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7

Final Report on the Safety Assessment of Polyvinylpyrrolidone/ Vinyl Acetate Copolymer

Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers. The ingredient is used primarily in hair care products and secondly in skin and nail products.

Acute oral toxicity studies on mice and rats showed low to no toxicity. Chronic oral and inhalation studies produced no effects. The acute ocular irritation of PVP/VA Copolymer at concentrations ranging from 25% to 50% in alcohol produced no reaction to severe irritation. Acute skin irritation studies of 50% PVP/VA Copolymer in alcohol on abraded and intact skin produced mild skin irritation. PVP/VA Copolymer was not a sensitizer to guinea pigs after intracutaneous injections. Formulations containing 1.75%, 4.0%, and 5.0% PVP/VA Copolymer produced no irritation in 24-hour clinical patch tests nor any evidence of sensitization in a repeated insult patch test at a concentration of 5.0%.

On the basis of the available information, it is concluded that Polyvinylpyrrolidone/Vinyl Acetate Copolymer is safe as a cosmetic ingredient under present conditions of concentration and use.

CHEMICAL AND PHYSICAL PROPERTIES

Structure/Composition

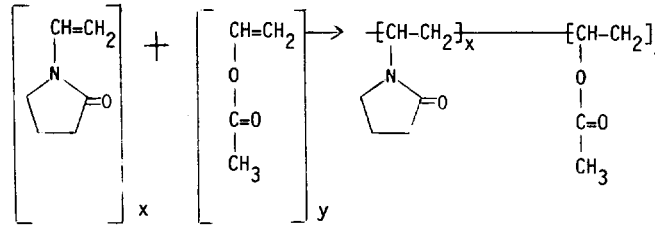
Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers.[1] The copolymers vary in their ratio of VP to VA and range from 70:30 to 30:70 VP to VA.[2]

Production

PVP/VA Copolymer can be prepared by free radical polymerization in ethyl alcohol: some monomer(s) is added to the ethyl alcohol solvent, a free-radical initiator (an azo or peroxide compound) is added to catalyze the formation of the additional polymer, and the remaining monomer(s) is added at a rate to control

the polymerization and to obtain the desired end product.[3] Emulsion polymerization using various catalysts is an additional method of preparation.[4] Another, but commercially unimportant, production method combines solutions of vinyl acetate and vinyl pyrrolidone varying between 0.1 and 0.9 *M*. These solutions are irradiated with a Cobalt-60 source at dose rates of 1,965 and 35,600 rads/min., and copolymerization occurs at a constant temperature of 5°C.[5]

The equation for the production of PVP/VA Copolymer is as follows:[2,3]



vinylpyrrolidone (VP) vinyl acetate (VA) PVP/VA Copolymer

CAS number: 25086-89-9

Properties

PVP/VA Copolymer has properties similar to those of the PVP monomer. It is a white, free-flowing amorphous powder, dispersible in water and soluble in organic solvents.[3,6,7] PVP/VA Copolymers are supplied in 100% concentration as a powder and diluted to 50 ± 2% in either 95% ethanol or isopropanol. The specific gravity at 25°C is 1.27 ± 0.01 for the powder and 0.955 ± 0.01 for the alcohol solutions. These copolymers are stable for at least one year under normal conditions of storage but readily absorb atmospheric moisture. Films of the copolymers are permeable to air. Photospectroanalysis revealed that PVP/VA Copolymers do not absorb energy in the UVA, UVB, or visible light spectrum.[2,3,7-9] See Table 1.

Analytical Methods

Trace amounts of PVP/VA Copolymers can be determined with colorimetric-chromatographic methods. Samples are treated with various dyes that complex with the PVP and are then passed through a chromatographic column; PVP is absorbed at the top as a colored band. This method can determine as little as 0.1 ppm copolymer.[10]

The impurities in PVP/VA Copolymer may be determined with the following methods: Kjeldahl or Dumas method for nitrogen; USP method for arsenic; Fischer method for moisture content of solid copolymers; Cenco moisture balance method for moisture content in solutions; Standard Iodometric titration for determination of residual monomers, and spectrographic emission for heavy metal determination.[3,4]

TABLE 1. Chemical and Physical Properties of PVP/VA Copolymer.[a]

Properties	*Values*
Physical form	White powder; clear liquid in solution
Vehicles	Ethanol; isopropanol
Residual vinyl pyrrolidone	0.5% max
Residual vinyl acetate	1.0% max
Specific gravity	1.27 ± 0.01 (solid) 0.955 ± 0.01 (alcohol solution)
Soluble in:	Alcohols Ether alcohols Ketone alcohols Butyrolactone Triethanolamine Aromatic hydrocarbons Esters Water (partially)
Odor	Slight and characteristic

[a]Data from Ref. 7.

Impurities

The impurities in PVP/VA Copolymer are the residual, uncombined monomers, vinyl acetate (1.0% max), vinyl pyrrolidone (0.5% max), and moisture (0.5% max).[2,3,7]

USE

Noncosmetic Uses

PVP/VA Copolymer is used in tablet coating, spray bandages, protective masks, spray or rub-on gloves, plant leaf sprays, shoe polishes, and film production; it is also used as a dye medium in adhesive sticks and in the synthesis of peptides.[3,7,10-13]

Cosmetic Uses

Industry's voluntary submission of cosmetic product formulation data to the Food and Drug Administration (FDA) lists PVP/VA Copolymer in 114 formulations.[14] The 1979 FDA list includes PVP/VA Copolymer in 133 formulations.[15]

The cosmetic product formulation computer printout which is made available by the FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[16] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not

necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to tenfold error in the assumed ingredient concentration.

Purpose in Cosmetics

PVP/VA Copolymer is the hair-holding ingredient in hair sprays, hairsets and conditioners, hair dressings, and wave lotions.[4,6]

PVP/VA Copolymer is used in eye and facial makeup preparations in concentrations of >0.1% to 5%. In manicuring and skin care preparations, it is used from >1% to 5%, and in hair care preparations, from >0.1% to 50%.[14] See Table 2.

PVP/VA Copolymer may be applied several times a day in facial makeup or a few times yearly as in permanent wave products. The material may stay in contact with the body from minutes, as in shampoos, to several days, as in hair sprays and grooming aids.[14]

PVP/VA Copolymer may come in contact with the eyes, the skin of the hands and face, the scalp, the hair, and the nails. Since it can be dispersed in aerosols, PVP/VA Copolymer may also come in contact with the respiratory mucosa.

Potential Interactions with Other Ingredients

PVP/VA Copolymers are compatible with water, common propellants, and with many plasticizers and polymers.[7] No information was available on interactions of the copolymer with other cosmetic ingredients.

BIOLOGICAL PROPERTIES

General Studies

Storage and Excretion

PVP/VA Copolymer storage in the body was studied in 30 female Wistar rats by injecting it under the skin of the back. Up to seven daily 2 ml doses of solution containing 10 g of solid copolymer in 15 ml of physiological saline were given. Animals were sacrificed between 1 and 365 days later, and tissues were examined. Most of the copolymer was found in the spleen, and repeated injections caused up to an 80% increase in splenic weight. Two to three days after treatment, large reticular cells were found in the spleen; later, similar but vacuolated cells were found. There were macrophages in the follicular germinal center. After one to six months, copolymer-containing macrophages decreased in size and number and often showed an iron-positive reaction. Large vacuolated cells were also present in the portal regions of the liver lobes. The podocytes of the kidney

TABLE 2. Product Formulation Data.[a]

Product category[b]	*Total no. containing ingredient*	*No. product formulations within each concentration range (%)*[b]							
		Unreported concentration	*>50*	*>25–50*	*>10–25*	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Mascara	2	–	–	–	–	–	2	–	–
Hair conditioners	17	–	–	1	1	7	8	–	–
Hair sprays (aerosol fixatives)	27	–	–	–	–	2	19	6	–
Permanent waves	1	–	–	–	–	–	–	1	–
Hair shampoos (noncoloring)	2	–	–	1	–	–	–	1	–
Tonics, dressings, and other hair grooming aids	6	–	–	–	1	1	2	2	–
Wave sets	50	–	2	4	2	12	16	14	–
Other hair preparations (noncoloring)	4	–	–	–	3	1	–	–	–
Hair bleaches	1	–	–	–	–	–	1	–	–
Makeup fixatives	1	–	–	–	–	–	–	1	–
Other makeup preparations (not eye)	1	–	–	–	–	–	–	1	–
Cuticle softeners	1	–	–	–	–	–	1	–	–
Skin care preparations	1	–	–	–	–	–	1	–	–
1976 TOTALS	114	0	2	6	7	23	50	26	0
1979 TOTALS[c]	133	48	1	5	2	19	38	19	1

[a]Data from Ref. 14.
[b]Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).
[c]Data from Ref. 15.

glomeruli contained PVP/VA, and some kidney specimens showed large aggregates of foam cells. Some PVP/VA seemed to be stored in epithelial cells and lymphatics of the testes. There were no inflammatory changes in any of the tissues. Some reticular cells in bone marrow and lymph nodes showed PVP/VA Copolymer storage, and large macrophages were found in the interstitial tissue of the lungs. After 12 months, there was no evidence of tumors or systemic disease related to administration of the compound. The author reported that one-half hour after a single subcutaneous 2 ml dose was administered, a color reaction was induced in the urine by a KJ_3-solution; this indicated that PVP/VA was in the urine. Maximum excretion occurred one and one-half hours after injection.[17]

Animal Toxicology

Acute

Oral

The acute oral toxicity of PVP/VA Copolymer in aqueous alcohol solutions and in formulations has been studied. The results are tabulated in Table 3 and summarized as follows:

Five lots of 50% PVP/VA Copolymer in alcohol were tested in albino rats. One sample was tested at the 50% concentration and four at 25% (w/v) aqueous suspensions (final concentrations were 12.5%). In these four tests on the 12.5% copolymer, 5 g/kg of the material were administered by gastric intubation into ten young, fasted albino rats per solution. During the following 14 days, the animals showed decreased activity and ataxia for an unspecified length of time, but none died. These results show that the test solutions are slightly toxic according to the classification of Hodge and Sterner.[18-22] A dose of 5 ml/kg (4.78 g/kg) of the 50% solution administered orally by stomach tube caused piloerection in some of the six rats. None of the animals died, and necropsy examinations showed no pathology. This solution is also practically nontoxic.[23] See Table 3.

Five product formulations containing actual concentrations of 0.25% (setting lotion), 0.5% (setting lotion), 1.75% (mascara), 4.0% (setting lotion), and 24% (setting lotion) PVP/VA Copolymer in doses of 5.0–15 g/kg were administered orally by stomach tube to groups of Sherman–Wistar and Sprague–Dawley albino rats. Two out of five animals died after administration of the hair setting formulation containing 4.0% PVP/VA Copolymer in a 15 g/kg dose; none of the surviving rats showed signs of toxicity during the 7- to 13-day observations periods. None of the other formulations produced toxicity.[24-28] See Table 3.

Ocular

Formulations and solutions containing PVP/VA Copolymer were studied for acute ocular toxicity. These studies are detailed below and summarized in Table 4.

A Draize eye irritation test of a 50% alcohol solution of PVP/VA Copolymer was conducted on six rabbits. This same solution was then diluted in petrolatum to 75% and 50% of its original concentration (actual concentration of copolymer was 37.5% and 25%) and tested on rabbits. A 0.1 ml volume of each solution was instilled into one eye of each of six animals with no rinse. Observations, made for

TABLE 3. Acute Oral Toxicity PVP/VA Copolymer.

Ingredient conc. (%)	Dose/kg	Tested in	Species and number of animals	LD50 (g/kg)		No. dead	Days of observation	Comments	Ref.
				Formulation or solution	Ingredient (as PVP/VA)				
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	19
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	20
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	21
12.5	5 g	25% aqueous solution of 50% alcohol solution	Albino rats–10	>5 g	>0.63	0	14	Decreased activity; ataxia for unspecified time.	22
50	5 ml 4.78 g)	50% alcohol solution	Albino rats–6	>5 ml	>2.5 ml	0	–	Piloerection; necropsy not remarkable	23
0.25	5 g	formulation –setting lotion	Sherman-Wistar albino rats–10	–	–	0	14	No signs of toxicity.	24
0.5	5 g	formulation –setting lotion	Sherman-Wistar albino rats–10	–	–	0	14	No signs of toxicity.	25
1.75	15 g	formulation –mascara	Albino rats–5	–	–	0	7	No signs of toxicity.	26
4.0	15 g	formulation –setting lotion	Albino rats–5	–	–	2	7	2 deaths. All other animals appeared normal with no signs of toxicity.	27
24	15 g	formulation –setting lotion	Sprague-Dawley rats 5–10	–	–	–	–	LD50 not reached.	28

TABLE 4. Eye Irritation PVP/VA Copolymer.

Ingredient conc. (%)	*Dose (ml)*	*Tested in*	*Number of albino rabbits*	*Days of observation*	*Greatest irritation score/110 (max)*	*Comments*	*Ref.*
25	0.1	solution of alcohol and petrolatum	6	7	14(max)	Minimal irritation at day 1; effect disappeared by day 7.	23
37.5	0.1	solution of alcohol and petrolatum	6	7	23(max)	Mildly irritating on day 1; effect disappeared by day 7.	23
50	0.1	solution of alcohol	6	7	30(max)	Moderate irritation on day 1; Minimal irritation by day 7.	23
50	0.1	alcohol solution	9	7	NW[a] 43(max) W[b] 33(max)	Moderately irritating with and without wash. Some irritation lasted through 7 days.	29
50	0.1	alcohol solution	9	7	NW 43(max) W 26(max)	Moderately irritating with and without wash. Some irritation lasted through 7 days.	30
50	0.1	alcohol solution	9	7	NW 63(max)	Severely irritating. Some lasted through day 7.	31
					W 29(max)	Moderately irritating. Some effects lasted through day 7.	
50	0.1	alcohol solution	9	7	NW 16(max)	Corneal and conjunctival involvement.	
					W 10(max) (2 sec)	No reaction to conjunctival involvement. Clear by day 3.	32
					W 10(max) (4 sec)	No reaction to conjunctival involvement. Clear by day 3.	
0.25	0.1	formulation setting lotion	6	7	0	No irritation.	33
0.5	0.1	formulation setting lotion	6	7	0	No irritation.	34
1.75	0.1	formulation mascara	6	7	1	Practically nonirritating.	35
4.0	0.1	formulation setting lotion	6	7	W 3 NW 26	Minimally irritating. Moderately irritating.	27
2.4	–	formulation setting lotion	3	2	–	Conjunctival irritation which cleared by day 2.	28
24	–	formulation setting lotion	3	2	–	Conjunctival irritation which cleared by day 2.	28

[a]No wash.
[b]Wash.

seven days, were scored according to the Draize method (maximum irritation score = 110). The 25% solution of PVP/VA in petrolatum was minimally irritating on the first observation day, and irritation disappeared by day 7. The 37.5% solution was mildly irritating on day 1 and practically nonirritating on day 7. The 50% solution in alcohol produced moderate irritation on day 1 and minimal irritation on day 7.[23]

A 50% solution of PVP/VA Copolymer in alcohol was tested for ocular irritation by the Draize method in three different studies. One eye of each of nine rabbits was instilled with 0.1 ml of solution; the other eye was used as control. In three out of nine animals, the eye was washed four seconds after instillation, and observations were made for seven days. Moderate irritation occurred in unwashed eyes instilled with two of the 50% test solutions, and severe irritation was produced by the third solution when not washed out. Eyes irrigated after four seconds were moderately irritated. In most animals, irritation persisted throughout the seven days.[29-31]

Another test of 50% PVP/VA Copolymer in alcohol was performed on nine rabbits. One eye of each animal was instilled with 0.1 ml of solution. The eyes of three were washed two seconds after instillation, and a second group of three underwent a washout after four seconds. Observations were made for seven days. The three eyes that remained unwashed had some conjunctivitis for a maximum of six days. Eyes washed after two and four seconds showed some conjunctivitis for three days.[32]

Five product formulations containing PVP/VA Copolymer were tested for acute ocular irritation in rabbits. One setting lotion product containing 0.25% and another containing 0.5% PVP/VA were tested according to 16 CFR 1500.42. A 0.1 g sample of each solution was instilled into the right eye of each of six albino rabbits without rinse. No irritation occurred from either product at 1, 24, 48, and 72 hours and five and seven days after instillation.[33,34] One mascara formulation with 1.75% PVP/VA Copolymer and a setting lotion with 4.0% of the copolymer were tested according to a modified Draize method on six albino rabbits. A 0.1 ml volume of each full strength formulation was instilled into one eye of each rabbit per formulation. The eyes receiving the 1.75% concentration were not washed, and those of three rabbits instilled with the 4.0% concentration were rinsed four seconds after instillation. The 1.75% formulation was practically nonirritating.[35] The setting lotion containing 4.0% PVP/VA Copolymer, when washed, was minimally irritating on the first observation day, and the irritation cleared thereafter; the unwashed eyes had mild to moderate irritation on the first three observation days. The product was practically nonirritating on the fourth and seventh day.[27] A hair setting formulation containing 24% PVP/VA Copolymer was tested at full strength and at 10% concentration (2.4% of the Copolymer), on three New Zealand rabbits per concentration. One eye of each rabbit was instilled with 0.1 ml of solution. Both concentrations caused conjunctival irritation; the full strength product caused more severe irritation. There was no irritation by the second observation day.[28]

Skin Irritation

PVP/VA Copolymer, in alcohol solution and in formulation, was tested for

acute skin irritation. In general, the tests produced minimal to no irritation; the studies are detailed below and summarized in Table 5.

Four 50% solutions of PVP/VA Copolymer in alcohol and one solid 100% concentration were each applied to the backs of six albino rabbits. In one test, three repeated applications of the 50% solution caused definite erythema in five of six animals.[23] The remaining three 50% solutions were each applied in 0.5 ml (approximately 0.5 g) volumes under occlusive patching to the clipped abraded and intact skin of the rabbits. The patches were removed after 24 hours and the sites graded according to the Draize method, 24 and 72 hours after application. The solutions were mildly to moderately irritating.[36-38]

A primary dermal irritation test of solid, 100% PVP/VA Copolymer on six albino rabbits produced no irritation.[39]

Five formulations containing varying concentrations of PVP/VA Copolymer were tested for primary skin irritation on rabbits. Of these, one hair setting lotion containing 0.25% PVP/VA Copolymer and another setting lotion having 0.50% copolymer were each applied in 0.5 g amounts under occlusive dressing to the clipped intact and abraded skin of six albino rabbits and allowed to remain for 24 hours. The sites were scored 24 and 72 hours after application. According to the Draize method, neither product produced irritation.[40,41]

A hair conditioner formulation containing 1.5% PVP/VA Copolymer was tested on the abraded and intact skin of three rabbits. The 0.5 ml volume of test

TABLE 5. PVP/VA Copolymer Skin Irritation.

Ingredient conc. (%)	*Dose*	*Tested in*	*Number of albino rabbits*	*Hours of observation time*	*Irritation score/8.0 (max)*	*Comments*	*Ref.*
50	–	alcohol solution	6	72	–	5 of 6 animals showed definite erythema.	23
50	0.5 g	alcohol solution	6	72	1.71	Mildly irritating	36
50	0.5 g	alcohol solution	6	72	2.5	Mildly irritating	37
50	0.5 g	alcohol solution	6	72	2.54	Mildly irritating	38
100	0.5 g	solid	6	72	0.0	No irritation	39
0.25	0.5 g	formulation setting lotion	6	72	0.0	No irritation	40
0.50	0.5 g	formulation setting lotion	6	72	0.0	No irritation	41
1.50	0.5 ml	formulation hair conditioner	3	72	0.0	No irritation	42
1.75	0.5 ml	formulation mascara	9	48	0.61	Potential for minimal irritation	43
4.0	0.5 ml	formulation setting lotion	9	48	0.0	No irritation	44

material was applied under occlusion, and readings were taken 24 and 72 hours after application. The product caused no irritation.[42]

A mascara and a hair setting formulation containing 1.75% and 4.0% PVP/VA Copolymer, respectively, were tested by a modified Draize method. A 0.1 ml volume of each formulation was applied under occlusion to the shaved skin of nine albino rabbits for 24 hours. Sites were read 2 and 24 hours after patch removal. The mascara caused minimal irritation,[43] and the hair setting lotion caused no irritation.[44]

Sensitization Reaction

The skin sensitization potential of PVP/VA Copolymer in a product formulation was studied. A hair conditioner containing 1.5% PVP/VA Copolymer was diluted in physiological saline to make the actual copolymer concentration 0.015%; this was injected intradermally into eight guinea pigs. A 4 cm^2 area of skin was clipped, and injections were given every other day, the first at a dose of 0.05 ml and the nine subsequently at 0.2 ml each. A 0.05 ml injection was administered two weeks after the last injection, and the skin was inspected 24 hours after each injection. The material was nonsensitizing to the guinea pigs.[45]

Endotracheal Injection

The storage of PVP/VA Copolymer in the lungs and other body organs was studied in 20 female Wistar rats. The animals were given single or an unspecified number of repeated endotracheal applications of 0.5 ml of a solution containing 10 g polymer in 15 ml of physiological saline solution. Fifteen control animals received physiological saline in similar doses. The animals were sacrificed between 1 and 365 days later, and tissues were examined. There were no signs of pneumonia, bronchitis, or bronchiolitis one or two days after injection. All pulmonary alveoli were closely packed with macrophages. After six days there were numerous large macrophages in the pulmonary interstitial tissues and particularly in the peribronchial and perivascular lymphatics. Macrophages were found in the lymph nodes of the hilar and tracheal regions. Four to six months after the last injection, lungs still contained PVP/VA Copolymer, predominantly in the macrophages in the alveoli near the bronchi and vessels and in the fibrous septae. Animals sacrificed one year after administration did not show further accumulation of storage cells in the lung. No copolymer was found in the liver, kidneys, and bone marrow of animals that had been treated repeatedly, but some was found in solitary or grouped storage cells in the spleen. There was no acute inflammatory reaction, and control animals showed no abnormalities.[17]

Inhalation

In an acute inhalation study, Draize et al.[46] exposed five rabbits to 30-second spray releases of an aerosol product containing 1.72% PVP/VA Copolymer. The sprayings were released every half hour until the contents of the container were exhausted, but the investigators did not report the duration of the exposure. Each 30-second spray released approximately 30 g of material. The animals were inspected during exposure and during the next four days; they were then sacrificed for gross and histopathological examination. The tissues and behavior of the animals during and after inhalation were normal.

Subchronic

Dermal Toxicity

A hair product containing 1% PVP/VA Copolymer was tested in a six-week subchronic dermal toxicity study on 50 albino rats. Volumes of 2.0 ml/kg of the product were applied five days a week for six weeks for a total of 30 applications to the clipped skin of the animals. All rats survived, and their body weight, physical appearance, behavior, and gross and microscopic anatomy were normal. No systemic toxic effects could be attributed to the test material.[47]

Inhalation Toxicity

Rats and hamsters were exposed for 13 weeks to a spray containing 4.0% PVP/VA Copolymer. Each of three groups comprised of 12 rats and 12 hamsters per group inhaled the spray for four hours per day, five days per week for 13 weeks in doses of 5.4 mg/m^3 (calculated to be the equivalent of one hundred times the normal human use level of the product). No gross or microscopic changes occurred that could be attributed to the test material. Lungs and other tissues were similar in control and tested animals.[48]

Chronic

Oral

White mice and rats were given daily in their drinking water an aqueous 10.2 mg/l solution of PVP/VA Copolymer for one year. Each mouse ingested an average of 2–3 ml per day and 650 ml for the duration of the experiment, and each rat ingested 15–20 ml per 24 hours and 4140 ml for the year. There were no changes attributable to the copolymer in either mice or rats. Furthermore, there were no histological changes in the internal organs.[49]

Inhalation

Mokler et al.[50] conducted a chronic study of hair spray aerosols containing high and low concentrations of PVP/VA Copolymer. Thirty-six male and 36 female Syrian hamsters were exposed to the low concentration of 0.08 ± 0.08 mg/l PVP/VA in air, 4–32 minutes a day, once a week for up to two years. The high-level group consisted of 36 male and 36 female hamsters exposed to 0.35 ± 0.09 mg/l, 9–35 minutes a day, once a week for up to two years. A similar group of 36 males and 36 females was exposed to air as a control. All animals were repeatedly exposed by inhalation until they were sacrificed. Six males and six females from each group were sacrificed at three, six, and nine months. This assured that at least 12 animals (six male, six female) were available for study at each time period and that 36 animals were available for long-term (2-year) study. Necropsies were performed on all that were sacrificed or that died spontaneously. Survival time, body weight, and weight and appearance of lungs were similar in control and aerosol-exposed animals.

Draize et al.[46] exposed five rabbits to a spray formulation containing 1.72% PVP/VA Copolymer. During the 90-day test, the animals received one 30-second exposure each morning and afternoon and were left in the spray atmosphere for 15 minutes. The animals remained normal during the entire study; radiographs of the chest and upper body and hematological tests remained normal.

Special Studies

Mutagenicity

The residual monomers of PVP/VA Copolymer, vinyl acetate and vinyl pyrrolidone, found at 1.0% and 0.5%, respectively, have been tested for their mutagenic potential. *Salmonella typhimurium* strains TA100, TA98, TA1530, TA1535, and TA1537 were exposed to vinyl acetate. No mutagenic effects were detected when the organisms were exposed to the chemical with and without the addition of rat liver metabolic activation preparation.[51-55]

Vinyl pyrrolidone was tested for mutagenicity in three different assays. In the Mouse Lymphoma Assay, concentrations of up to 5.0 μl/ml vinyl pyrrolidone did not induce a significant change in mutant frequency at the TK locus in L5178Y cells in the presence or absence of rat liver S-9 microsomal activation.[56] In the Balb/3T3 in vitro transformation assay, vinyl pyrrolidone did not induce a significant increase in transformed foci over the applied concentration range of 0.1–0.5 μl/ml. This concentration range produced 83%–52.3% survival in the cytotoxicity test, and the material was considered to be mutagenically inactive.[57] In the primary rat hepatocyte unscheduled DNA synthesis (UDS) assay, vinyl pyrrolidone did not induce detectible UDS in primary rat hepatocytes over an applied concentration range of 0.284–9.09 μl/ml. This concentration range produced a cell survival rate of 84.5%–6.2% 24 hours after treatment; whereas, exposure to 18.2 μl/ml was completely lethal. The material was considered to be inactive in producing UDS in this assay.[58]

Polyvinyl pyrrolidone polymers including PVP/VA Copolymers have been deleted from the list of 39 priority chemicals selected for testing by the National Toxicology Program (NTP) in June 1980. According to NTP, adequate screening toxicity testing data have been reported in the literature.[59]

Carcinogenicity

No carcinogenicity studies have been reported on PVP/VA Copolymer. IARC has noted the subcutaneous tumorigenic activity of PVP in animals. Despite this fact, NTP has deleted it from its list of chemicals selected for testing.[59,60] Vinyl Acetate, a residual monomer impurity in PVP/VA Copolymer, was used as a comparative compound in a carcinogenicity assay of vinyl chloride. Ninety-six Sprague-Dawley rats were exposed four hours per day, five days per week, for 52 weeks to vapor concentrations of 8.8 g/m^3 (2500 ppm) vinyl acetate in air. No tumors occurred after 135 weeks; however, only 49 animals survived longer than 26 weeks.[55,60-64]

Clinical Assessment of Safety

The human clinical studies of PVP/VA Copolymer are summarized in Table 6.

Patch Testing

A dose of 0.1 ml of 5.0% solution of PVP/VA Copolymer in alcohol was applied in a single occlusive 24-hour patch to either the forearms or upper arms of 20 individuals without causing a reaction.[65]

A dose of 0.1 ml of mascara containing 1.75% PVP/VA Copolymer was applied in a single, full strength occlusive 24-hour patch to either the forearms or

TABLE 6. PVP/VA Copolymer Human Clinical Data.

Test							
Ingred. conc. (%)	*Dose/ml*	*Tested in*	*No. of subjects*	*No. of test days*	*Irritation max*	*Comments*	*Ref.*
24-Hour occlusive patch							
5.0	–	solution	20	1	0.0	No irritation	65
1.75	0.1	mascara formulation	18	1	0.0	No irritation	66
4.0	0.1	setting lotion formulation	20	1	0.0	No irritation	67
Repeated insult patch test							
50	–	solution	50	15	0.0	No reactions on abraded or intact skin	68
50	0.15	solution	150	34	–	No irritation or sensitization	69
50	0.15	solution	150	34	–	No irritation or sensitization	
5	0.4	hair spray formulation	51	24	0.0	No irritation	70

the upper arms of 18 subjects. No irritation occurred.[66] Similar patch tests of hair setting lotion containing 4.0% PVP/VA on 20 individuals caused no irritation.[67]

Repeated Insult Patch Test

A 50% solution of PVP/VA Copolymer in alcohol was tested in a repeated insult patch test on 50 subjects. Abraded and intact sites were used on each person for a total of 15 patches per person according to the procedure of Shelanski and Shelanski.[71] No irritation occurred in either intact or abraded skin, and the investigators concluded that the compound is neither a primary irritant nor a sensitizer and is not a fatiguing agent.[68]

Two samples of 50% PVP/VA Copolymer in alcohol were each tested on 150 subjects according to the Draize-Shelanski patch technique under semiocclusion. Volumes of 0.15 ml were applied to the upper backs for nine induction patches within a period of 21 days. Patches were removed after 24 hours and sites scored. After a ten-day rest period, a challenge patch was applied for 24 hours to an adjacent site and scored immediately after patch removal and again after two and three days. The first of the two samples produced moderate irritation in five subjects and mild irritation in two subjects during induction. The second sample produced slight irritation in three subjects. These reactions were categorized as singular, random occurrences, and there was no evidence of skin irritation or sensitization following the challenge application.[69]

A hair spray formulation containing approximately 5% PVP/VA Copolymer was tested on 51 black people. The material was applied to the upper arms under occlusion, each Monday, Wednesday, and Friday for 9–24 hours. Patch sites were scored immediately after each patch removal. The product was found to be essentially nonirritating.[70]

Thesaurosis and Epidemiological Studies

PVP/VA Copolymer is one of several resins used in hair spray formulations.[2] Whether these hair spray polymers cause "thesaurosis," a unique pulmonary disorder caused by the accumulation and storage of polymers on the pulmonary epithelium, has been disputed for over 20 years. The potential occurrence of thesaurosis owing to such storage was considered and discounted in a previous literature review prepared by the Cosmetic Ingredient Review.[72]

DISCUSSION

The animal toxicity studies on PVP/VA Copolymer alone and in cosmetic formulations are adequate; the ingredient causes little to no irritation. Studies on the ingredient in alcohol solution have shown slight oral toxicity, substantial eye irritation, and mild skin irritation. However, since assays with powdered 100% PVP/VA Copolymer elicit no deleterious dermatological effects, the irritation caused by the solution is due to the alcohol. Although data are not available on animal and human phototoxicity and photoallergenicity, photoabsorption curves show that PVP/VA Copolymer does not absorb radiant energy in the UVA, UVB, or visible light spectra. Absence of absorption in these ranges makes it unlikely that the ingredient has photosensitivity potential. Furthermore, there are no reports in the literature of photodermatological disorders from the use of this copolymer.

Epidemiological surveys of cosmetologists who routinely work in an environment containing high concentrations of respirable copolymers have shown no adverse effects from exposure to these ingredients. It appears that when properly used, the copolymer in these products should be of minimal risk to the general public.

SUMMARY

Polyvinylpyrrolidone/Vinyl Acetate Copolymer (PVP/VA Copolymer) is the copolymer of vinyl pyrrolidone (VP) and vinyl acetate (VA) monomers; it is prepared by free radical polymerization in ethyl alcohol. The molecular weight of the copolymer varies directly with both the ratio of VP to VA in the molecule and with the length of the polymer chain. PVP/VA Copolymer is supplied either in 100% concentration as a powder, which is partially soluble in water and soluble in organic solvents, or as a 50% solution in alcohol. This copolymer does not absorb energy over the UVA, UVB, or visible light spectrum. In cosmetics, PVP/VA Copolymer is used primarily in hair sprays and other hair products and

secondarily in skin and nail products. Noncosmetic uses include applications in adhesives and films.

Acute oral toxicity studies were performed with PVP/VA Copolymer in formulation and in solutions of the raw ingredient. Tests on mice and rats showed low to no toxicity on more than 76 animals. Two animals died from administration of a formulation containing other, unidentified ingredients. The survivors showed, at most, decreased activity and ataxia at maximum doses of 5 g/kg of a solution containing 12.5% PVP/VA Copolymer.

The acute ocular irritation of PVP/VA Copolymer, as supplied, and in formulation, was tested on albino rabbits. Solutions of 25%–50% PVP/VA in alcohol produced no reaction to severe irritation. Formulations containing 2.5%–24% PVP/VA also produced no reaction or moderate irritation.

Acute skin irritation studies of PVP/VA Copolymer were conducted on the abraded and intact skin of rabbits. Formulations containing 0.25%–4.0% PVP/VA Copolymer produced mild irritation. Solutions of 50% PVP/VA in alcohol produced mild irritation, and one sample of the 100% powder moistened in water produced no irritation.

PVP/VA (10 g in 15 ml of saline) was administered repeatedly in 0.5 ml doses to rats by endotracheal injection. The animals were sacrificed at different times for up to one year later. PVP/VA Copolymer was found in the lung, primarily in alveoli and in the spleen, although no inflammation was found.

After subcutaneous injection, PVP/VA Copolymer was stored in the spleen, the liver, kidneys, lung, and bone marrow. Some of the copolymer was excreted in the urine.

PVP/VA Copolymer was not a sensitizer to guinea pigs after intracutaneous injection. No irritation or systemic effects occurred when 30 subchronic dermal applications of 1% PVP/VA Copolymer in formulation were given to rats. Subchronic inhalation of 4.0% PVP/VA in a spray by rats and hamsters caused no abnormalities.

Chronic oral ingestion of a solution containing 10.2 mg/l of PVP/VA Copolymer produced no effects in mice or rats. Likewise, chronic inhalation of aerosols containing 1.72%, 0.08 ± 0.08 mg/l, and 0.35 ± 0.09 mg/l for three months to two years produced no effects in rabbits and hamsters.

Polyvinyl Pyrrolidone polymers were deleted from the list of 39 priority chemicals selected for testing by NTP in 1980 because "adequate toxicity data exist in the literature." PVP/VA Copolymers may contain the residual monomers, vinyl acetate at 1.0%, and vinyl pyrrolidone at 0.5%. In a test using *S. typhimurium*, with and without metabolic activation, vinyl acetate was nonmutagenic. Vinyl pyrrolidone was nonmutagenic in the Mouse Lymphoma assay, the Balb/3T3 in vitro transformation assay, and in the primary rat hepatocyte unscheduled DNA synthesis assay.

Vinyl acetate was not carcinogenic to rats when they were exposed to its vapor for one year.

PVP/VA Copolymer was tested in human clinical studies. Formulations containing 1.75%, 4.0%, and 5.0% PVP/VA Copolymer produced no irritation in 24-hour patch tests. Repeated insult patch tests of a 5.0% formulation of PVP/VA Copolymer caused no irritation or sensitization in 50 subjects. Likewise, three

solutions of 50% PVP/VA Copolymer in alcohol caused no irritation in 150 subjects. No photosensitization data were available for review, but the UV absorption characteristics suggest that photosensitization is unlikely.

CONCLUSION

On the basis of the available information presented in this document, the Panel concludes that Polyvinylpyrrolidone/Vinyl Acetate Copolymer is safe as a cosmetic ingredient under present conditions of concentration and use.

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