FINAL REPORT ON THE SAFETY ASSESSMENT OF POLYVINYL ALCOHOL[1]

Polyvinyl Alcohol is a synthetic alcohol used as a binder, film former, and viscosity increasing agent in a wide range of cosmetic formulations at concentrations up to 13%. Typical molecular weights range from 25,000 to 300,000. The acute oral LD_{50} in rats is reported to be >10 g/kg in one study and >21.5 g/kg in another. Dermal exposures of 5 and 13 weeks (the latter using 13% Polyvinyl Alcohol) produced no significant effects in rats. Various organ lesions and hypertension were noted in rats following repeated subcutaneous or intravenous dosing. Central nervous system depression and anemia, followed by renal damage, was seen in beagle dogs given daily intravenous injections of Polyvinyl Alcohol for a week. Several studies tested the carcinogenicity of subcutaneous implants of Polyvinyl Alcohol sponges or powder. Although the majority of these studies were positive, tumors were localized to the site of implantation. In another study in which Polyvinyl Alcohol was used as the vehicle for another agent and tested itself as the vehicle control, Polyvinyl Alcohol had no effect on the incidence of histiocytic sarcoma. Although no data were available assessing the reproductive or developmental toxicity, these endpoints were not considered to be likely with external exposure to this polymer. Polyvinyl Alcohol was not an ocular irritant in animal or clinical studies, nor was it a sensitizer. Some evidence of dermal irritation in animal and clinical studies was seen, but in the clinical studies it was not considered clinically significant. Based on these data, it was concluded that Polyvinyl Alcohol is safe as used in cosmetic formulations.

The following report reviews the data available on Polyvinyl Alcohol applicable to its cosmetic use.

CHEMISTRY

Definition and Structure

Polyvinyl Alcohol (CAS No. 9002-89-5) is a synthetic alcohol that conforms to the structure shown in Figure 1 (Wenninger and McEwen 1995a). Synonyms for Polyvinyl Alcohol include: ethanol homopolymer and PVA (IARC 1979; Budavari 1989).

The International Agency for Research on Cancer (IARC) (1979) lists the following properties of fully hydrolyzed (containing no unhydrolyzed

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Bindu Nair, Scientific Analyst and Writer, prepared this report. Address correspondence to her at Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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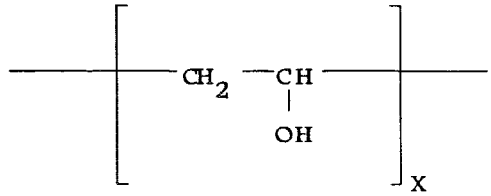

Figure 1. Chemical formula for Polyvinyl Alcohol (Wenninger and McEwen 1995a).

acetate groups) Polyvinyl Alcohol: it is a white, tasteless, and odorless powder. It has a melting point of 22°C and the flask point is 78.4°C. It degrades slowly at temperatures >100°C and decomposes rapidly at temperatures >200°C; it degrades under ultraviolet (UV) radiation and softens or dissolves in acids or bases.

As it contains a secondary hydroxyl group, under proper experimental conditions Polyvinyl Alcohol can undergo esterification and etherification. The solubility of Polyvinyl Alcohol in water decreases with increasing molecular weight. It is also soluble in glycol and glycerin. Polyvinyl Alcohol is insoluble in ethyl alcohol, acetone, and several other organic solvents (Hueper 1939).

Method of Manufacture

Polyvinyl Alcohol (PVA) is produced by the controlled hydrolysis (saponification) of polyvinyl acetate (q.v.) and normally contains unhydrolyzed acetate groups (Wenninger and McEwen 1995a; 1995b). The polyvinyl alcohol used may itself contain trace amounts of acetaldehyde as an impurity. The process is based on the partial replacement of ester groups in the vinyl acetate with hydroxyl groups and is done in the presence of anhydrous sodium methylate or aqueous sodium hydroxide (IARC 1979). Typically, polyvinyl acetate is dissolved into methanol, and sodium hydroxide (the saponification agent) is gradually added; Polyvinyl Alcohol is precipitated and then washed and purified (CTFA 1995b). The stage at which this reaction is stopped determines the number of residual acetyl groups, which, in turn influences the physical properties (Andermann, Zimmermann, and Schilling 1980). Typical molecular weights range from 25,000 to 300,000 (IARC 1979).

Impurities

Following the manufacturing described above, impurities that may be present in Polyvinyl Alcohol include: nonsaponified polyvinyl acetate, sodium acetate, solvent such as methanol, and residual catalyst (benzoyl peroxide and sodium hydroxide) (CTFA 1995b).

UV Absorption

One study presented in the General Biology section of this report performed a UV analysis on a commercial PVA sample and detected an absorbance maximum at ~325 nm (Haskell Laboratories 1960). A recent UV analysis was conducted on two commercial cosmetic grade Polyvinyl Alcohol samples in purified water. The samples were tested at 1, 5, and 10% in the 200–400 nm range using a UV/VIS spectrophotometer. Both samples had weak absorptions between 250–360 nm with one sample having stronger absorbance relative to the other. The researchers attributed the absorptions as dependent on the "K-band of conjugated double bonds in PVA [polyvinyl alcohol]." These K-band absorptions correspond to conjugated double bonds and end-chain carbonyl groups. The researchers stated that Polyvinyl Alcohol typically contains <0.01% end-carbonyl groups. However, as they have a high absorption coefficient value, at high concentrations the UV spectra have high absorption. The intensity of the peak also increased with heat treatment (CTFA 1995c).

Analytical Methods

Andermann, Zimmermann, and Schilling (1980) reported a detection technique in which Polyvinyl Alcohol forms a brown complex after reacting with iron (III) hydroxamic acid. A postreaction absorbance analysis establishes the type of Polyvinyl Alcohol present in that the amount of residual acetate groups on the alcohol affects the reading. The researchers specify it as a technique to detect the presence of Polyvinyl Alcohol in contact lens solutions and eyedrops.

USE

Cosmetic

Polyvinyl Alcohol is used in cosmetic formulations as a binder, film former, and viscosity increasing agent-aqueous (Wenninger and McEwen 1995b). As of January 1996, Polyvinyl Alcohol was reported to Food and Drug Administration (FDA) to be used in 37 cosmetic formulations (FDA 1996) (Table 1).

Concentrations of use are no longer reported to FDA (FDA 1992). In 1984 polyvinyl alcohol was reported to have been used in various formulations at concentrations ≤25% (FDA 1984). In data submitted to Cosmetic Ingredient Review (CIR) from the cosmetics industry, Polyvinyl Alcohol was used in facial masks at 10%, masks at 3%, eye shadow/brow products at 3%, and lipliners at 2%. Hydrolyzed Polyvinyl Alcohol was used in face and neck skin care products at 10% and in paste masks (mud packs) at 13%. Hydrolyzed LV Polyvinyl Alcohol was used in face

Table 1. Cosmetic product formulation data on Polyvinyl Alcohol (FDA 1996)

Product category	Total no. of formulations in product category	Total no. containing polyvinyl alcohol
Eyeliner	533	1
Mascara	218	5
Other eye makeup preparations	136	1
Hair spray (aerosol fixative)	334	1
Blushers (all types)	277	1
Nail polish and enamel	113	7
Other manicuring preparations	83	1
Moisturizing	942	1
Paste masks (mud packs)	300	14
Skin fresheners	244	2
Other skin care preparations	810	3
1996 Totals		**37**

and neck skin care products at 3% and in paste masks (mud packs) at 4% (CTFA 1995a).

International

Polyvinyl Alcohol is listed in the *Comprehensive Licensing Standards of Cosmetics by Category* (CLS) and must conform to the specifications of the *Japanese Standards of Cosmetic Ingredients* (Yakuji Nippo, Ltd. 1994). It can be used without restrictions in all CLS categories.

Noncosmetic

Polyvinyl Alcohol is approved for use as an indirect food additive (Rothschild 1990). It is used by the plastics industry in molding compounds, surface coatings, films, finishing compositions, and in the manufacture of artificial sponges and fuel hoses (Budavari 1989). It is used in pharmaceutic products as a viscosity increasing agent and often as a lubricant in ophthalmic solutions (Andermann, Zimmermann, and Schilling 1980; Budavari 1989; Fassihi and Naidoo 1989).

In clinical applications, Polyvinyl Alcohol sponges and foams have been used as embolic material in some surgical patients (Tadavarthy, Moller, and Amplatz 1975; Castenda-Zunga, Sanchez, and Amplatz 1978; Quisling et al. 1984). Polyvinyl Alcohol films have been investigated as carriers for spermicide (Sanders and Matthews 1990). In addition, Davis et al. (1993) have investigated the tumor-targeting potential of photosensitizers conjugated to an antibody in a Polyvinyl Alcohol carrier molecule.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Polyvinyl Alcohol of three different grades was used in an absorption assay (Haskell Laboratories 1960). Commercial grade Polyvinyl Alcohol was supplied with the following characteristics: (A) high viscosity, completely unhydrolyzed, average molecular weight of 148,000; (B) high viscosity, partially hydrolyzed, average molecular weight of 150,000; and (C) low viscosity, partially hydrolyzed, average molecular weight of 32,000. The researchers synthesized ^{14}C-Polyvinyl Alcohol to match the specifications of the commercial grades. However, the UV spectrum of the radioactive solution B differed from that of the corresponding commercial solution. Specifically, a broad absorbance maximum at approximately 325 nm found in the commercial solution B was missing in the laboratory-created B. Nonetheless, the researchers considered the two solutions to be identical. The method employed to test each grade was as follows: six adult Charles River albino rats received 100 mg of nonradioactive (commercial) Polyvinyl Alcohol by intubation on each of 7 days. Following this acclimation period, each rat was given 100 mg of radioactive Polyvinyl Alcohol (2 ml of a 5% solution) daily; three rats were dosed for 5 days, the other three for 10 days. Feed and water were supplied ad libitum. Urine and feces were tested daily for radioactivity. At the end of the dosing, the rats were killed and the liver, brain, kidneys, and a sample of body fat were removed for examination. The same protocol was followed using four male mongrel dogs, except that 2 g of nonradioactive Polyvinyl Alcohol was fed during the acclimation period, followed by 2 g of radioactive test material each day for either 5 (two dogs) or 10 (two dogs) days. For one rat and dog per treatment group, the feces were collected and the gastrointestinal tract was sampled in addition to the other organs. All animals had satisfactory weight gain and no clinical signs of toxicity. No treatment-related lesions were noted at necropsy. No radioactivity was detected in urine samples at any time; the feces did have some radioactivity. In the case of the two high viscosity Polyvinyl Alcohol solutions (A and B), absorption of less than 1 ppm was detected in the brain, kidneys, and liver of the animals in the study. For solution C, Polyvinyl Alcohol was detected in the following ranges: brain, 0.6–1.29 ppm; kidneys, 0.52–1.35 ppm; and liver, 1.21–6.91 ppm. The researchers attributed the greater absorption to the higher water solubility and/or water sensitivity due to the molecular weight of this solution.

Radioactive Polyvinyl Alcohol with an estimated molecular weight between 5000 and 50,000 was used to determine the extent of absorption via various routes in Fischer 344 rats (Sanders and Matthews 1990).

Groups of three male rats were given either a single or 10 consecutive daily oral doses of ^{14}C-Polyvinyl Alcohol (0.01 mg/kg body weight; 4.8 μCi; 1 ml/L water). Necropsy was performed 48 hours after the single dose or 24 hours after the last of 10 doses. No radioactivity above background was detected in any tissues following the single dose. Radioactivity recovered in tissues following repeated oral exposure represented 0.05% of the total administered. Virtually all the Polyvinyl Alcohol was excreted via the feces. Female rats were given a single tail injection containing 0.1 mg/ml/kg of ^{14}C-Polyvinyl Alcohol (48 μCi). Necropsy was performed at 24 hours, 3 days, and 10 days postdosing. At 24 hours postdosing, >17% of the total dose was retained in the liver; 64% of the dose had been excreted in the urine, and 3% in the feces. Three days following the injection, the radioactivity in the liver was reduced to 12% of the total; the amount recovered in the urine had not changed, but the feces accounted for 5% of the total. Ten days following administration, 4% of the total radioactivity was detected in the liver and cumulative elimination via the feces accounted for 13%; no additional elimination was detected in the urine. As Polyvinyl Alcohol is present in some intravaginal contraceptives, the researchers assayed for absorption in rats via this route. Exposure consisted of one, three, or ten intravaginal administrations of 3 mg/kg ^{14}C-Polyvinyl Alcohol (28 μCi) in 5 μl of water, which is the estimated human exposure in a contraceptive. A light CO_2 anesthetic was used and the vaginal opening was left uncovered to allow for the continuation of normal grooming habits. Following 10 dosings, the liver concentrations reached a peak of >1750 ng equivalents/g tissue at 24 hours; >300 ng equivalents/g tissue were still present 30 days following the last dose. The researchers remarked that although absorption was greater via the intravaginal route as compared to oral administration, the fraction of the dose detected in the major tissues after vaginal administration never exceeded 2% of the total administered dose. No signs of toxicity were observed.

Uptake by Kidneys

Polyvinyl Alcohol administered subcutaneously is almost exclusively localized in the glomerular mesangium (Kuhn et al. 1976; Mauer, Staffs, and Brown 1979; Romen and Morath 1979; Sterzel, Krauss, and Kregeler 1976).

In order to characterize the uptake by rat kidneys, male Lewis rats were subcutaneously injected with 50 mg/day of a 5% aqueous Polyvinyl Alcohol suspension (Seiler, Hoyer, and Sterzel 1983). Rats received between 1 to 28 doses of the suspension. Renal tissue samples were

obtained at various times during dosing and were examined using electron and fluorescence microscopy. Monoclonal antibodies to rat la (la antigens are expressed by bone marrow–derived cells which reside in the glomeruli of normal rats) were used to detect the presence of Polyvinyl Alcohol. Samples obtained on day 1 had Polyvinyl Alcohol in areas of attenuated mesangial matrix. By day 3, glomeruli were hypercellular and Polyvinyl Alcohol was detected within the phagocytic vacuoles of immature macrophages in the mesangium and occasionally in the endocytic vacuoles of endothelial and mesangial cells. With time, Polyvinyl Alcohol was found within mature mesangial macrophages and by week 2, epithelioid transformation of the macrophages was evident. By weeks 3 and 4, many glomeruli contained mesangial microgranulomas. The researchers concluded that macrophages of the monocytic/macrophage system play a primary role in the uptake of Polyvinyl Alcohol. Similar results were reported by Sterzel et al. (1983) in a comparable study using 54 male Sprague-Dawley rats.

As it was determined that Polyvinyl Alcohol accumulates in the glomerular mesangium, Mauer, Numata, and Sutherland (1979) studied the effects of such an accumulation on the uptake of colloidal carbon. Inbred Lewis rats were given Polyvinyl Alcohol (molecular weight 35,000 to 240,000) in 28 daily subcutaneous doses of 50 mg/100 g body weight and served as kidney donors to untreated Lewis recipients. Experimental rats received one kidney from the Polyvinyl Alcohol treatment group. Nine controls each received a kidney from untreated rats. Four days following transplantation, the recipient rats received colloidal carbon, intravenously, 70 mg/100 g. Bilateral renal biopsies were obtained 3 days, 3 weeks, and 8 weeks following colloidal carbon injection. No difference was noted in the uptake and processing of the carbon when Polyvinyl Alcohol was deposited as finely dispersed droplets. When Polyvinyl Alcohol accumulated as moderately large aggregates, an increased localization of carbon, as compared to nonpretreated controls was observed. Decreased carbon uptake was noted in areas of the mesangium which contained large masses of Polyvinyl Alcohol.

In a comparable study, Seiler et al. (1986) reported a marked increase in the uptake of iron dextran by the glomeruli of rat kidneys previously exposed to Polyvinyl Alcohol. Similar to the findings of Mauer, Numata, and Sutherland (1979), large clumps of iron were found most often in cells that had relatively little Polyvinyl Alcohol. However, whereas Mauer, Numata, and Sutherland (1979) suggested that the Polyvinyl Alcohol aggregates had interfered with mesangial drainage, Seiler et al. (1986) suggested that a change in phagocytic function had occurred.

Immunologic Effects

Phagocytosis

In an in vitro assay using guinea pig sera, Polyvinyl Alcohol of molecular weights 32,560, 60,280, and 89,760 did not reduce the phagocytic ability of leukocytes (Grzybek-Hryncewicz and Podolska 1968). Further, treatment of *Staphylococcus aureus* with 1–8% solutions of the polymer neither inhibited nor stimulated phagocytosis. Polyvinyl Alcohol of molecular weight $\leq$32,560 significantly decreased the opsonizing properties of guinea pig serum and markedly decreased the serum complement titer.

Immune Response

Lee et al. (1980) described a study where $B_6D_2F_1$ mice were pretreated with benzylpenicilloyl (BPO) that had been conjugated with Polyvinyl Alcohol of molecular weights between 10,000 to 14,000. The combination abrogated a de novo anti-BPO IgE response when the mice were subsequently exposed to a single intraperitoneal injection of the BPO determinant and ovalbumin. The BPO–Polyvinyl Alcohol conjugate also suppressed the ongoing anti-BPO IgE response in sensitized mice. Polyvinyl Alcohol was selected to create the tolerogenic conjugate because it was identified as a nonimmunogenic polymer.

Hubbard, Lee, and Sehon (1981) also reported suppression of an anti-DNP IgE response in $B_6D_2F_1$ mice after treatment (either pre- or post-immunization) with 2,4-dinitrophenyl (DNP) coupled with Polyvinyl Alcohol.

TOXICOLOGY

Acute Oral Toxicity

The oral LD_{50} in male albino rats of a trade Polyvinyl Alcohol compound in which the active ingredient (unknown molecular weight) was considered to be 100% was >10 g/kg body weight (Hazleton Laboratories 1959). Another trade Polyvinyl Alcohol compound, also with a reported purity of 100% (unknown molecular weight), had an oral LD_{50} of >21.5 g/kg body weight in male albino rats. This same molecular weight Polyvinyl Alcohol had an LD_{50} of >20.0 g/kg body weight in adult mongrel dogs (Hazleton Laboratories 1959). Other rat studies reported oral LD_{50} values of >5.0 g/kg for undiluted Polyvinyl Alcohol and >15.0 g/kg for 13.0% Polyvinyl Alcohol. The molecular weights were not reported (CTFA 1980a).

Dermal Toxicity

Short-Term

Undiluted Polyvinyl Alcohol (1.0 ml/kg for a dose of 1000 mg/kg) was applied to the shaved skin of 20 albino rats (10 of each sex) once daily, 5 days a week for 5 weeks (total of 27 applications). Daily observations were made and a blood sample (after a 16-hour fast) was obtained prior to the termination of the study. Animals were necropsied. No differences in body weights, and physical appearance were found between treated and control animals. The mean hematocrit and red blood cell values were significantly lower ($p < .05$) for treated males as compared to controls. No changes attributable to Polyvinyl Alcohol treatment were found at necropsy (CTFA 1975).

Subchronic

Ten female albino rats were treated for 13 weeks (65 applications) with 5 weekly applications of a peel-off facial mask containing 13% Polyvinyl Alcohol. The test substance was applied to the shaved dorsal skin. Due to the increasing severity of skin irritation and concerns for animal survival, the facial mask was applied and wiped off after a 15-minute exposure for the five applications in week 3, after which the test protocol (which detailed the substance not being removed) was again followed. The skin irritation "stabilized." Blood samples were obtained at the 6th and 13th week and hematologic and serum chemistry parameters were measured. Necropsy was performed. No significant toxic effects attributable to the test material were noted (CTFA 1977b).

Parenteral Toxicity

Short-Term

In a study by Hueper (1939), 12 albino rats (70–88 g) each received 20 injections (1 ml) of a 5% Polyvinyl Alcohol solution (unknown molecular weight) within a 4-week period. At the end of dosing, six rats were killed; the remaining five (one died during dosing) were killed 2 weeks later for necropsy. Pathologic alterations were more severe in the animals killed 2 weeks after dosing. A substantial amount of Polyvinyl Alcohol was at the site of injection, resulting in necrosis and granulomatous inflammatory tissue. Little of the administered Polyvinyl Alcohol was detected in the lymph nodes. Aggregates of Polyvinyl Alcohol were concentrated in the glomeruli of the kidneys. Polyvinyl Alcohol was detected in the lumen of blood vessels of various organs where it remained

in dispersion and occluded the lumen by forming globules. The vascular occlusion was especially noted in the lungs of some rats. Swollen endothelial cells with foamy cytoplasm were noted in the occluded capillaries. Histocytes in various tissues contained Polyvinyl Alcohol in granular form. Of parenchyma cells, only the renal tubular epithelium, adrenal cortical cells, and ganglion cells of the brain contained Polyvinyl Alcohol. The spleens were moderately enlarged, dark red, and firm. An increased number and swelling of the Kupffer cells was noted in the liver of all rats. Other organs were grossly normal but had small groups of foam cells; multinucleated giant cells and swollen macrophages were observed occasionally.

Hueper (1939) also administered 5% Polyvinyl Alcohol solution via the marginal vein of the external ear of three male rabbits such that one animal received 10 doses, the second received 15 doses, and the third received 25 doses in the course of 5 days. Findings were similar to those noted in rats, with the exception that the most severe and extensive lesions were found in the lungs, spleen, and testes following intravenous administration, whereas the subcutaneous route resulted in marked changes in the kidneys, liver, and spleen.

Hall and Hall (1967) performed a hypertension study using female Houston-Cheek rats (a Sprague-Dawley–derived strain) weighing between 65–75 g. Four groups of seven animals were given 1 ml of a 5% solution of Polyvinyl Alcohol in physiologic saline daily for 28 days; two groups (1 and 2) received the test material subcutaneously, the other two (3 and 4), intraperitoneally. The Polyvinyl Alcohol used had an average molecular weight of 133,000. Twenty-eight days following the last dosing, animals from treatment groups 2 and 4 received twice daily injections of 0.1 mg *d*-aldosterone-21 acetate in sesame oil for 7 consecutive days; animals in groups 1 and 3 received injections of vehicle alone. Animals in groups 5 and 6, which served as non-polyvinyl-alcohol–dosed controls, received hormone in vehicle or were left untreated, respectively. Feed and water were provided ad libitum; systolic blood pressures were taken periodically, as well as immediately before and after aldosterone administration. Four animals died in the 28-day interim following Polyvinyl Alcohol dosing and prior to aldosterone or vehicle treatment. At this time the average blood pressure for each group was: (1) 208, (2) 204, (3) 252, (4) 225, (5) 137, and (6) 141 mm Hg. Three additional animals died during the week of aldosterone treatment; one of these three (from group 4) had developed severe peripheral edema and ascites. Surviving animals were killed, organs weighed, and tissues were microscopically examined. Three rats had elevated blood pressures after subcutaneous administration of Polyvinyl Alcohol (combined groups 1 and 2); the pressures in all other rats, dosed and control, were normal. All surviving rats which had been treated with Polyvinyl Alcohol

followed by vehicle-alone injections (groups 1 and 3) developed hypertension; the pressure rose from 208 to 213 mm Hg in group 1 animals and remained essentially the same (252 versus 251 mm Hg) in group 3 animals. Reduction in blood pressure was noted in hormone-treated rats irrespective of the route of Polyvinyl Alcohol administration; the blood pressure decreased from 204 to 187 mm Hg and from 225 to 208 mm Hg in animals of group 2 and 4, respectively. Controls had relatively unchanged (nonhypertensive) blood pressures: from 141 to 136 mm Hg in group 5, and from 137 to 128 mm Hg in group 6. In the controls, aldosterone treatment alone did not induce or exacerbate hypertension. At necropsy, the liver, kidneys, spleen, and heart of Polyvinyl Alcohol–treated rats weighed significantly more than those organs in controls. Further, the heart and kidneys weighed significantly more in the intraperitoneally treated rats as compared to those treated subcutaneously. Adrenal glands were smaller, though not significantly, in aldosterone treated animals; the adrenal glands were, however, significantly smaller in groups administered Polyvinyl Alcohol subcutaneously versus those in untreated controls. Noted histopathologic changes included: dilated hepatic sinusoids in Polyvinyl Alcohol–treated rats, abundant multinucleate giant cells in livers of those intraperitoneally treated, numerous Polyvinyl Alcohol deposits in spleen (and kidneys) and intense macrophage and giant-cell proliferation (more marked in spleen of rats given intraperitoneal doses). Splenic arteries in hypertensive rats had hypertrophy, inflammatory changes, and necrosis (similar arterial changes were noted in the heart and kidneys); polyarteritis nodosa was observed in the pancreas of 5 of 13 rats given Polyvinyl Alcohol subcutaneously (3/5 were also in the aldosterone group). Foam cells in the arterial media or foam-cell transformation of the media were noted in the hearts of the intraperitoneally treated rats. Swollen and ischemic glomeruli and thickened capillaries were found along with peritubular sclerosis in the kidneys of several rats. No lesions could be specifically attributed to aldosterone treatment.

Riviere et al. (1980) used purebred Beagle dogs to determine whether Polyvinyl Alcohol–induced toxicosis could serve as a model for glomerulonephritis. A silastic cannula was surgically implanted in the right external jugular vein of four dogs. Three were given daily injections through the cannula of 20 ml solutions containing 47 mg Polyvinyl Alcohol/ml; the fourth dog was injected with saline. The Polyvinyl Alcohol used had a molecular weight of 125,000 and was 88% hydrolyzed. Blood samples were obtained every other day for the determination of blood urea nitrogen (BUN) and packed cell volume (PCV) values. Urine specimens were collected biweekly. At the end of treatment, blood and urine samples were obtained for complete analysis and necropsy was performed. After 1 week of treatment, a decrease in PCV was observed;

the values continued to drop such that by the end of the study they were 64% of the initial value. No changes in BUN were noted. An increase in the specific gravity of urine was noted; however, the increase alone could not explain the proteinuria which occurred by the end of the study. Body weight, feed consumption, and gastrointestinal function remained normal. The study was terminated after 3 weeks of dosing due to low grade central nervous system (CNS) depression as indicated by bilateral depression of the extensor postural thrust, hopping, front limb placing, and rear limb righting reflexes. At the end of the study treated animals had decreased total serum protein, sodium, potassium, and phosphorus concentrations. Hematologic assays found monocytosis, immature neutrophilia, marked polymorphonuclear leukocyte toxicity, decreased PCV, decreased hemoglobin, and decreased erythrocyte counts, slight anisocytosis, and many large platelets. No gross lesions were observed. Light microscopic examination found diffuse vacuolation of the red pulp cells in the spleen and formation of foam cells in the glomeruli. No changes in the brain were noted. In electron micrographs, a granular precipitate was present on the luminal surface of most endothelial cells. Mesangial cells and, to a lesser extent, endothelial and epithelial cells had cytoplasmic vacuolation. Because anemia and CNS depression occurred before development of significant renal damage, the researchers rejected the usefulness of Polyvinyl Alcohol induced glomerulonephritis in the dog as a model for studying glomerular disorders.

Hall and Hall (1983) conducted a study using female Holtzman rats and three solutions of Polyvinyl Alcohol of different molecular weight to determine the effect of the degree of polymerization. Groups of 12 rats received daily subcutaneous injections of 1 ml of 5% Polyvinyl Alcohol dissolved in physiological saline. The grades of Polyvinyl Alcohol used had molecular weights of 37,000 (low), 133,000 (medium), or 185,000 (high). A fourth group of animals received only vehicle and served as the control. The animals were provided feed ad libitum and access to 1% NaCl in distilled water to drink. Fluid intakes were measured daily, and blood pressures taken weekly. Systolic pressures greater than 150 mm Hg were considered hypertensive. The animals were killed on day 29 and various tissues and organs were examined. The smallest molecular weight Polyvinyl Alcohol was not detected in any of the tissues examined and produced a mild elevation of blood pressure in a third of the animals of that treatment group. The high molecular weight Polyvinyl Alcohol accumulated in a number of organs and tissues and caused swelling and multiplication of endothelial and epithelial cells of the renal glomeruli. Half the animals in the high molecular weight treatment group developed mild hypertension and the heart, kidneys, liver, and spleen were enlarged. The intermediate polymer was the only one of the three tested that produced polydipsia. In the resulting nephrotic syndrome, ascites

and edema were accompanied by severe hypertension, marked renal damage with severe glomerulonephritis, and widespread cardiovascular lesions. Animals of this treatment group consumed on the average more of the salt solution than those of the other groups. The researchers considered that molecular size rather than chemical structure influenced the toxic effects and lesion development.

Carver et al. (1985) reported daily subcutaneous (1 ml) doses of 5% aqueous Polyvinyl Alcohol of medium molecular weight (133,000) administered for 21 days to male Sprague-Dawley rats resulted in a benign glomerulopathy with accumulation of the macromolecule in the glomerular mesangium. These rats subsequently had an early transient dose–related sensitivity to gentamicin nephrotoxicity. However, after 12 days of daily dosing with gentamicin (between 0 to 120 mg/kg), no difference was found in the response of Polyvinyl Alcohol–treated rats as compared to nontreated controls.

Subchronic

Burgener, Gutierrez, and Logsdon (1982) used repeated intraportal injections of Polyvinyl Alcohol particles into male mongrel dogs to develop a model of hepatic cirrhosis. Portal hypertension and hepatic fibrosis were induced using Polyvinyl Alcohol ranging in size from 100–400 microns; the particles were suspended in 0.9% NaCl solution. To maintain stable portal hypertension of $\geq$20 cm water, weekly to biweekly injections of between 0.1 to 0.9 g of Polyvinyl Alcohol were necessary; single doses per day and per dog were determined by the portal vein pressure. The total dose needed varied among the dogs and ranged from 0.8 g administered over 22 months in four fractions to 4.8 g administered over 6 months in 14 fractions.

Short-Term Vaginal Toxicity

A Polyvinyl Alcohol sponge was inserted into the vagina of each of three New Zealand white adult female rabbits (4–5 kg) and kept in place for 10 days (Chvapil et al. 1979). Animals were then killed and the vagina and uterus of each examined by light and electron microscopy. No changes were noted with light microscopy in the vaginal tissue as compared to samples from sham controls. Electron microscopy of microvilli and cell borders indicated minimal irritation.

A 30-day intravaginal study of Polyvinyl Alcohol in $B6C3F_1$ mice was conducted by the National Toxicology Program (NTP) (1992). Two groups of 50 female mice were treated with daily intravaginal applications of 25% (w/w) polyvinyl alcohol for 30 days. Animals of one group were restrained for several minutes following each application. A control animal was treated with vehicle alone. No mortality was observed during the

dosing period and no significant effects were observed on body weight or total weight gain. Vaginal irritation and enlargement of uterine horns were found in some animals from all groups.

Dermal Irritation

Occlusive patches containing 0.3 ml of 10% Polyvinyl Alcohol in distilled water (molecular weight not specified) were applied to groups of four Kb1:JW female albino rabbits. The material was applied to the clipped back for 24-hours of contact. The skin of one group was abraded. Skin reactions were scored according to the Draize scoring system at the time of patch removal and 72 hours after removal. The Primary Irritation Index (PII) was 0.2 (max score 8.0). Erythema was noted at the 24-hour observation in three of four rabbits with abraded skin; no reactions were noted at the 72-hour observation (Shiseido Research Center 1978).

No dermal irritation was noted in nine rabbits following a single exposure to undiluted Polyvinyl Alcohol in an occlusive patch. Observations were made at 2 and 24 hours after unwrapping. In a second study using six rabbits and, following the same procedure, irritation was minimal. Scores of 1 (maximum score 8) were noted in five animals at the 2-hour observation; at the 24-hour observation, three of the five animals continued to have reactions scored as 1 (CTFA 1974).

Dermal Sensitization

A group of five Hartley albino guinea pigs was used in a modified maximization test of 10% Polyvinyl Alcohol in distilled water (Shiseido Research Center 1977). On the first day of induction, a pair of the following three samples (0.1 ml) were injected intradermally into the nuchal region: emulsified Freund's Complete Adjuvant (FCA) in distilled water; 10% Polyvinyl Alcohol in distilled water; 10% Polyvinyl Alcohol emulsified with FCA. One week later, 10% sodium lauryl sulfate (SLS) in petrolatum was applied to the region. One day following SLS treatment, 0.2 ml of Polyvinyl Alcohol was applied under a 48-hour occlusive patch. The control group of four animals was treated with distilled water following the same protocol. During challenge (3 weeks following the first induction); 0.1 ml Polyvinyl Alcohol was applied under an occlusive patch to the flank. Reactions were scored at 24 and 48 hours after challenge application. No reactions were observed.

Ocular Irritation/Toxicity

Knight and Link (1979) investigated various materials to find a suitable coating for intraocular lenses (IOLs) made of polymethylmethacrylate

(PMMA) so as to reduce corneal endothelial cell loss. To evaluate effectiveness, freshly excised rabbit corneas were touched to the coating material and then subjected to endothelial cell staining. On a scale of 0–4, with 0 being no damage and 4 being extensive damage (>50%), the control (rabbit cornea touched to the rabbit's natural lens) scored 0, the untreated PMMA lens scored an average of 2.5 after static contact (13 samples) and 3.6 after dynamic contact (4 samples), and the Polyvinyl Alcohol–treated cornea scored an average of 0.7 (11 samples) after static contact and 0.8 after dynamic contact (9 samples).

These authors also report three in vivo toxicity assays on Polyvinyl Alcohol (specific details not provided). In the first assay, five times the amount of Polyvinyl Alcohol as would appear on a lens was injected into the anterior chamber of one globe in each of 12 rabbits. Saline was injected into the other globe as a control. Intraocular pressure (IOP), slit-lamp examinations and whole-eye microscopic studies were performed regularly for 6 months. No significant differences were noted between the control and experimental eyes. In the second assay, radioactive Polyvinyl Alcohol was injected into the anterior chamber of the eyes of 21 rabbits. In tissue samples taken, almost 50% of the applied dose had cleared the globe within 45 minutes and was cleared by the kidneys and excreted in the urine within 48 hours. Polyvinyl Alcohol was not detected in any organ, including the globe. In the third assay, 20 IOLs (10 coated, 10 uncoated) were unilaterally implanted in 20 cats. A sham operation was performed on the opposite eye. Endothelial cell counts, IOP measurements, pachometry, and slit-lamp examinations were performed for 6 weeks postoperatively. A reduction in endothelial cell loss was observed in the gloves implanted with a coated lens. No other differences between control and treated globes were noted (Knight and Link 1979).

A single instillation of undiluted Polyvinyl Alcohol into the conjunctival sac of six rabbits did not produce irritation. Eyes were not rinsed after treatment and were scored using the Draize standard (maximum score 110). Similar results were reported in another study in which instillation of a peel-off mask containing 13.0% Polyvinyl Alcohol did not produce ocular irritation in six rabbits (CTFA 1980b).

MUTAGENICITY

In Vitro Bacterial

An Ames assay was conducted using *Salmonella typhimurium* TA100, TA98, and TA1537 to test the mutagenicity of Polyvinyl Alcohol alone and as one of two components of a vaginal contraceptive (the other component being polyoxyethylenenonylether). Polyvinyl Alcohol alone

at concentrations up to 1000 μg/plate did not induce statistically significant numbers of revertants either with or without metabolic activation. In the case of the contraceptive, the TA98 plates with metabolic activation did have a slight increase in the number of revertants, but the increase was less than twice the spontaneous rate and was not considered meaningful. All other plates tested with the contraceptive at doses up to 1000 μg/ml were negative (Shibuya et al. 1985).

In Vitro Mammalian

Dilutions of Polyvinyl Alcohol as it appears with polyoxyethylenenonylether were added to cultures of Chinese hamster V-79 cells 48 or 72 hours following the start of cultivation. The cultures were maintained for another 24 or 48 hours, colchicine was added 2 hours prior to completion, the cells were isolated, and stained slides prepared. Microscopic observations were conducted on 100 metaphase chromosomes. The contraceptive at concentrations between 0.0075–0.03 mg/ml did not induce any significant increase in chromosomal aberrations. Polyvinyl Alcohol alone at a dose of 0.03 mg/ml served as a reference and was nonmutagenic, producing aberrations in 4 cells as compared to the 19 cells with abnormalities induced by 0.1 μg/ml of the positive control, Mitomycin C (Shibuya et al. 1985).

In Vivo

Groups of six female SLC-BDF_1 mice (weight not reported) were used in a micronucleus test of Polyvinyl Alcohol, both alone and as a vaginal contraceptive with polyoxyethylenenonylether. The test material(s) were administered to mice divided into the following treatment groups: intraperitoneal administration of 156, 311, or 622 mg/kg of the two-compound mixture; a 622-mg intraperitoneal dose of Polyvinyl Alcohol; or a 5-day intravaginal dose consisting of the sheet contraceptive (26.2–29.8 mg). Mitomycin C (1 mg/kg) and saline (20 ml) were administered intraperitoneally to serve as positive and vehicle control, respectively. Mice were killed 24 hours after dosing; femur bone marrow was isolated and slides were prepared. Polychromatic erythrocytes (2000/per mouse) were examined by each of four examiners and the number of reticulocytes/500 erythrocytes was counted as an indicator of depression of bone marrow proliferation. A slight (not significant) increase in micronuclei for the group treated intraperitoneally with a high dose of the mixture was noted. No significant induction of micronuclei was noted in cells isolated from mice of the other treatment groups, and the contraceptive was considered nonmutagenic. The English translation does include the

statement that polyvinyl alcohol is capable of acting as a spindle poison; however, no details were provided (Shibuya et al. 1985).

CARCINOGENICITY

The IARC monograph (1979) cited several studies which tested for the carcinogenicity of subcutaneous implants of Polyvinyl Alcohol sponges or powder. In five of the seven studies, some test animals developed tumors at the site of implantation. Table 2 summarizes the methods and findings of these studies. The IARC group considered the human and animal data to be inadequate and required further studies before a carcinogenic evaluation of Polyvinyl Alcohol could be made. In a 1987 IARC update, Polyvinyl Alcohol was categorized in Group 3, "not classifiable as to (its) carcinogenicity in humans" (IARC 1987).

Crispens and Sorenson (1988) reported inhibition of cancer activity in female SJL/J mice by a copper complex (CuDIPS) delivered in a Polyvinyl Alcohol vehicle. This inbred mouse is characterized by a high susceptibility to type B reticulum cell sarcoma (RCS) (histocytic sarcoma). Groups of 20 mice aged 20, 30, or 40 weeks received biweekly or weekly subcutaneous injections (total of 6 or 12 doses) of varying concentrations of the copper complex suspended in 1.4% Polyvinyl Alcohol. The vehicle control consisted of groups of 10 mice (in same age groups as experimental) receiving 0.1 ml injections of 1.4% Polyvinyl Alcohol alone. A negative-control group received injections of saline. Mice that survived for 52 weeks were killed for necropsy. The survival incidence was comparable among the experimental and two control groups. The groups receiving the copper complex did have a significantly lower incidence of RCS. The groups receiving Polyvinyl Alcohol alone had the same incidence of RCS as the saline controls (8/10). Polyvinyl Alcohol when used as the carrier had no effect on the development of RCS.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Cumulative Irritation

Twelve panelists were instructed to place patches containing 13% Polyvinyl Alcohol (in formulation) onto their backs for 23 hours of exposure for 21 consecutive days. Applications were made to the same site and were evaluated daily. The total irritation score of Polyvinyl Alcohol for all subjects for all 21 applications was 10 (maximum 756). The formulation containing Polyvinyl Alcohol was classified as a "mild material" (Hill Top Research, Inc. 1984).

Table 2. Carcinogenicity studies of subcutaneous implants of Polyvinyl Alcohol*

Species, animal	Method	Findings	Reference
Male Wistar rats	Implants of sponge into abdominal wall; life-span observed	3 local sarcomas found in 34 animals; 1st noted on day 567	Oppenheimer et al. 1955
Male and female Wistar rats	Implants of (4 × 5 × 0.16 mm) sponge into abdominal wall; survivors killed within 800 days	21/25 survived to day 300; no local tumors detected	Russell et al. 1959
Chester Beatty rats 70 days old	Implants of thick (20 × 20 × 5 mm) and thin (20 × 20 × 2 mm) sponges into right flank	14/20 with thick implant lived ≥10 months and developed local sarcomas; 18/20 with thin implant lived ≥1 year and 1/18 developed a local sarcoma	Dukes and Mitchley 1962
Male Holtzman rats 5–6 wks old	Implant of 2 (20 mm diameter, 3–4 mm thick) sponges	12 survived ≥18 months (original number not reported); 9/12 developed local sarcomas, 1 had tumors at both implant sites	Dasler and Milliser 1963
Albino rats	Implant of (20 × 20 × 5 mm) sponge into back, 20/39 animals killed at intervals from 2 days to 1 year, other 19 maintained until natural death to a maximum of 29 months	Local tumors in 3 rats; 2 were malignant	Walter and Chiaramonte 1965

Male, Chester Beatty rats 8 wks old	Implants of sponges of varying dimensions into right flank; observations made until day 800	20 × 20 × 5 mm: local sarcomas in 9/24 33 × 33 × 2 mm: local scarcomas in 1/24 12.6 × 12.6 × 5 mm: local sarcomas in 5/24 20 × 20 × 2 mm: local sarcomas in 1/24 8 × 8 × 5 mm: local sarcomas in 1/24	Roe, Dukes, and Mitchley 1967
Bethesda black rats	Implant of 500 mg of polyvinyl alcohol powder (mol. wt. 120,000) into 25 animals; observed for 2 years	No local tumors seen; 3 benign and 6 malignant tumors seen at other sights, in 200 controls 3 benign and 17 malignant noted	Hueper 1959

*Commercially available sponges made of polyvinyl alcohol cross-linked with formaldehyde were used (Holund et al. 1979).

Human Repeat Insult Patch Test

A human RIPT was conducted using 100 panelists and testing a peel-off facial mask containing 13% Polyvinyl Alcohol. Patches containing the test material were applied to the backs of panelists for 24 hours of exposure three times a week for 3 weeks (nine induction patches). Following a 2-week nontreatment period, a 24-hour challenge patch was applied to a previously untreated site. Reactions were scored 24 and 48 hours after removal. During induction, three panelists each had one reaction described as "barely perceptible—minimal faint (light pink) uniform or spotty erythema." No reactions were observed during challenge (CTFA 1976).

A summary of the findings of a human RIPT reported that a 5.00% effective concentration of Polyvinyl Alcohol (tested in a noncosmetic product) did not induce allergic contact sensitization in any of 104 panelists. No evidence was found of "significant" dermal irritation during either the induction or challenge phase (TKL Research 1991).

In-Use Study

A 4-week use study was conducted testing a facial mask containing 13% Polyvinyl Alcohol. Fifty-two women who were not regular users of facial masks applied the product to half of the face three times per week (12 applications). A control facial mask was applied to the other side of the face. Evaluations were made by dermatologists at the start of the study and 1, 2, and 4 weeks after product usage. Four panelists each had one reaction; two of these four had barely perceptible scaling, the third had barely perceptible dryness, and the fourth had mild irritation. These reactions were not considered product induced (Industrial Bio-Test Lab, Inc. 1975).

The above-described protocol was used in a second study testing a peel-off facial mask containing 13% Polyvinyl Alcohol. In this study, 21 of 54 panelists had "intermittent changes in facial skin condition (transient redness and/or acne)." In all but four cases, the findings were not of clinical significance. One subject developed erythema after the first three applications, which was considered as resulting from pulling during mask removal. The second subject experienced transient postapplication erythema following applications 7 and 10. The third subject experienced slight nasal erythema after the first application and "slight tingling and tightness" after applications 4 and 5 which the researchers attributed to unfamiliarity with mask use. The fourth subject experienced slight dryness and erythema at various times on the cheek treated with the control mask and on both cheeks after application 7, which was relieved with moisturizer (CTFA 1977a).

Ocular Irritation

Fassihi and Naidoo (1989) conducted a double blind cross-over study using four commercial tear-replacement solutions on 16 subjects, six of whom were afflicted with dry eye syndrome. Of the four formulations tested, one contained 1.4% Polyvinyl Alcohol along with 0.5% chlorobutanol. In addition, two control solutions were prepared containing 1.4% Polyvinyl Alcohol in saline and 1.4% Polyvinyl Alcohol in saline preserved with 0.5% chlorobutanol. On each of 6 days, subjects were administered three test solutions, 1 drop (50 μl) in the conjunctival sac of both eyes at 0800, 1200, and 1600 hour. The commercial formulation containing Polyvinyl Alcohol was instilled on days 1, 3, and 5 whereas the control Polyvinyl Alcohol solutions were instilled on days 2, 4, and 6. Subjects scored their own response after the drops were administered. Nine of the 16 panelists reported irritancy and reddening to the control Polyvinyl Alcohol with chlorobutanol solution; these same nine reported an identical irritancy response to the commercial solution containing Polyvinyl Alcohol and chlorobutanol. None of the panelists reported any discomfort after instillation of the control solution containing Polyvinyl Alcohol alone.

SUMMARY

Polyvinyl alcohol is a synthetic alcohol with molecular weights ranging from 25,000 to 300,000. It is used as a binder, film former, and viscosity increasing agent. As of January 1996, it was used in 37 cosmetic formulations. It is approved for use as an indirect food additive.

Polyvinyl alcohol administered subcutaneously to Lewis rats was almost exclusively localized in the glomerular mesangium. Macrophages played a primary role in its uptake. Polyvinyl alcohol was identified as a nonimmunogenic polymer.

Two samples of polyvinyl alcohol each with a reported purity of 100% (and unknown molecular weights) had oral LD_{50} values in male albino rats of >10 g/kg body weight and >21.5 g/kg body weight, respectively. Various lesions and hypertension were noted in rats following repeated subcutaneous or intravenous dosing. Anemia, glomerulonephritis, and central nervous system depression developed in beagle dogs following repeated intravenous dosing. In one subchronic dermal study, increasing irritation was found in female rats following repeated exposure to 13% Polyvinyl Alcohol. Other animal studies found no evidence of irritation or sensitization.

Polyvinyl alcohol was nonmutagenic in the Ames and micronucleus assays as well as in an assay using Chinese hamster cells. The IARC working group categorized Polyvinyl Alcohol as a Group 3 agent, "not

classifiable as to (its) carcinogenicity in humans". Subcutaneous injections of 1.4% Polyvinyl Alcohol did not affect the rate of type B reticulum cell sarcoma (RCS) in SJL/J mice.

Polyvinyl Alcohol was not an ocular irritant in either in vivo animal studies or in a clinical study. In an RIPT assay, 5.00% Polyvinyl Alcohol did not induce sensitization and no significant dermal irritation was noted.

DISCUSSION

In assessing the safety of Polyvinyl Alcohol, the CIR Expert Panel was concerned over an absorbance peak at 325 nm in a commercial grade Polyvinyl Alcohol (Haskell Laboratories 1960). As this peak was not noted in a laboratory-created solution of radioactive Polyvinyl Alcohol, the Panel was of the opinion that the absorption peak would not be found in cosmetic material. Recent data confirms the absence of UV absorbance in Polyvinyl Alcohol preparations (CTFA 1995b).

The Panel noted that a peel-off facial mask containing 13% of the ingredient caused increasing dermal irritation in female rats in a subchronic study (CTFA 1977b). However, clinical studies did not indicate similar irritation. In an RIPT study, 13% Polyvinyl Alcohol had a low incidence of irritation during induction (three of 100 panelists each had one instance of a "barely perceptible" reaction), and no evidence of sensitization upon challenge (CTFA 1976). Further, a cumulative irritation study using 12 panelists and 13% Polyvinyl Alcohol reported a total irritation score of 10 out of a possible 756 maximum (Hill Top Research, Inc. 1984). The bulk of animal data supported that Polyvinyl Alcohol was safe at higher concentrations. No changes were found in rabbits following a single dermal exposure or in albino rats following short-term dermal exposure to undiluted Polyvinyl Alcohol (CTFA 1995c; 1975). The Panel holds the opinion that the ingredient does not present a reproductive or developmental toxicity risk. No ocular irritation was noted in rabbits following instillation of undiluted Polyvinyl Alcohol (Knight and Link 1979; CTFA 1995b). The Panel concluded that Polyvinyl Alcohol was safe as used in cosmetics.

The Panel is aware of an ongoing study under the National Toxicology Program and expects to review this conclusion when those results are available.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes Polyvinyl Alcohol to be safe as used in cosmetic formulations.

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