FINAL REPORT ON THE SAFETY ASSESSMENT OF POLYVINYLPYRROLIDONE (PVP)[1]

Polyvinylpyrrolidone (PVP) is a linear polymer of 1-vinyl-2-pyrrolidone monomers used as a binder, emulsion stabilizer, film former, hair fixative, and suspending agent–nonsurfactant. The molecular weight of the polymer ranges from 10,000 to 700,000. PVP K-30, with an average molecular weight of 40,000, is typically used in cosmetic formulations. The highest concentration reported to be used is 35%. There was no significant absorption of PVP K-30 given orally to rats, and the acute oral LD_{50} was >100 g/kg for rats and guinea pigs. Neither toxic effects nor gross lesions were found in rats maintained for two years on a diet containing 10% PVP K-30. Short-term PVP inhalation studies produced mild lymphoid hyperplasia and fibroplasia in rats, but no inflammatory response. In animal studies, no evidence of significant ocular irritation, skin irritation, or skin sensitization was found at PVP-iodine solution concentrations of 10%. While PVP-iodine is not a cosmetic ingredient, these negative findings were considered to support the safety of the PVP component. Undiluted PVP K-30 was not a dermal irritant or sensitizer in clinical tests. No developmental toxicity was seen in vehicle controls where PVP was used as a vehicle for another agent. In certain assay systems, PVP was genotoxic, but was negative in the majority of studies. Orally administered PVP significantly decreased the rate of bladder tumors in mice exposed to bracken fern. Several studies tested the carcinogenicity of subcutaneous implants of particulate PVP in rats, mice, and rabbits. Although the majority of these studies conducted in rats were positive, tumors (sarcomas) were localized to the site of implantation. Based on the available data, it was concluded that PVP is safe as used in cosmetics.

DEFINITION AND STRUCTURE

Polyvinylpyrrolidone (PVP) (CAS No. 9003-39-8) is a linear polymer consisting of 1-vinyl-2-pyrrolidone monomers conforming to the formula shown in Figure 1 (Wenninger and McEwen 1997). The monomer has a molecular weight (MW) of 111.1; the molecular weight of the polymer can range from 10,000 to 700,000 (IARC 1979). Synonyms include: polyvinylpyrrolidone; 1-Ethenyl-2-Pyrrolidone, Homopolymer; Povidone (Wenninger and McEwen 1997); polyvidone; polyvidon; polyvidonum;

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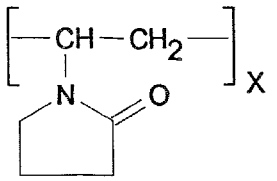

Figure 1. Chemical formula for polyvinylpyrrolidone.

poly(*N*-vinyl-2-pyrrolidone); poly(*N*-vinyl-butyrolactam); poly(1-vinyl-2-pyrrolidone); 1-vinyl-2-pyrrolidinone polymer and poly[1-(2-oxo-1-pyrrolidinyl)ethylene] (Robinson et al. 1990). A water insoluble crosslinked homopolymer of PVP is called polyvinylpolypyrrolidone or PVPP, crospovidone (Robinson et al. 1990).

PHYSICAL AND CHEMICAL PROPERTIES

PVP is a faintly yellow solid resembling albumin (Budavari 1989). It is soluble in water, ethanol, and chloroform and is insoluble in ether (USP 1975; Budavari 1989). PVP is defined by its viscosity in aqueous solution, relative to that of water. This viscosity is expressed as a K-value which ranges from 10 to 95 (USP 1990). A solution of PVP K-30 typically has an average MW of 40,000, though the MW range and distribution can vary among batches with the same nominal K-value (Robinson et al. 1990).

UV Absorption

The amide region of the pyrrolidone substituent absorbs in the UV region at wavelengths below ~235 nm (International Specialty Products [ISP] 1995).

Method of Manufacture

The synthesis of PVP is shown in Figure 2. It begins with formaldehyde and acetylene and proceeds through 2-butyne-1,4-diol and γ-butyrolactone to α-pyrrolidone and *N*-vinyl-2-pyrrolidone (the monomer), which is then polymerized to form PVP (Robinson et al. 1990). Usually, the monomer is polymerized in water using the method described by Reppe (1949). According to Robinson et al. (1990), commercial polymerization is carried out in isopropyl alcohol. The alcoholic solution is subsequently converted to an aqueous solution by steam distillation and then either spray or drum dried.

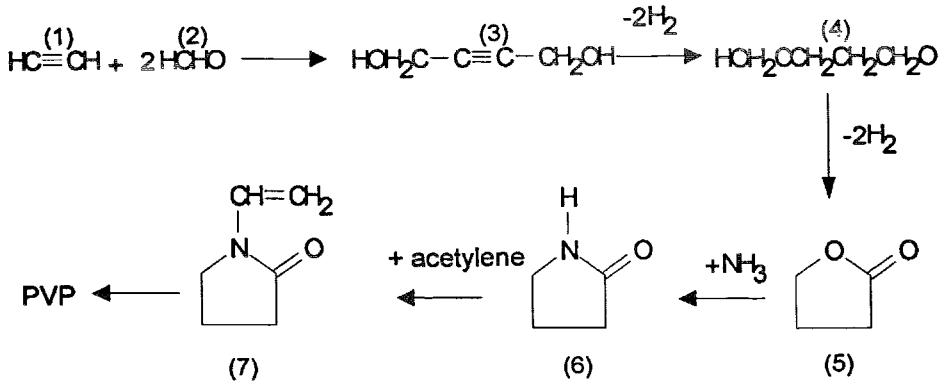

Figure 2. Steps in the chemical synthesis of PVP. Intermediates are (1) acetylene; (2) formaldehyde; (3) 2-butyne-1,4-diol; (4) 1,4-butanediol; (5) gamma-butyrolactone; (6) alpha-pyrrolidone; and (7) *N*-vinyl-2-pyrrolidone.

Impurities

The following specifications are defined for cosmetic grade PVP: 95.0% minimum PVP (as vinylpyrrolidone); 0.5% maximum aldehyde (as acetaldehyde); 1.0% maximum vinylpyrrolidone; 0.05% maximum sulfated ash; 5.0% maximum water; 2 ppm maximum arsenic (as elemental As); and 10 ppm maximum lead (as elemental Pb) [Nikitakis and McEwen 1990]. For pharmaceutic grade PVP, the United States Pharmacopeia (USP) (1990) placed limits of 1 ppm hydrazine, 0.2% aldehydes as acetaldehyde, and <0.2% *N*-vinyl-2-pyrrolidone monomer. ISP (1995) stated that typical PVP preparations have hydrazine contamination of 200 ppb.

USE

Cosmetic

PVP functions in cosmetic formulations as a binder, emulsion stabilizer, film former, hair fixative, and suspending agent–nonsurfactant (Wenninger and McEwen 1997). According to Robinson et al. (1990), PVP can be combined with cationic substances, such as disinfectants or basic dyes; therefore, care is needed as it does have a marked affinity for dyes.

In January of 1996, PVP was reported to the Food and Drug Administration (FDA) to be used in 395 cosmetic formulations (Table 1). Concentrations of use are no longer required to be reported to the FDA (FDA 1992). Data submitted directly to Cosmetic Ingredient Review (CIR) by the cosmetics industry indicated that PVP is used at a variety of concentrations (see Table 1.) In addition to the values listed in Table 1, the cosmetics industry reported that PVP is used at 1–5% in hair

Table 1. Cosmetic product use of PVP

Product category	Formulations in category	No. containing PVP	Concentration of use (%)
Baby shampoos	23	1	0.5
Eyebrow pencil	99	2	5
Eyeliner	533	23	5.23
Mascara	218	96	8
Other eye makeup preparations	136	8	2; > 5–10
Cologne and toilet waters	834	1	1
Other fragrance preparations	195	1	
Hair conditioner	715	37	1
Hair spray (aerosol fixatives)	334	21	0.25; PVP K90 < 0.15
Hair straighteners	50	1	
Permanent waves	434	2	
Rinses (noncoloring)	60	3	
Shampoos (noncoloring)	972	15	2
Tonics, dressings, and other hair grooming aids	604	76	4
Wave sets	95	21	2
Other hair preparations	395	28	2
Hair rinses (coloring)	50	4	
Hair bleaches	113	1	
Foundations	355	4	1.5
Lipstick	997	1	0.5
Other oral hygiene products	3	1	
Bath soaps and detergents	372	3	
Other personal cleanliness products	339	2	
Preshave lotions (all types)	20	2	
Shaving creams	158	4	
Other shaving preparation products	63	1	
Cleansing	820	6	
Face and neck	300	5	
Body and hand	1012	4	
Moisturizing	942	5	
Night	226	1	
Paste masks	300	8	
Skin fresheners	244	1	
Other skin care preparations	810	6	
1996 total		**395**	

Source. FDA, 1996; CTFA, 1995.

fixatives, at 8% in blushers, at 7.5% in lip products, and up to 35% in makeup fixatives (CTFA 1995).

Robinson et al. (1990) reported that PVP K-25 and K-30 (average MW 40,000) are commonly used in cosmetic formulations. PVP K-90 may be used in aerosol hair sprays (CTFA 1995). Most hair fixative dispensers emit a spray with a mass median aerodynamic dimaeter of ~60 microns, with usually less than 0.5% of the particles being smaller than 10 microns (ISP 1995).

International

PVP is listed in the Comprehensive Licensing Standards (CLS) of Cosmetics by Category 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

Food

PVP is cleared for the following uses: as a clarifying agent in beverages and vinegar; as a tableting adjuvant; and as a stabilizer, bodying agent, and dispersant in nonnutritive sweeteners in concentrated liquid form, and vitamin and mineral concentrates. It is also cleared for use in packaging that comes in contact with various foods (Rothschild 1991). Robinson et al. (1990) reported that PVP K-30 (average MW 40,000) is used as a food additive. In 1986, the 30th Joint Expert Committee on Food Additives (JECFA) set an acceptable daily intake (ADI) level for PVP of 0–50 mg/kg (World Health Organization 1986b). At the 29th meeting, the committee had acknowledged the possibility of a hydrazine contaminant in PVP K-30 (a possible by-product of the polymerization process). In a 1987 report on hydrazine, the IARC working group declared that although there was "inadequate" evidence of carcinogenicity in humans, there was "sufficient" evidence of carcinogenicity in animals, citing studies in which rodents were exposed via inhalation and the oral route. However, the 29th JECFA stated, "the probability of carcinogenic effects arising from such low levels of hydrazine seems remote in view of the large amount of data that indicate that polyvinylpyrrolidone itself is not a carcinogen" (World Health Organization 1986a).

OTC Drugs

The FDA has approved PVP as safe and effective for use as a demulcent (FDA 1991). FDA has proposed that PVP is not recognized as safe and effective against poison ivy, oak, and sumac (FDA 1991). In the medical setting, PVP was used during World War II as a blood plasma

extender. This practice eventually lost favor as PVP was not easily broken down by the body and settled in the monocyte/macrophage system (MMS), which is referred to as the reticuloendothelial system (RES) in some early literature (Wessel, Schoog, and Winkler 1971). As reported by Robinson et al. (1990), the German drug regulatory body (Bundesgesundheitsamt) issued the following recommendations concerning parenteral use of drugs containing PVP: (1) For intravenous use, drugs may contain an unrestricted (but identified) amount of PVP up to K-18 (average MW 9,000); (2) for i.m. use, each dose should not contain more than 50 mg PVP with an upper limit of K-18; (3) care should be used with repeated dosing on patients with renal function complications; (4) care should also be taken to avoid repeated injection into either the same site or sites with reduced perfusion; and (5) observations should be made for accumulation of PVP in the MMS and the production of foreign body granulomas (see Clinical Assessment–General Biology section for more historic details). PVP is an ingredient in some commercially available artificial tear preparations (York et al. 1988).

PVP has been associated with iodine (I_2) to form the antiseptic Betadine (Pietsch and Meakins 1976). The structure of the resulting tri-iodide is shown in Figure 3 (Schenck et al. 1980). The tri-iodide is in rapid equilibrium with iodine and iodide (the iodine reacts with water and is reduced to iodide). The equilibrium is a function of pH (at lower pH the iodine is released from the complex), concentration, solvent, and temperature. The toxicity of iodine is reduced because most of it remains as a reserve in the complex whereas the small amount of free iodine that is present retains antimicrobial properties (York et al. 1988). PVP, which has a high membrane affinity, serves as the carrier polymer delivering the free iodine directly to the bacterial cell surface (Zamora 1986). There is discrepancy in the published literature as to the iodine content of a PVP-iodine formulation. According to Zamora (1986), a 10% solution of PVP-iodine is comprised of 90% water, 8.5% PVP, and 1% available iodine and iodide. He reported a free iodine concentration of 0.0001% (1 ppm). However, Tosti et al. (1990) reported a free iodine level of 0.001%

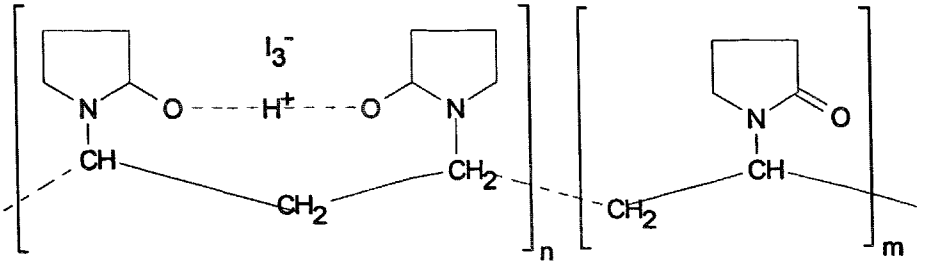

Figure 3. Chemical formula for PVP-iodine antiseptic (m ≅ 18n)

and still others referred to a free iodine content of 1% (Ancona 1985; van Ketel and van den Berg 1990). FDA has proposed that PVP-iodine is safe and effective as an antifungal agent and first-aid antiseptic (FDA 1991).

GENERAL BIOLOGY

Absorption, Metabolism, Distribution, Excretion

In a study of the permeability of the capillaries in normal kidneys reviewed by Wessel, Schoog, and Winkler (1971), PVP of varying MWs was injected into rats and rabbits. It was determined that the capillaries of the glomeruli allow only PVP molecules of a MW of < 25,000 to pass through the ultrafilter. However, the postglomerular capillaries have pores of three different sizes, allowing PVP with MWs of 11,500, 110,000, and 650,000 to pass through. Thus, the permeability for macromolecules is greater in the postglomerular capillaries than in the glomerulus. The researchers considered that most higher molecular weight PVP (up to MW 650,000) goes directly from the postglomerular capillaries into the interstice or lymphatic channels without passing the ultrafiltrate.

In a review of early literature, Wessel, Schoog, and Winkler (1971) reported that PVP elimination was inversely related to MW. They noted discrepancies among the published literature concerning the renal threshold for PVP (reports of limits have ranged from 25,000 to 60,000). However, it was generally agreed that polymers with a MW < 20,000 were completely eliminated through healthy kidneys. In their review, Robinson et al. (1990) cited studies, which provided evidence that PVP was taken into the monocyte/macrophage system via low affinity pinocytosis, though phagocytes may also play a role.

Ravin, Seligman, and Fine (1952) conducted an excretion study in which 300 mg ^{131}I-PVP (of K values between 25 and 50) were rapidly infused into groups of dogs (50,000 to 500,000 counts per minute). Blood samples were taken at 5, 15, and 30 minutes, and 1, 2, 6, and 12 hours after the PVP injection. Urine samples were taken at 3, 6 and 12 hours. The plasma level of radioactivity declined rapidly during the first two hours following infusion. A short inflection phase followed during which the rate of PVP disappearance from the plasma changed rapidly. Finally, a straight-line decay curve was reached. In a complement experiment, ^{131}I-PVP was administered by rapid injection to dogs which had thoracic-duct fistulas. Analysis of lymph samples established that the initial rapid fall of serum radioactivity was matched by a rapid rise in extracellular-fluid radioactivity. The inflection point in the blood-disappearance curve coincided with a peak concentration of PVP in the lymph; the levels in the serum and lymph approached one another at a rate that was related to the K-value of the solution. For example, it was

determined that PVP with a MW of < 20,000 (the lower half of the K-25 sample) established an equilibrium within an hour. Within 48 hours, 40–80% of the infused dose of ^{131}I-PVP was recovered in the urine.

In a metabolism study, ^{14}C-PVP (K-33) was rapidly infused via the i.v. route into rats and dogs. Radioactive PVP was also infused in a 45-minute timespan into humans (rapid infusion was not conducted in order to avoid rapid expansion of the circulating blood volume). Blood and urine samples were taken at the same intervals as in the above-described excretion study. The blood-disappearance and urinary excretion curves were similar to those noted in dogs infused with ^{131}I-PVP. Approximately 0.3–0.5% of the administered dose appeared in the stool of both man and dog within 24 hours of infusion. Fecal excretion declined thereafter to an average of 0.001%/day. Between 0.15–0.20% of the administered dose was found in the expired air during the first 12 hours after infusion in man; the value fell to 0.01% in subsequent 12-hour periods. After 36 hours, no radioactivity was detected in the respired air. The researchers concluded that there was no metabolic degradation of PVP and no significant route of excretion except by the kidneys (Ravin, Seligman, and Fine 1952).

Distribution was determined by injecting six rats with 350 mg of ^{14}C-PVP (K-33) via the i.v. route (Ravin, Seligman, and Fine 1952). Pairs of rats were killed at 2, 4, and 7 hours after infusion. In a similar experiment, rabbits were given 8–9 g of the same preparation daily in seven divided doses. The rabbits were killed at 1, 2, and 6 months after infusion. Five moribund human patients received the same preparation of PVP. A similar distribution pattern was observed in all three species. The skeletal muscle, skin, and subcutaneous tissue contained the largest fraction but lowest concentration of PVP; the organs of the MMS had the highest concentration. Samples were taken at different times following infusion; the amount and concentration of PVP retained in the skin and subcutaneous tissue and in skeletal muscle decreased progressively, whereas the values remained constant for organs with large populations of monocytes/macrophages.

The effect of MW on retention was examined by separating a sample of K-30.2, C^{14}-PVP into K-37 and K-27 fractions. (Analysis determined that 23% of the K-30.2 sample had a mean MW of 117,000.) Groups of rats were infused with 35 mg of either fraction or the original unfractionated solution. Two animals from each group were killed after 2 weeks. Overall retention was greater with increasing K-value. Most significant was the finding that retention by the spleen (representative of the MMS) increased with increasing K-value disproportionately to retention by other organs. An estimated 10% of the unfractionated PVP was retained by the MMS. It was therefore concluded that the MMS retained molecules with a MW > 117,000 (Ravin, Seligman, and Fine 1952).

In humans, it was determined that the K-value of PVP excreted within the first 6 hours following infusion was lower than the K-33 of the infused preparation. The K-value of urinary PVP rose 48–96 hours following infusion to a peak corresponding to a MW of 40,000. PVP continued to be excreted at the rate of 25 mg/day (0.06% of a clinical dose of 17.5 g) for as long as one year. The excreted dose was of MW between 40,000–120,000 as smaller particles passed rapidly through the glomerulus and larger particles were retained in the MMS (Ravin, Seligman, and Fine 1952).

In a study by Hespe, Blankwater, and Wieriks (1975), male Wistar rats were dosed (via the i.v. route) with 500 mg/kg PVP along with the antibiotic oxytetracycline (OTC). Of the PVP administered, 50 mg/kg was radioactive. Although there were some particles with MWs of 190,000, 94% of the PVP had MW of $\leq$ 20,000. The researchers noted a slight, reversible disturbance in respiration 15 minutes after injection. One animal was killed at each time of 15, 30 minutes, 1, 2, 4, 8, 24, and 72 hours postdosing, and a whole-body autoradiography was performed. (A fluorograph was also performed to detect the presence of the antibiotic.) At 15 and 30 minutes postdosing, a high level of radioactivity was detected in the blood, kidneys, urinary bladder, lungs, skin and hair follicles, sclera, connective tissue, interstitial tissue, and tissue spaces. Particularly at 15 minutes, the stomach wall and portions of the intestinal wall had high activity. (No levels were reported.) With time, greater activity was detected in the gastrointestinal lumen. A slight uptake was noted in the liver with the maximum activity being attained at 30 minutes. Elimination was rapid. By 8 hours, only the kidneys, areas of the lungs, and intestinal contents had high levels of activity. By 72 hours, the kidneys, as well as localized areas of the lungs and skin, still had high radioactivity; residual levels were noted in the liver, connective tissue, and spleen. No radioactivity was detected at any time in the central nervous system; radioactivity was not detected in the bulk of skeletal muscle and fatty tissue. By comparing the autoradiographs to the fluorographs of the same animals as well as to the fluorographs of rats treated only with the antibiotic, the researchers considered a PVP-OTC complex to have formed in solution, which remained in equilbrium with free PVP and OTC. The complex allowed for penetration of the antibiotic into various organs that were inaccessible by free OTC alone. PVP had no effect on the activity of the antibiotic.

Hespe, Meier, and Blankwater (1977) used male Wistar rats to determine the effects on distribution and excretion of two radioactive PVP (3.2 mCi/g) preparations both with a low mean MW but differing MW distributions. Ninety-five percent of the particles in sample A were below a MW of 25,000. In contrast, 99.5% of the particles in sample B had a MW below 25,000. Each of the samples were administered intravenously at

doses of 50 and 200 mg/kg. Bile was continually collected over a 5-hour period from animals dosed with 50 mg/kg. Excretion products were collected and analyzed by liquid scintillation. Animals were sacrificed at 4, 6, 8, 12, or 24 days after dosing and whole-body autoradiography was performed. During the 72-hour period following administration of the 50 mg/kg dose, radioactivity was detected in the following distribution. For sample A, 92.6 (± 11.3)% of the administered dose was detected in the urine, 7.0 (± 6.3)% in the feces, and 0.43 (± 0.04)% as respired CO_2. For sample B, 93.1 (± 4.6)% of the administered dose was detected in the urine, 4.4 (± 3.4)% in the feces, and 0.47 (± 0.01)% as respired CO_2. The researchers considered the data to indicate good recovery; however, they noted that the standard deviation values indicated large individual differences. In the period 0–1 day following dosing, 84.5% of the administered 200 mg/kg dose of sample A was recovered as compared to 91.0% of sample B. By day 22, 86% of the administered amount of sample A and 92.2% of sample B had been recovered. The differences were not statistically significant. Analysis of the bile collected for 5 hours after dosing with 50 mg/kg indicated that within the first hour postdosing, 61.1 μg of sample A had been recovered compared to 123.2 μg of sample B. The bulk of the administered dose of both samples was eliminated by 24 hours. Radioactivity continued to be detected in the bile samples. By 5 h, 94.5 μg of sample A and 176.0 μg of sample B had been recovered, which represented 1.2 and 1.9% of the administered dose, respectively. In autoradiographs taken 6 days postadministration of the 200 mg/kg dose, the kidneys and gastrointestinal tract of animals dosed with either sample had high levels of radioactivity. However, high levels were also detected in the urinary bladder, liver, spleen, pancreas, skin, sclera, connective tissue, bone marrow, and joints of animals treated with sample A, whereas levels in these same areas were difficult to detect in sample B–treated animals. The researchers considered that sample B was retained in the body to a lesser extent. They attributed the difference in elimination to sample B having 0.5% of its molecules with a MW > 25,000, "which is regarded as the limit for rapid glomerular filtration", whereas sample A had 5% of its molecules with a MW >25,000.

Digenis et al. (1987) performed a single-dose oral study using groups of five male Sprague-Dawley rats. Radioactive PVP (0.9 mg/rat, 10.6 μCi/dose) with an average MW of 40,000 was administered by gavage. Animals were killed at 6, 12, 24, and 48 hours postdosing, and major organs and blood samples were collected. Samples were weighed and then combusted and analyzed by a liquid scintillation counter. The feces was the major pathway of elimination; 90.8% of the dose was recovered after 12 h (five animals) and 98.4% after 48 hours (three animals). After 6 hours, approximately 0.04% of the administered dose was detected in the urine. The researchers reported that radioactivity detected

in major tissues and in the blood was not significantly different from untreated controls (data not provided). Dialysis studies suggested that the absorbed oligomer (referring to the small amount detected in the blood and subsequently in the urine during the first 6 hours) was of MW < 3500. It was estimated that perhaps 4% of the total sample was of such size. The researchers considered that an oral dose of PVP was not significantly absorbed in the rat.

Oral Drug Absorption

Stupak and Bates (1973), using groups of 15 Sprague-Dawley rats, found that oral administration of a coprecipitate of digitoxin-PVP had a higher solubility and dissolution rate than did either a physical mixture of digitoxin and PVP or digitoxin alone. The PVP used in both the physical mixture and the coprecipitate had a MW of 40,000. The drug-PVP physical mixture (1:9) was administered at drug doses of 50 and 75 mg/kg body weight (hence, PVP doses of 450–675 mg/kg); the coprecipitate (1:9) was administered at doses of 6–10 mg digitoxin/kg body weight (54–90 mg/kg of PVP). Animals were observed for 72 hours postdosing. Drug absorption was measured indirectly by determining oral toxicity. The coprecipitate had markedly lower LD_{50} values than did digitoxin alone (7.80 mg/kg for the coprecipitate versus 88 mg/kg for digitoxin alone). Pure PVP had no untoward effects when administered at doses up to 100 g/kg and thus, the increased toxicity of the coprecipitate was due to "an increase in the amount of drug in the body produced by a marked enhancement in the rate at which drug absorption occurs."

Immunologic Effects

In their review, Robinson et al. (1990) cited studies which indicate that PVP functions as a thymus-independent antigen that produced a primary 19S immune response. (The reviewers noted that linear molecules with repeating antigenic determinants are typically expected to incite a T cells–dependent immunologic response.)

Lymphocyte Transformation

Robinson et al. (1990) described a study in which three beagle dogs were innoculated subcutaneously with 50 mg PVP in phosphate-buffered saline into the front and rear right feet on each of days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, and 31. The MW of the PVP was not reported. On day 16, the treated dogs, as well as an additional three dogs, were inoculated with 50 μg of turkey gamma-globulin (TGG) in

Freund's adjuvant. The right and left popliteal lymph nodes were removed on days 32 and 33. Lymph node cells were used in in vitro assays where the response to various stimuli was measured by incorporation of tritiated thymidine (thus indicating lymphocyte transformation). The researchers found variable responses among the animals. However, no difference was observed in lymphocyte transformation in cells from the right node (PVP inoculated) versus those cells from the left node (control). It was considered that the effect of the nonspecific T-cell mitogens, concanavalin A, and phytohemagglutinin (PHA), was not inhibited by previous inoculation with PVP. Further, PVP inoculation did not alter the proliferative response of lymph node cells to specific antigen challenge with PVP. A slight (not statistically significant) increase in mitogen response was observed in control dogs which received TGG alone.

Hoshi et al. (1986) reported that PVP (MW 500,000) did not induce a recognized plasma cell reaction, germinal cell development, or formation of new lymph follicles in mice following injection into the rear foot pad. PVP was not considered very immunogenic.

ANIMAL TOXICOLOGY

Oral Toxicity

Acute

The oral LD_{50} for PVP with an average MW of 40,000 was > 100 g/kg body weight in both rats and guinea pigs (Burnette 1962).

Chronic

For two years, groups of Sherman Wistar albino rats (50 males and females per group) received feed containing the following: 1% PVP (group I), 10% PVP (group II), or unmodified diet (group III, control) (Antara Chemicals, unknown date a). PVP K-30 (average MW 40,000) was used. Ten animals from each group were necropsied at the end of the study. The animals in all groups gained weight. For the last 12 months of the study, the pattern of growth was identical between groups I and III. Body weight gain was depressed by 10% in animals of group II as compared to controls. All hematologic parameters were comparable. For 15 months of the study, urinalysis results were similar among the groups. By 18 months, albumin was noted in the urine of animals from group II. By 21 months, albumin was detected in the urine from all animals. The animals of group II had more frequent and more fluid stools. No toxic effects or gross lesions attributable to PVP consumption were noted.

Antara Chemicals (unknown date b) also conducted a 2-year feeding study using beagle dogs. Groups of four dogs received feed containing either 10% cellulose (group 1, control), 2% PVP K-30 plus 8% cellulose

(group 2), 5% PVP K-30 plus 5% cellulose (group 3), or 10% PVP K-30 (group 4). Findings at microscopic examination were generally unremarkable among the groups. Of note, swollen monocytes/macrophages in the lymph nodes were found in group 4 dogs. To a lesser extent, this observation was also noted in dogs of groups 2 and 3. The researchers suggested that the effect appeared reversible and was perhaps a transient stage in the elimination of the PVP. Growth curves were within the normal range, as were results from periodic blood and urine analysis. Organ weights and other gross observations were normal.

Inhalation Toxicity

Short-Term

Four Sprague-Dawley rats were exposed 8 h/day, 5 days/week (30 exposures) to an aerosol of PVP K-30 dissolved in water at an average concentration of 118 mg/m^3 (MW 40,000; 99.3% of the particles had a mean particle diameter $< 4\ \mu$, and 87.6% were $< 2\ \mu$). Animals were killed 4 days following the last exposure. Lungs were removed and stained with hematoxylin and eosin. Macrophages were filled with a granular material that, when stained with iodide-iodate solution, was compatible with PVP, though the material did not stain with periodic acid-Schiff (PAS), congo red, and chlorazol fast pink. No evidence of inflammation was found in the lungs (Lowsma et al. 1966).

Lowsma et al. (1966) also reported a study in which eight rats were exposed to aerosolized PVP-water solution at an average concentration of 146 mg/m^3. Exposure conditions and duration were the same as in the above described study. Two animals were killed at 1, 3, 4, and 6 months after exposure. Lungs were removed for analysis. Lungs from animals killed at 1 month were identical to those from the first experiment where animals had been killed days after exposure. Lungs from animals killed at 3 months had mild lymphoid hyperplasia in the peribronchial, perivascular, and subpleural lymphoid tissue. A few giant cells with vacuoles and free particles were seen in these areas. The PAS, congo red, and chlorazol fast pink stains were negative. Lungs of animals killed at 4 months had areas in peribronchial and perivascular regions containing particles which were positive in the PAS and congo red stains. Giant cells were observed, which were negative when stained. Lungs from animals killed after 6 months were microscopically similar to those from animals killed at 3 and 4 months. Particles staining with PAS, congo red, and chlorazol fast pink were noted in the peribronchial lymphoid tissue. No PVP was seen in sections of the liver, spleen, and hilar lymph nodes until the sixth month at which time, small PVP particles were noted within the lymph nodes. The particles were stained

by PAS, congo red, and chlorazol fast pink stains. Particles were also noted in the macrophages of the lymph nodes. In one lung from each test animal, the PVP concentration was 7.6–26.5 mg/g wet weight versus a PVP concentration of 1 mg/g wet weight in nonexposed controls. The researchers considered PVP to be inert in that it did not cause an inflammatory response.

Chronic

Groups of 20 Sprague-Dawley rats were exposed to 5, 15, 45, or 120 ppm of *N*-vinylpyrrolidone-2 (NVP, the component monomer of PVP) in the air for 6 hours a day for 3 months (BASF 1985). Two control groups were exposed to fresh air. Sixteen of 20 animals of the 120-ppm group died by the fifth exposure. Another four animals of this group were moribund after the fifth exposure and were killed. Signs of toxicity observed in rats of the highest-dosing group included irritation of the mucous membranes, apathy, atony, and cyanosis. Generalized hemorrhagic diathesis, especially of the mucous membrane of the stomach, was noted. At necropsy, most of the animals were cachectic and had fatty degeneration of the liver with transitions to toxic dystrophy and necrosis of the olfactory epithelium of the nasal cavity. None of the animals of the control or other treatment groups died during the study and no clinical signs were observed. However, changes were noted in the liver of animals of the 15- and 45-ppm groups and changes in the nasal mucosa were noted in all treated animals. Some changes in hematologic and biochemic parameters were indicative of liver damage. A dose-related decrease in total protein, albumin, and α_1-globulin was more pronounced in female rats than in males, especially in samples taken during the testing period rather than at termination. Female rats also had noticeably lower values for creatinine (significantly), urea (significantly), and potassium. (Values not reported). The changes were dose-dependent. Increases in the total bilirubin content and alkaline phosphatase activity and a decrease in the cholesterol level were pronounced in males. Rats of both sexes of the 15- and 45-ppm groups had slight decreases in values for hemoglobin, hematocrit, and erythrocytes, a reduction in the mean cell volume, and a slightly increased platelet count. With the exception of males of the 15-ppm group, the absolute and relative liver weights were increased in both sexes of the 15- and 45-ppm groups. The animals of these two groups had "centro-acinar enlargement of hepatocytes (hypertrophy) together with foci, with distinct boundaries, of atypical hepatocytes." Atrophy of the olfactory epithelium and hyperplasia of the respiratory epithelium were noted. NVP was considered hepatotoxic in rats when inhaled at concentrations $\geq$15 ppm. The no-adverse-effect level was $<$ 5 ppm; earlier studies had found no effects at 1 ppm (BASF 1985).

A review, supported by the GAF Corporation, of the above study provided more detail. A follow-up study had been conducted in which female rats were exposed to 45 ppm NVP in the air for 3 months; animals were killed at 7 weeks (during treatment), 3 months (at the end of treatment), 12 months, or 24 months. At the end of the study, 4 control and 6 treated rats of the 15 animals designated to be killed at 24 months had survived. Hepatic toxicity was noted at 7 weeks and was more severe at 3 months. Recovery from toxicity was noted in the livers of animals killed at 12 months. A variety of lesions was noted in both groups including foci of altered cells. A hepatocarcinoma was noted in a treated animal; however, the GAF reviewers dismissed it as not significant, citing the 45-ppm dosage exceeded the maximum tolerated dose for a carcinogenicity study, the small number of survivors in both the control and dosed groups, the absence of hepatic neoplasms in animals which died before the end of the study, and the historical 1/30 incidence of liver tumors in the particular rat strain (Anonymous 1985).

Dermal Toxicity

Short-Term

A 13-week dermal toxicity study was conducted using groups of albino rats (10 of each sex). The test material, a shampoo containing 2.0% PVP, was applied to a shaved anterior dorsal site, once a day, 5 days a week, for 66 to 67 days. One group was dosed with 240 mg/kg of a 2.5% (w/v) dilution of the test material. Another three groups received 2400 mg/kg of a 25% dilution of the test material; one of these groups was rinsed with tap water 15 minutes after dosing. (It is unclear why there were two high-dose leave-on groups.) The doses were based on multiples of observed human use levels of the product calculated from a product use of 240 mg/kg (for a hypothetical 50–70 kg person). The control groups consisted of an untreated group and a rinse-off with water only group. Blood and urine samples were obtained after weeks 7 and 13; at the termination of the study animals were necropsied. Dermal irritation was noted in rats of the high-dose group, irrespective of rinse-off or leave-on protocol. All animals survived the full term of the study. Body weight gains for rats of the 2400 mg/kg group were significantly depressed as compared to controls. This depression was more noted in rats of the leave-on groups. Body weight gains for the low-dose group were comparable to control values. Glucose values were significantly depressed for male rats in both high-dose leave-on groups; blood urea nitrogen (BUN) values were elevated in both male and female rats of one high-dose leave-on group and in males of the second high-dose leave-on group. The researchers considered these discrepancies "may be related to a proposed decrease

in food intake in these animals causing increased protein catabolism which elevates BUN in circulating blood." Other blood parameters, as well as urine analysis and organ weight values were within normal range (CTFA 1978).

Ocular Toxicity/Irritation

MacRae et al. (1984) used rabbits to compare various presurgical skin antiseptics including a 7.5% PVP-iodine solution (with detergent) and 10% PVP-iodine solution (without detergent). The test substance was applied topically to one eye of each of six animals. The animals were examined by slit-lamp and corneal thick measurements made 5, 10, 30, 90, and 180 minutes after application. The tests were repeated on days 1, 3, and 7 after application. Five minutes after application, moderate corneal epithelial edema was noted in all groups except the saline control. After 3 hours, marked corneal deepithelialization, conjunctival chemosis, and anterior stromal edema were noted in all treated groups except for the 10% PVP-iodine (without detergent) and the control. After 1 week, all corneas had returned to normal appearance. The 10% PVP-iodine solution without detergent caused minimal corneal toxicity in rabbits whereas the other antiseptics tested, including the 7.5% PVP-iodine with detergent, were toxic to the cornea.

York et al. (1988) studied the effects of frequent dosing with PVP-iodine by evaluating ocular irritation in 18 rabbits according to the McDonald-Shadduck method. The right eye of each animal was dosed once each hour for 8 hours, on each of three consecutive days. Concentrations of 0.5% PVP-iodine or less were practically nonirritating when administered six times a day. Corneal epithelial wound healing was studied in 16 rabbits with superficially abraded corneas. The right eye was dosed four times daily for 7 days; eyes were examined for wound closure and the corneas stained with fluorescein. Eyes treated with 0.33% PVP-iodine had epithelial healing comparable to 0.3% gentamicin treated eyes. PVP-iodine, at concentrations of 0.5%, delayed healing by one day. Mild conjunctival congestion and swelling were noted in all eyes.

Dermal Irritation and Sensitization

Shelanski and Shelanski (1956) applied a PVP-iodine solution (10% PVP) to the hairless backs of 25 rabbits. The sites were occluded for 96 hours of contact. After 2-weeks of nontreatment, a second patch was applied in the same manner for 48 hours of contact. No dermal reactions were noted after either exposure.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Claussen and Breuer (1975) employed the yolk-sac method to determine the teratogenic effects, if any, of tetracyclines administered in a PVP vehicle. On the ninth day of gestation, New Zealand White rabbits were laparotomized. The baseline control had physiologic saline injected into both horns of each yolk sac. The vehicle control had 500 μg PVP (average MW 11,500), dissolved in saline and distilled water, injected into one horn of each sac; the other horn was injected with a saline/water solution. The yolk sacs of the experimental group were injected with a solution containing 50 μg doxycycline, and 500 μg PVP (6.07 μg magnesium was also added as a stabilizing agent). The rabbits were killed and examined on the 28th day of gestation. Results from females with lesions were omitted, thus leaving 20 control animals, 17 PVP-treated animals, and 13 doxycycline and PVP–treated animals. Resorptions and living and dead fetuses were counted. Each fetus was weighed and macroscopically examined. The skeletons were stained with alizarin blue and the crown-rump length was measured. Results were statistically evaluated with the Wilcoxon test at the 5% significance level. In the group treated with PVP alone, no difference was observed in any of the parameters measured as compared to the saline control. Adverse effects/malformations noted in fetuses treated with doxycycline and PVP were attributed to the antibiotic. PVP alone had no teratogenic effects.

MUTAGENICITY

Bacterial

The studies detailed in this section are summarized in Table 2.

Wlodkowski, Speck, and Rosenkranz (1975) tested the mutagenic potential of the PVP-iodine complex following the Ames protocol and using *Salmonella typhimurium* strains TA1530 and TA1538. Concentrations of the complex up to 20 μl did not induce a significant amount of histidine revertants when compared to positive controls capable of inducing either base substitutions (ethyl methanesulfonate, methyl methanesulfonate, and β-propiolactone) or frameshift mutations (2-nitrofluorene) The researchers also tested the in vivo mutagenic potential of the complex in *Escherichia coli* (pol A_1-). These cells are deficient in an enzyme needed in the DNA-repair process and are unable to recover from the actions of a DNA-modifying agent. Thus, the growth of these bacteria would be inhibited by a test substance that alters the wild type genotype (pol A+). (Substances which interfere with structures other than DNA would inhibit the two strains to the same extent.) In this assay, concentrations of PVP-Iodine greater than 2 μl produced positive results.

Table 2. Mutagenicity studies on polyvinylpyrrolidone

Assay/strain	Concentration/procedure	Results/comments	Reference
Bacterial			
Ames Assay/*Salmonella typhimurium* TA1530 and TA1538	PVP-iodine up to 20 μl	Not mutagenic; PVP-I in contact with bacteria for 48 h	Wlodkowski et al. 1975
Escherichia coli (pol A-)	PVP-iodine at various amounts	Mutagenic at concentrations > 2 μl	Wlodkowski et al. 1975
Salmonella typhimurium TA1530 and 1538	Not stated	Mutagenic in TA 1530; capable of base-substitution mutations; test conducted at 4°C as opposed to 37°C	Rosenkranz et al. 1976
Modified Ames/tested ability of PVP to inhibit the mutagenicity of benzo(a)pyrene (BP) in *S. typhimuriumTA98*	10 and 50 times the concentration of BP	Weak inhibitor of BP mutagenicity	Calle and Sullivan 1982
Mammalian			
In vitro mouse (TK +/−) lymphoma assay	PVP up to 100 mg/ml PVP-I up to 10 mg/ml with and without activation	Not mutagenic without activation; with activation, aberrant non-dose related mutations observed with PVP-I; PVP alone not mutagenic	Kessler et al. 1980

Balb/c 3T3 transformation assay	48-h incubation of cells with up to 100 mg/ml PVP; number of transformed foci counted	Not mutagenic (non–dose-related transformations observed)	Kessler et al. 1980
In vivo			
Dominant lethal assay/20 male NMRI mice	Intraperitoneal injection of 72 mg PVP-I/kg (11.2% available iodine); males then mated with untreated females	Not mutagenic; initial decrease in conception rate in females mated with treated males; average number of implantations not affected	Merkle and Zeller 1979
Micronucleus test/10 NMRI mice	Intraperitoneal injection of 36 mg PVP-I/kg (11.2% available iodine); animals killed 6h after dosing; bone marrow smears prepared	Not mutagenic	Merkle and Zeller 1979
Chinese Hamster bone marrow test	Single dose: three groups of 12 mice received 38.3 mg PVP-I/kg; another three groups received 82.5 mg PVP-I/kg; animals killed at various times, metaphases evaluated Repeated dosing: five application of 38.3 mg PVP-I/kg; killed 6 h after application; metaphases examined	Not mutagenic after either single or repeated application	Merkle and Zeller 1979

In response to the above described results of Wlodkowski, Speck, and Rosenkranz, Rosenkranz, Gutter, and Speck (1976) demonstrated the mutagenic ability of PVP-iodine in *Salmonella typhimurium* TA1530, but not TA1538, when the bacteria were exposed to the test substance in suspension at 4°C (as opposed to the 37°C of most assays). The researchers concluded that the PVP-iodine complex was capable of inducing base-substitution mutations in *Salmonella*. They considered the studies of Wlodkowski, Speck, and Rosenkranz (1975) to have obscured these findings by counting mutants per plate as opposed to mutants per survivors, which was important, considering the bactericidal action of the complex. Further, the assay by Wlodkowski, Speck, and Rosenkranz (1975) allowed for 48 hours contact between the bacteria and the complex that may have resulted in toxic conditions, although those authors did not report cytotoxicity.

Calle and Sullivan (1982) used the Ames test to determine the effectiveness of several compounds, including PVP, as inhibitors of benzo-(a)pyrene (BP) mutagenicity for *Salmonella typhimurium* strain TA98. For the initial screening, the test substances (dissolved in dimethylsulfoxide) were used at 10 and 50 times the concentration of BP. Plates containing 8.2 nmoles of a BP solution were incubated with 50 μl of a test substance and the bacterial strain. The cultures also contained biotin and histidine and an S-9 activation fraction obtained from liver homogenates of β-naphtholflavone–induced rats. A BP blank, consisting of five plates, was run with each batch and served as the control. In the assay with PVP, the BP control had 270 ± 46 His revertants per plate, the plates containing 10 times as much PVP as BP had 219 ± 30 revertants per plate, and the batch containing 50 times as much PVP as BP had 141 ± 22 revertants per plate. PVP was defined as a weak inhibitor of BP mutagenicity as it produced greater than 25% inhibition at concentrations no more than 50 times the concentration of BP.

Mammalian

In Vitro

Kessler et al. (1980) used two assays to test the mutagenic potential of various chemicals including PVP and the PVP-iodine complex. In the L5178 mouse (TK+/−) lymphoma assay, concentrations of PVP up to 100 mg/ml and concentrations of the PVP-iodine complex up to 10 mg/ml did not significantly alter the mutation frequency (MF) as compared to established positive controls. The researchers considered the 100 mg/ml PVP-iodine exposure similar to typical human exposure; higher concentrations of PVP-iodine could not be tested due to cytotoxicity. In order to determine whether metabolic activation was a necessary condition for

mutagenic ability, the compounds were also tested in the presence of an S-9 fraction of liver microsomes. At a concentration of 5 mg/ml, the PVP-iodine complex produced an MF score of 4.7; this value was significant ($p < .01$). However, the MF value of 3.2 at a dose of 10 mg/ml was not significantly different from controls (high incidence of cytotoxicity was observed at this dose). PVP alone at concentrations up to 100 mg/ml was inactive in the presence of S-9. The positive controls dimethylnitrosamine (DMN) and *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) had MF scores of 25 and 4, respectively, and were classified as potent mutagens.

The second assay used by Kessler et al. (1980) was the Balb/c 3T3 transformation assay. Ten thousand 3T3 cells were incubated with the test agents for 48 hours after which the cell sheets were rinsed and cultured for 21 days. Cells were then stained and the number of transformed foci were counted. Values of 2.5 times greater than those observed in the negative control were considered to be positive transformational events. The media alone culture (negative control) had 1.22 transformed foci. In comparison, concentrations of PVP up to 100 mg/ml were inactive in this assay. PVP-iodine at a concentration of 5 mg/ml had a significant number (3.67) of transformed foci ($p < .01$); however, the results at 10 mg/ml were not significant (.67). Similarly, iodine alone produced significant results at 170 μg/ml (3.67 transformed foci), but not at 340 μg/ml (2.33 transformations). Thus, no dose-response relationship was established. The positive control, MNNG, produced 7.50 transformed foci. The authors concluded PVP and PVP-iodine were nonmutagenic.

In Vivo

Merkle and Zeller (1979) tested the mutagencity of the PVP-iodine complex in mice using either the micronucleus test or the dominant lethal assay and in Chinese hamsters using the bone marrow test. All three assays used a PVP-iodine complex (11.2% available iodine) dissolved in distilled water and administered intraperitoneally. Feed and water were provided ad libitum. The significance of results were determined using the X^2 test or *U* test. In the dominant lethal assay, germ cell mutations in treated male animals are indirectly indicated by changes in the reproductive capacity of untreated females following mating. One group of 20 male NMRI mice received 72 mg of PVP-iodine/kg. A second group, the vehicle control, received one dose of 10 ml distilled water/kg. A third group was left untreated. Each male was mated with three females for 8 weeks. The animals tolerated a single dosing without incidence. The conception rate in the treated animals decreased significantly in the first week, but the average number of implantations (and resultingly, the mutagenicity index) was not affected. In the remaining weeks, all parameters remained similar between control and treated groups.

The micronucleus test screens for structural and numeric chromosome aberrations in somatic cells. An increase in micronuclei in the erythrocytes indirectly indicates mutations and spindle poisons. Groups of 10 NMRI mice (five each sex) received two intraperitoneal injections of either 36 mg of PVP-iodine/kg, or 10 ml distilled water/kg within a 24-hour period. A third group was left untreated. Six hours after the final dose, the animals were killed and bone marrow smears were prepared; 4000 normochromatic and 2000 polychromatic erythrocytes were examined per animal. The parameters evaluated in the normochromatic erythrocytes were comparable between treated and nontreated groups. In the polychromatic erythrocytes examined, micronuclei were detected in 4.3% of the cells from the treated group as compared to rates of 2.9% in the vehicle control and 3.7% in the untreated control. While the increase was of significance in comparison to control values ($p < .05$), the researchers stated that the value was within normal range (Merkle and Zeller 1979).

The bone marrow assay was conducted using groups of twelve (six of each sex) Chinese hamsters. Three groups received a single i.p. injection of 38.3 mg PVP-iodine/kg, another three received 82.5 mg PVP-iodine/kg. Three groups remained untreated and served as controls. Animals were killed 6, 24, or 48 hours after the application; 100 metaphases were evaluated. In the repeated application assay, a group received injections of 38.3 mg PVP-iodine/kg on five successive days. A vehicle control received five injections of saline solution and another group of animals remained untreated. Animals were killed 6 hours after the fifth dose; 100 metaphases were examined. The animals tolerated the single exposure without incidence; repeated injections caused signs of pain in the animals which lasted ~ 1 minute. No increases were observed in the rates of aberrant metaphases after the single or repeated dosings as compared to controls (Merkle and Zeller 1979).

CARCINOGENICITY

Pamukcu, Yalciner, and Bryan (1977) studied the ability of several compounds to inhibit the carcinogenic effects of bracken fern (BF) in albino rats. According to the researchers, BF is "strongly carcinogenic for rat bladder and intestine." The rats received a weekly s.c. injection of thiamine hydrochloride in order to maximize tumor formation. One group of 28 rats received feed containing 0.33 g BF/g of diet and 50 mg PVP/g of diet for 12 months. Another group of 20 rats received 50 mg PVP/g of diet without BF. The positive-control group (30 rats) received 0.33 g BF/g of diet; the negative-control (20 rats) group remained untreated. Intestinal tumors were found in 100% and tumors of the urinary bladder were

detected in 73% of the positive control. No such tumors were detected in the untreated control group. Rats which received a diet of both BF and PVP had a 93% incidence of intestinal tumors and an 18% incidence of urinary bladder tumors. This decrease in the incidence of bladder tumors was significant ($p < .001$). As with the untreated control, neither intestinal nor urinary bladder tumors developed in animals which received feed supplemented only with PVP.

In 1979, the International Agency for Research on Cancer (IARC) issued a monograph which evaluated the carcinogenic risk of PVP (IARC 1979). The cancer studies cited in the monograph are summarized in Table 3. Based on these studies, the IARC working group concluded "the available data do not permit an evaluation of the carcinogenicity of ... Polyvinyl Pyrrolidone to humans. The *limited evidence* of the carcinogenicity of PVP in experimental animals, together with the widespread human exposure to both compounds, suggest the need for epidemiological studies and for animal studies using the dermal, inhalational, and oral routes." In a 1987 update of the earlier monograph, PVP was classified as a "group 3" agent (IARC 1987). That is, "not classifiable as to its carcinogenicity to humans." A review by Robinson et al. (1990) of these same studies as well as of others conducted earlier concluded "the local administration of PVP results in the development of sarcomas (a 'foreign body' type reaction) but no metastases."

CLINICAL ASSESSMENT OF SAFETY

Intravenous Toxicity

In their review, Robinson et al. (1990) summarized the findings of early literature concerning human exposure to PVP via the intravenous route. These publications reported "storage disease" in humans who had received > 70 g of PVP (when it was used as a plasma expander). "Foam cells and/or deposits of vacuolar amorphous clumps" were observed in spleen, bone marrow, kidneys, and liver. The storage observations were related to dose and MW. Robinson et al. (1990) noted that the same effects were observed following administration of dextran, sucrose, and gelatin. Prolonged high-dose administration of PVP has been associated with "marginal alterations" of liver function. Robinson et al. (1990) also cited studies in which PVP storage and foreign body reactions were mistakenly diagnosed as malignant tumors.

In early studies, terms such as Dupont-Lachapelle disease, cutaneous storage syndrome, or cutaneous thesaurismosis were used to describe storage following s.c. or i.m. administration of at least 200 g of PVP. Again, storage was dependent on MW and dosing conditions (frequency, site of injection). Storage was noted in lymph nodes, kidneys, liver,

Table 3. Carcinogenicity Studies on polyvinylpyrrolidone cited in IARC monograph (1979)

Animal (no. and strain)	Dosage/route	Results	Comments	Reference
Subcutaneous				
S50 C57BL mice	Implant of 200 mg of powder of PVPs I, II, III, IV[a] surviving animals were killed after 23 months	PVP IV: 1/50 reticulum-cell sarcoma. PVP II: 3/50 lymphosarcomas. None noted among 75 untreated controls		Hueper 1957
30 C57BL mice	Implant of 200 mg of powder, MW of 10,000	No tumors detected during 2 years of observation		Hueper 1959
30 female Bethesda black rats	500 mg of powder, implanted of PVPs I, II, III, and IV	PVP IV: 1/30 squamous-cell carcinoma of skin at site of implantation. 14 benign and 24 malignant neoplasms were observed in treated animals after 26 months (see comments). Of 23 controls (observed for 13 months), 1 developed reticulum-cell sarcoma[b]	Tumors observed in treated animals were mainly RES sarcomas[b], adenocarcinomas or squamous-cell carcinomas of the uterus and adenocarcinomas of the ovary. These were similarly distributed among groups I, III, and IV (none were found in those treated with PVP II)	Hueper 1957

20 female Bethesda Black rats 30 female Bethesda black rats	Implant of 500 mg of powder, MW of 10,000 1–3 implants of 300 mg of powder, MW of 50,000	4 reticulum-cell sarcomas Reticulum-cell sarcomas developed in 5/30 receiving a single implant and 2/30 receiving repeated implants	Malignant tumors reticulum-cell sarcomas and carcinomas of the uterus were found in 17/200 untreated controls	Hueper 1959 Hueper 1959
20 Osborne-Mendel rats and 10 male Bethesda black rats	1 ml s.c. injections of 6% PVP in water weekly for 73 weeks	Injection site sarcomas in 13/30; none observed in rats given 0.9% saline solutions		Lusky and Nelson 1957
Intraperitoneal				
Groups of 50 C57BL mice	i.p implants of 200 mg of powder of PVPs I, II, III, and IV	In 23 months: PVP II: 1 lymphosarcoma. PVP III: 2 lymphosarcomas, 1 reticulum-cell sarcoma	None seen 75 controls	Hueper 1957
PV30 C57BL mice	200 mg implant, MW of 10,000	1 lymphoma and 1 mesothelioma of the pericardium		Hueper 1959

(*Table continued on next page.*)

Table 3. Carcinogenicity Studies on polyvinylpyrrolidone cited in IARC monograph (1979) (*continued*)

Animal (no. and strain)	Dosage/route	Results	Comments	Reference
30 Bethesda black rats	i.p. implant of 500 mg of powder of PVPs I, II, III, and IV	PVP I: 1 squamous-cell carcinoma at incision site. A total of 13 benign and 29 malignant neoplasms were found in treated animals (see Comments). One reticulum-cell sarcoma noted among 23 controls observed for 13 months[b]	Tumors seen in treated animals were mainly RES sarcomas, adenocarcinomas and squamous-cell carcinomas of the uterus	Hueper 1957
20 female Bethesda black rats	Injection of 10,000 MW PVP	3 reticulum-cell sarcomas in treated rats	Malignant tumors, mostly reticulum-cell sarcomas and carcinomas of the uterus were found in 17/200 untreated controls	Hueper 1959
Groups of 20-35 female NIH black rats	(A) 2 g PVP average MW 10,000 (max MW: 38,000). (B) 2 g PVP average MW 18,000 (max MW: 80,000). (C) and (D) 15 g of 2 types of PVP (each of MW of 50,000) [Note: IARC described dose as 9 g]	Cancers observed in treated animals were identical or very close in number, location and structure to those seen in untreated controls.		Hueper 1961

Intravenous				
15 female rats	8 injections of 2.5 ml of a 7% solution of PVPs I, II, III, and IV (weekly intervals)	2 benign and 14 malignant tumors (10 were RES sarcomas) occurred at different sites.	1 reticulum-cell sarcoma noted among 23 untreated controls in 13 month observation period[c]	Hueper 1957
27 Dutch rabbits	PVPs I, II, III, IV, and the two PVPs of MW 50,000 were injected as 7% saline solutions for a total dose of between 22,000–56,000 mg in the different groups	No tumors seen within 4 years.		Hueper 1961

[a]PVP I, average MW 20,000; PVP II, average MW 22,000; PVP III, average MW 50,000; PVP IV, average MW 300,000
[b]RES sarcomas: lymphosarcomas, reticulum-cell sarcomas, Kupffer cell sarcomas
[c]IARC working group noted the short observation period for controls

spleen, bone, and bone marrow (Robinson et al. 1990). Parenterally administered PVP accumulated in neoplastic tissue. In discussion of these studies, Robinson et al. (1990) considered selective concentration of PVP by monocytes/macrophages to occur when the renal excretory system was overwhelmed by injections of very large amounts of material.

Inhalation Toxicity

In the early literature, several reports asserted a relation between use of hair sprays and pulmonary toxicity. Bergmann, Flance, and Blumenthal (1958) reported that women who used hair spray daily for 2 to 3 years had x-ray abnormalities which disappeared after discontinuation of hair spray use. Later, Bergmann et al. (1962) reported observations varying from slight hyperplasia to marked granuloma formation resembling sarcoidosis in lymph node biopsies of six of twelve patients who had used hair sprays. Robinson et al. (1990) reported on literature from 1958–1972 including eleven epidemiologic studies of hair dressers, totaling 2155 individuals. Twelve cases of tissue storage were recorded, eleven of which were in a single study. They state that identifiable material should be detected in the lungs or lymph nodes before a diagnosis of storage disease can be made. In their review, Robinson et al. (1990) did not consider any of these studies to report "unique pulmonary effects following the inhalation of PVP sprays."

Ocular Toxicity

The anterior chamber was reformed with 25% PVP K-60 (MW 160,000) in salt solution after 124 cataract extractions. No postoperative infections occurred and no evidence of corneal edema was observed. Twelve patients developed small hyphemas within the first 10 postoperative days which cleared quickly and without sequellae. After slit-lamp examination, it was found that in all but one case, the PVP had disappeared from the anterior chamber 1 day after surgery; in the one exception, it disappeared after the third day. Further, in the six cases where the vitreous had been lost during the cataract extractions, no complications were noted with the mixing of vitreous and PVP. Follow-up examinations done from 1 month to 2 years postsurgery found no evidence of PVP-related complications. The investigators also reported no PVP-related complications in 25 cases of penetrating keratoplasties and eight cases of open angle glaucoma where the 25% PVP K60-balanced salt solution was used to restore the anterior chamber (King and McTigue 1964) Similar findings were reported by Sarda, Makhija, and Sharma (1969).

Dermal Irritation and Sensitization

Shelanski and Shelanski (1956) reported no dermal irritation in 200 panelists after 96 hours of contact with a patch containing PVP-iodine (10% PVP and 2% iodine). After 2 weeks, the patches were reapplied for 48 hours. No reactions were noted.

In three studies, groups of 20 panelists received a single occlusive patch of a foundation containing 2.0% PVP. One to two panelists in each group had minimal faint uniform or spotty erythema. The Primary Irritation Indexes for the three studies were 0.03, 0.03, and 0.05, respectively (CTFA 1993).

There are various published case reports of contact dermatitic reactions to the PVP-iodine antiseptic. In those cases in which patch testing of the individual components was performed, iodine was determined to be the sensitizer (Ancona 1985; Lachapelle 1984; Marks 1982; Torinuki 1990; Tosti et al. 1990). However, a different conclusion was reported by van Ketel and van den Berg (1990) who patch tested eight individuals with contact eczema to PVP-iodine. Positive reactions were noted to 5 or 10% PVP-iodine in petrolatum or to the commercial PVP-iodine solution, ointment, or scrub, but negative reactions were noted in 5 of 8 individuals also tested with 5–20% potassium iodide in petrolatum. Further, no positive reactions were observed in three of the eight who were open tested with iodine tincture. The researchers ruled out iodine as the cause of sensitization.

Repeat Insult Patch Test

A human Repeat Insult Patch Test (RIPT) was conducted by Shelanski and Shelanski (1956) using 100 panelists. During induction, patches containing PVP-iodine (10% PVP, 2% iodine) were applied for 24-hour contact, every other day for 15 applications. No reactions were noted during induction. After a 3-week nontreatment period, a 48-hour challenge patch was applied. PVP-iodine "elicited no subjective complaints and no visible reactions." Although details were not provided, the investigators reported that the study was also conducted on human skin which had been purposely abraded with coarse sandpaper. The findings were similar to those observed in intact skin with no development of infection (the abrasions were healed or healing when the patches were removed).

In an exaggerated-use study, the Draize-Shelanski patch technique was used to test powder PVP K-30 on 150 panelists. Within the 21-day induction period, nine moistened occlusive patches containing PVP were applied to the same site (usually the upper back) on panelists. Patches were removed after 24 hours, and the site was graded for irritation. A 10-day nontreatment period followed induction. At challenge, a single 24-hour occlusive patch was applied to an area adjacent to, but not in

contact with, the induction area. The challenge site was evaluated at the time of patch removal and after an additional 24 and 48 hours. During induction, "slight" reactions (graded as 2, maximum score 8) were noted at one isolated observation in five panelists (0.35% incidence). No reactions were noted at challenge (Toxigenics Inc. 1981).

PVP K-30 was tested as a 10% aqueous solution in an RIPT on 27 panelists (5 male and 22 female; age range 20–59). During the 3-week induction period, nine 24-hour occlusive patches were applied to an area of the arm. Patches were applied every other day and the site was evaluated prior to application of successive patches. Following a 2-week nontreatment period, panelists were challenged at a previously unexposed site with a 24-hour occlusive patch of the test material. The challenge site was evaluated at the time of patch removal and after an additional 24 and 48 hours. No reactions were noted during induction or challenge (Harrison Research Laboratories, Inc. 1983b).

Maximization Test

A clinical maximization assay tested a foundation containing 2.0% PVP on 25 healthy panelists (Ivy Laboratories 1993). The test consisted of three phases: pretesting, induction, and challenge. During pretesting, an occlusive patch containing the test material (0.1 ml) was applied for 48 hours of skin contact. As no irritation was noted in any of the panelists at the time of patch removal, sodium lauryl sulfate (SLS) was used in the induction phase. During induction, 1% of SLS (0.1 ml) was applied under an occlusive patch for 24 hours. The patch was then removed and replaced with a 48-hour patch containing the test substance. If no irritation was observed at the time of patch removal, the same protocol was repeated for a total of five induction exposures. Following a 10-day nontreatment period, panelists were challenged with a single 48-hour patch of the test substance placed on previously unexposed skin site (pretreatment with a 10.0% SLS patch applied for 1 hour was done prior to challenge). The challenge site was evaluated at 1 and 24 hour after patch removal. No instances of contact allergy were observed.

Phototoxicity

A 24-hour patch containing a 10% aqueous solution of PVP K-30 was applied to both volar forearms of ten panelists (2 male and 8 female; age range 18–50). One arm was irradiated with UVA light from four F40 BL Fluorescent tubes (source emits $\sim$ 3.3 J/cm^2 at a distance of 10 cm). Care was taken to avoid irradiating the other arm during the study, and panelists were cautioned against sunlight exposure during the test period. Arms were scored immediately after irradiation and after an additional 24 and 48 hours. No reactions were noted (Harrison Research Laboratories, Inc. 1983a).

Photoallergenicity

A 10% aqueous solution of PVP K-30 was tested for induction of photosensitivity by immunologic pathways (in such cases, the absorption of ultraviolet energy is required for the formation of the hapten or complete antigen). During the 3-week induction period, nine 24-hour occlusive patches containing 0.2 ml of the test material were applied to both forearms of 31 panelists (3 male and 28 female; age range 24–63). One arm of each panelist was irradiated with UVA and UVB light following each patch removal. Arms were irradiated for 15 minutes with UVA light emitted from four F40 BL Fluorescent tubes (source emits ~ 3.3 J/cm^2 at a distance of 10 cm). Length of exposure to UVB light (from a Solarium 300 lamp which emits 1.4 mJ/cm^2/sec at a distance of 20 cm) was dependent on skin type and varied from 75–105 seconds. Both arms were scored immediately before and after irradiation of the designated arm. A 2-week nontreatment period followed induction. At challenge, 24-hour patches were applied to a previously untreated site on each forearm. The challenge site of the designated arm was irradiated at the time of patch removal. Challenge sites on both arms were evaluated after patch removal, after irradiation, and at 48 and 72 hours postpatching. During induction, all panelists had slight reactions (graded as minimal erythema or erythema and/or slight edema) at the irradiated (test material applied) site. Similar reactions were noted at the control (no test material applied) irradiated site. Tanning of the irradiated arm was noted. At one induction observation, minimal erythema was noted in one panelist at the nonirradiated (test material) site. No reactions were noted at challenge. PVP K-30 did not induce contact dermal photoallergy or contact dermatitis sensitization (Harrison Research Laboratories, Inc. 1983c).

SUMMARY

PVP is a linear polymer consisting of 1-vinyl-2-pyrrolidone monomers. The monomer has a MW of 111.1; the polymer can range from 10,000–700,000. The viscosity of PVP solutions, expressed as a K-value, gives an indication of the average MW of polymers present. Typically, PVP K-30 (average MW 40,000) is used in cosmetic formulations, food additives, and pharmaceutics.

The World Health Organization (WHO) set an ADI for PVP of 0–25 mg/kg. The USP specifies that pharmaceutical grade PVP cannot contain more than 1 ppm hydrazine. PVP has been associated with iodine to form the antiseptic Betadine.

PVP is used in cosmetic formulations as a binder, emulsion stabilizer, film former, hair fixative, and suspending agent–nonsurfactant. In January 1996, there were 395 reported cosmetic uses. PVP is used in cosmetic formulations up to 35%.

PVP induces a thymus-independent immune response, but local injection does not transform lymphocytes.

The absorption, distribution, metabolism, and excretion of PVP is dependent on MW, amount and frequency of dosing, and route of administration. PVP is taken up by cells of the monocyte/macrophage system via either pinocytosis or phagocytosis. Polymers with a weight < 25,000 are eliminated through the kidneys. An oral dosing study using 0.9 mg per rat of PVP K-30 found no significant absorption.

The oral LD_{50} of PVP K-30 is >100 g/kg body weight for both rats and guinea pigs. Neither toxic effects nor gross lesions attributable to PVP were found in rats maintained for 2 years on a diet containing up to 10% PVP K-30. A similar 2-year feeding study in dogs found swollen phagocytic cells in the lymph nodes. In two short-term inhalation studies using rats, PVP was detected in lung samples but no inflammatory response was noted. Mild lymphoid hyperplasia and fibroplasia were noted in the subpleural, perivascular, and peribronchial lymphatics. A 3-month inhalation study using rats and testing the PVP monomer determined a no observable adverse effect level of < 5 ppm.

In ocular studies using rabbits, a 10% PVP-iodine solution (without detergent) was minimally toxic, whereas repeated dosing with 0.5% PVP-iodine was nonirritating. A 10% PVP-iodine solution caused neither dermal irritation nor sensitization in rabbits.

No teratogenic effects were observed when up to 500 μg of PVP (MW 11,500) was injected into the yolk sac of rabbits. PVP was negative in the majority of mutagenicity studies conducted. Orally administered PVP significantly decreased the rate of bladder tumors in mice exposed to bracken fern. IARC classified PVP as a "group 3" agent, "not classifiable as to its carcinogenicity in humans." Implantation of PVP sponges into mice and rats resulted in development of local sarcomas, but without metastases.

Early literature reported "storage disease" in humans given large doses of PVP via the i.v., i.m., or s.c. routes. There also existed an unproven hypothesis relating hair spray use with pulmonary thesaurosis. In clinical studies, PVP K-30 did not induce either sensitization or a phototoxic response.

DISCUSSION

In reviewing the available data, the CIR Expert Panel elected not to delete studies on the PVP-iodine complex. The Panel acknowledged that although the complex is a separate entity from the polymer, the majority of studies done on the complex demonstrated its safety. Because fewer adverse effects would be expected from PVP compared to the PVP-iodine

complex, the Panel was confident that studies conducted on the PVP-iodine complex supported the safety of PVP.

Animal toxicity studies conducted on PVP supported its safety. Further, in a clinical sensitization study, PVP K-30 powder did not induce sensitization in any of 150 panelists. The Panel decided that PVP is safe for use in cosmetics.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that PVP (polyvinyl pyrrolidone) is safe as used in cosmetics.

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