetic Ingredient Review, 1101 17th St, NW, Suite 412, Washington, DC 20036, USA.

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