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Final Report on the Safety Assessment of Polyacrylamide

Polyacrylamide is a polymer of controllable molecular weight formed from the polymerization of acrylamide monomers. Average concentrations of the monomer were reported as less than 0.01% by several manufacturers. Polyacrylamide is used as a foam builder and stabilizer in shampoo products and as a vehicle in sunscreen preparations.

An acute oral toxicity study of Polyacrylamide in rats reported that a single maximum oral dose of 4.0 g/kg body weight was tolerated. In a subchronic oral toxicity study in both rats and dogs, animals were given a maximum dose of 464 mg/kg body weight, with no signs of toxicity in any animals. Two separate studies in rats reported no absorption when the compound was administered by gavage. In a 2-year chronic oral toxicity study, rats fed between 500 and 10,000 ppm in their diet had no significant adverse effects. Similar results were obtained in dogs. A 2-year feeding study in rats fed up to 5.0% Polyacrylamide reported no significant adverse effects.

Cutaneous tolerance tests performed to evaluate the irritation of Polyacrylamide indicated that the compound was relatively well tolerated. Undiluted Polyacrylamide applied to the conjunctival sac of the rabbit caused a very slight response.

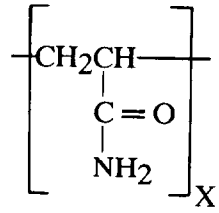
No compound-related lesions were noted in a three-generation reproductive study in which rats were fed either 500 or 2000 ppm Polyacrylamide.

On the basis of data presented in this report, it is concluded that Polyacrylamide, with less than 0.01% acrylamide monomer content, is safe as a cosmetic ingredient as currently used.

CHEMICAL AND PHYSICAL PROPERTIES

Definition and Chemical Structure

Polyacrylamide is the polymer formed from the polymerization of acrylamide monomers that generally conforms to the formula:[1]



Polyacrylamide

A synonym of Polyacrylamide is 2-Propenamide, Homopolymer. Polyacrylamide is a white, granular, solid that is practically odorless.[2] Polyacrylamide is soluble in water, slightly soluble in glycerol, ethylene glycol, and lactic acid, but is insoluble in ethanol, methanol, and ether.[3] When Polyacrylamide is prepared by polymerization of acrylamide at pH 9 or above, the polymers generally are water soluble. The amide groups give Polyacrylamide a highly hydrophilic character in this state. When polymerization takes place at pH 2.5 or below, the resulting Polyacrylamide is not water soluble. In its cross-linked form, Polyacrylamide is defined as "water-swollen" rather than water soluble.[4–6]

The molecular weight of Polyacrylamide is controllable; experimental conditions can produce specific desired weights. The molecular weight for documented cosmetic preparations of Polyacrylamide is 30,000 to 12 million.[7]

When using small quantities of this material, high viscosities may be obtained in aqueous systems.[6,7] A 1% aqueous solution of a cosmetic formulation containing Polyacrylamide had a pH of 6.5. Aqueous solutions of Polyacrylamide are stable over a pH range of 3 to 10, with little effect of viscosity.[6]

The chemical and physical properties of Polyacrylamide are summarized in Table 1.

ANALYTICAL METHODS

In the infrared absorption spectra of Polyacrylamide, specific absorptions are exhibited at wave numbers 3310 cm^{-1}, 3140 cm^{-1}, 1610 cm^{-1}, and 1420 cm^{-1} using the potassium bromide disk method.[2]

Reactivity

Vinyl polymerization of acrylamide monomers yields a variety of homopolymers and copolymers of controllable molecular weight and performance characteristics.[6]

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF POLYACRYLAMIDE

Property	*Description*	*Reference*
Physical form	White, granular solid	2
Molecular weight	Controlled by experimental conditions, cosmetic grade 30,000–12,000,000	7
Odor	Odorless	2
Viscosity (dynes/cm)		
2% solution	3.1×10^{-4}	7
5% solution	2.6×10^{-3}	
8% solution	7.7×10^{-3}	
pH		
(1% solution)	6.5–6.8	6
Solubility		
Polymerized at pH 9 or above	Polymers water soluble	4,5
Polymerized at pH 2.5 or below	Polymers not water soluble	
Cross-linked form	Polymers not water soluble but water swollen	

Polymers produced from the homopolymerization of the monomer are anionic, and polymers produced from the co-polymerization of the monomer are anionic. These polymerization reactions normally reach 98% completion and can occur in aqueous solutions as well as oil emulsions. In the presence of free radicals, acrylamide is readily polymerized.[4]

Polyacrylamide is chemically inert and nontoxic in enzyme carrier systems, but the polymer is subject to hydrolysis and increased viscosity when stored at pHs above 10.[7,8]

When dissociation occurred, the products of Polyacrylamide were generally smaller fragments of the polymer.[9] The resistance of Polyacrylamide to biodegradation resulted from the large molecular weight and the presence of amide groups on the molecule.[10]

IMPURITIES

The impurity of most concern in Polyacrylamide is the residual monomer, acrylamide. Because of the documented neurotoxic effects and carcinogenicity of acrylamide, the relevant information concerning the monomer is an important consideration in the safety assessment of Polyacrylamide.

In studies on Polyacrylamide,[11] the average concentrations of acrylamide in Polyacrylamide formulations were found to be less than 0.01%. Several current manufacturers of Polyacrylamide list a maximum of 0.1% for residual acrylamide monomer content.[12]

Complete analysis of acrylamide is documented in the World Health Organization (WHO) report on Acrylamide.[13] The carcinogenicity is reviewed by the International Agency for Research on Cancer[14] and by Abernathy et al.[15]

USE

Cosmetic Use

Polyacrylamide was contained in 43 cosmetic formulations voluntarily reported in 1984 to the Food and Drug Administration (FDA) by the cosmetic industry.[16] Reported concentrations of Polyacrylamide in these preparations of miscellaneous hair, nail, and skin care products, including hair dyes, hair colors, and paste masks, were $\leq 1\%$ (Table 2). The updated frequency of use data provided by the FDA grouped 43 products in the concentration range of $\leq 1\%$[17] (Table 3).

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators must conform to the format of concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[18] Since certain cosmetic ingredients are supplied to the formulator at less than 100% concentration, the concentration reported by the formulator may not necessarily reflect the actual concentration found in the finished cosmetic product. The actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of a "concentration range" provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of the concentration range is considered the same as one entered at the highest end of

TABLE 2. PRODUCT FORMULATION DATA FOR POLYACRYLAMIDE[16]

Product category	Total No. containing ingredient	No. of product formulations within each concentration range (%)	
		0.1–1	0–0.1
Hair dyes/colors (requiring caution statements)	24		24
Hair rinses (coloring)	11		11
Face/hand/body (excluding shaving preparations)	1		1
Moisturizing products	3	1	2
Paste masks (mud packs)	1	1	
Other skin care preparations	1	1	
Suntan gels/creams/liquids	2		2
1984 Totals	43	3	40

that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

In cosmetic preparations, Polyacrylamide is used as a foam builder and stabilizer for shampoos and foam baths. Additionally, it is used in sunscreen preparations to aid in retaining sunscreen on the skin after immersion in water. Polyacrylamide is used to impart lubricity and emolliency to many cosmetics and soaps, including moisturizing lotions, hand and body lotions, shaving creams, and soaps.[5,19–26]

Cosmetic products containing Polyacrylamide may be applied to all areas of skin. Application of products containing this ingredient to the face has the potential to come in contact with the eyes. Products containing Polyacrylamide may be applied several times, and may be in contact with the skin for several hours. A limited number of products may be used daily.

Noncosmetic Use

Polyacrylamide has a wide range of uses in industry as well as in biomedical research. It is used as a thickening and suspending agent in waste water treatment and

TABLE 3. PRODUCT FORMULATION DATA FOR POLYACRYLAMIDE[17]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)	
			>0.1–1	≤0.1
Hair colors, rinses, and conditioners	1613	41	1	40
Nail and skin care cosmetics	2649	7	4	3
1989 Totals		48	5	43

soil stabilization, and also is used as a strengthener in production of paper. The biomedical uses include ophthalmic drug inserts, tissue implant materials, tissue models, body fluid models, detectors of penicillin antibodies and hypersensitivity, carriers of hormones and drugs in animal studies, and as an environment for the growth of tumor cells in culture. The polymer also is used in the research laboratory for separation and purification of biomaterials.[20,27–36]

Polyacrylamide may be used safely as a film former in the imprinting of soft-shell gelatin capsules when the polymer does not contain more than 0.2% acrylamide monomer. Modified Polyacrylamide resin may be used safely in food in accordance with appropriate limitations. Use of Polyacrylamide as an indirect food additive and a component of adhesives and coatings is safe, provided that the prescribed limitations of acrylamide monomer content are followed. As a component of the coated or uncoated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, packing, processing, preparing, transporting, and holding of dry food, the use of Polyacrylamide also is subject to specific regulations.[18]

International Use

Polyacrylamide has been approved for use in cosmetic formulations marketed in Japan.[37]

BIOLOGY

Absorption and Excretion

Three female albino rats were given aqueous ^{14}C-Polyacrylamide by gavage in doses of 10 mg/2 ml H_2O, 37.5 mg/3 ml H_2O, and 75 mg/4 ml H_2O. The animals were then observed for 24 h. The results of the radioactivity analyses were presented as percent of total dose fed to each animal. No radioactivity was observed in any of the 3 rats. However, the validity of the detection of a trace of radioactivity found in the urine of the rat fed the highest dose was questioned by the investigator, and determined to be a result of possible contamination. When the amount of radioactivity found in the feces and gastrointestinal tracts of the 2 animals fed the lower doses was taken into account, there was a 97.6% recovery of the total dose in those 2 animals. ^{14}C-Polyacrylamide (molecular weight not stated) was not absorbed and, therefore, was not broken down into a lower molecular weight compound. The Polyacrylamide polymer was too large to pass through the walls of the gastrointestinal tract, and the molecule was not split in any manner allowing absorption.[38]

In a similar study by McCollister et al.,[3] in which an unspecified number of rats were fed 250 mg/kg or 500 mg/kg ^{14}C-Polyacrylamide by intubation, no radioactivity was observed in any of the animals. The total amount of radioactivity recovered from the feces and gastrointestinal tract of the animals was 98.2% of the original dose.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

In a 2-week study, groups of 2 to 6 female Dow-Wistar rats were fed preparations of nonionic and anionic Polyacrylamide by intubation. The single oral doses were 0.25,

0.5, 1.0, 2.0, and 4.0 g/kg body weight, either as a 10% or a 20% suspension in water or corn oil. All animals survived a maximum single oral dose of 4.0 g/kg body weight. The LD_{50} was not reached.[3]

A single oral dose of 4 g/kg body weight of Polyacrylamide produced no deaths in any female rats tested by Dow. The LD_{50} was not reached.[11]

A formulation of Polyacrylamide was fed by intubation in single oral doses to small groups of female rats. The number of animals ranged from 2 to 6 per group. The concentrations fed to the animals were 0.252, 0.500, 1.00, 2.00, and 3.98 g/kg body weight in corn oil or water. After a period of 2 weeks, no dose-related lesions were seen in the rats that received 1.0 g/kg body weight and below. One of the rats that received 2.0 g/kg died. At necropsy, very slight fatty change was found in the liver. The single animal fed the 3.98 g/kg dose died before the end of the initial 24-h observation time. The marked swelling and bulking of the Polyacrylamide formulation might have caused mechanical blockage that may have been responsible for the death of the animal.[11]

Subchronic Oral Toxicity

The toxicity of modified Polyacrylamide resins has been tested in feeding studies using both rats and dogs. The number of animals in the studies was not indicated. The animals were given a maximum dose of 464 mg/kg body weight without any signs of toxicity in either species. Concentrations of 500, 2000, 10,000, and 50,000 ppm were fed to rats for 90 days without alterations in growth rate, mortality, urinalysis, hematological findings, gross lesions, and microscopic findings. Dogs fed 500 or 2000 ppm Polyacrylamide for 90 days did not have any abnormal findings.[39]

Chronic Oral Toxicity

Rats were fed 500, 2000, or 10,000 ppm Polyacrylamide in their diet in a 2-year feeding study. No significant adverse effects were reported. The results from a similar study in which dogs were fed the same concentrations of Polyacrylamide demonstrated no adverse effects at the two lower doses. The number of animals tested was not indicated.[39]

Groups of 20 female and 20 male rats were fed diets containing either a 1.0 or a 5.0% Polyacrylamide formulation for a period of 2 years. Throughout the 2 years of observation, there were no significant changes in the appearance or behavior of any of the rats.[3]

Two different formulations of Polyacrylamide were fed to groups of 4 beagle dogs in 1- and 2-year feeding studies. During these studies, all dogs were normal in appearance and behavior.[3]

No toxic effects or significant lesions were found in 20 female and 20 male rats that were fed a diet containing either 1.0 or 5.0% Polyacrylamide. The only effect of any significance was a slight decrease in growth rate observed in both male and female rats receiving a 5.0% dietary formulation of Polyacrylamide.[40]

In an additional feeding study, groups of rats (number of animals reported in experimental design of Central Medical Department Report 60.6) were fed either 2.5, 5.0, or 10.0% Polyacrylamide for 2 years. No compound-related lesions were found.[40]

Three groups of beagle dogs, 4 per group, were fed diets containing either 1.0 or 5.0% Polyacrylamide, which contained 0.01% acrylamide monomer. No adverse effects were found when compared to the untreated controls.[41]

Two groups of beagle dogs, 4 per group, were fed dietary concentrations of either 2.5 or 5.0% Polyacrylamide for 2 years. No compound-related lesions were detected.[42]

Dermal Irritation

Cutaneous tolerance tests were performed to evaluate the irritation of synthetic polymers, including Polyacrylamide, in cosmetic formulations. The tests were performed according to the protocols described in the *Journal Officiel de la Republique Francaise*. After 24 h, a 5% (w/w) preparation of Polyacrylamide was relatively well tolerated.[43]

A 0.5 ml suspension of Polyacrylamide (0.5–2% w/w) in TEA-Stearate, an ionic oil and water emulsion, at concentrations close to those found in actual cosmetic preparations, was applied to intact and scarified clipped skin of 6 male New Zealand White rabbits for 24 h. Of the 17 gelling agents, polymers, and thickeners tested, Polyacrylamide was the least irritating at a 2% concentration. Previous data also indicated that tolerance to the polymer was rated as good to very good.[44]

Ocular Irritation

A small amount of an undiluted formulation of solid Polyacrylamide (molecular weight not stated) was placed in the right conjunctival sac of one rabbit, and the eye was washed 30 sec later. The left conjunctival sac of the same rabbit was treated with the same amount of solid Polyacrylamide without subsequent rinsing. There was no indication of corneal or conjunctival irritation when each eye was observed immediately after treatment, and then again within 2 or 3 min. A very slight conjunctival response, indicated by prominent capillaries, was observed in the unwashed eye after 1 h. At 24 h after treatment, both eyes were normal.[11]

Ocular irritation tests were performed on male white albino rabbits; the number of animals was not indicated. A 2% aqueous solution of fluorescein was used to help evaluate the extent of surface damage and corneal opacity. Ulceration and granulation also were measured. The results were scored at 1 h, 24 h, and 2, 3, 4, and 7 days. Polyacrylamide, at a concentration of 5% w/w, did not provoke significant injury to ocular membranes.[43]

Reproductive Effects

A three-generation reproduction study was performed on rats fed 500 or 2000 ppm Polyacrylamide. The number of animals in the study was not indicated. Normal reproductive functions, such as mating index, incidence of pregnancy and parturition, and gestation time, were recorded for the first and second generations. Body weight, growth rate, behavioral reactions, skeletal structure, and mortality rates were normal for both the parent rats and their progeny. No compound-related lesions were noted.[39]

CLINICAL ASSESSMENT OF SAFETY

Occupational Exposure

Chronic environmental studies carried out in Polyacrylamide production plants over a period of 5 years indicated that workers were being exposed to polymer dust through inhalation. Average airborne concentrations of the polymer were reported to be 1 mg/m^3. Approximately 5 mg/day of the dust, with a diameter greater than 50 μm per particle, had the potential to be trapped in the upper respiratory passages and swallowed. The data from physical examinations conducted from 1952 through 1959 and in 1962 had no indication of unusual pathological response. The number of men examined was not indicated. The results of these medical examinations showed no indication of adverse effects caused by exposure to Polyacrylamide dust.[3]

Research employees from a development and pilot plant and employees who worked on full-scale production of Polyacrylamide were examined periodically in tests designed to include any diagnostic test or procedure necessary to indicate any possible effects of Polyacrylamide exposure and to evaluate the general health of the study participants. The data from 162 examinations of 106 men who worked with Polyacrylamide did not indicate any abnormal effects from exposure to Polyacrylamide encountered in the research, development, or manufacturing processes. There was no indication of more disease than one might expect to find in a group of similar men in the general population.[45]

SUMMARY

Polyacrylamide is a polymer of controllable molecular weight formed from the polymerization of acrylamide monomers. Polymers can have different chemical characteristics based on the pH at polymerization. Polyacrylamide is chemically inert in enzyme systems and generally is stable. Dissociation of the compound usually leads to the formation of smaller fragments of the polymer. Acrylamide monomer is an impurity of concern in formulations containing the polymer. Average concentrations of the monomer were reported as less than 0.01% by several manufacturers. Polyacrylamide is used as a foam builder and stabilizer in shampoo products and as a vehicle in sunscreen preparations. Polyacrylamide is used to impart lubricity and emolliency to soaps, moisturizing lotions, hand and body lotions, and shaving cream. Polyacrylamide formulations are applied to all skin surfaces and may remain in contact with the skin for several hours.

Because of the large sizes of Polyacrylamide polymers, absorption of the compound does not occur. Two separate studies in rats reported no absorption when the compound was administered by gavage.

An acute oral toxicity study of Polyacrylamide in rats reported that a single maximum oral dose of 4.0 g/kg body weight was tolerated.

In a subchronic oral toxicity study in both rats and dogs, animals were given a maximum dose of 464 mg/kg body weight, with no signs of toxicity in any animals.

In a 2-year chronic oral toxicity study, rats fed between 500 and 10,000 ppm in their diet had no significant adverse effects. The same results were obtained in dogs in the same study. A 2-year feeding study in rats fed up to 5.0% Polyacrylamide reported no significant adverse effects. In 1- and 2-year feeding studies of Polyacrylamide in

beagle dogs, no significant changes were observed in either behavior or appearance. No toxic effects or significant lesions were found in rats fed diets containing up to 5.0% Polyacrylamide. Three groups of beagle dogs fed diets containing Polyacrylamide with 0.01% acrylamide monomer had no adverse effects. No compound-related lesions were found in beagle dogs fed dietary concentrations of 2.5 or 5.0% Polyacrylamide in a 2-year feeding study.

Cutaneous tolerance tests performed to evaluate the irritation of Polyacrylamide indicated that the compound was relatively well tolerated. Skin irritation tests of Polyacrylamide applied to the intact and scarified skin of rabbits showed that the compound was the least irritating of all the compounds tested. Tolerance of the compound was rated as good to very good.

Undiluted Polyacrylamide applied to the conjunctival sac of the rabbit caused a very slight conjunctival response, indicated by prominent capillaries. At 24 h post-treatment, the conjunctival sac was normal. Ocular irritation tests of Polyacrylamide on rabbits, using fluorescin to evaluate the extent of surface damage and corneal opacity, reported that 5% (w/w) Polyacrylamide did not provoke significant injury to ocular mucous membranes.

No compound-related lesions were noted in a three-generation reproductive study in which rats were fed either 500 or 2000 ppm Polyacrylamide.

Chronic environmental studies were carried out in Polyacrylamide production plants over a period of 5 years. No adverse effects were discovered in workers exposed to polymer dust. Medical examinations were made of employees exposed to Polyacrylamide at a full-scale production plant. No indication of more disease than one might expect to find in a group of similar men in the general population was found.

DISCUSSION

The Expert Panel is aware that there is a lack of human data concerning the effects of Polyacrylamide. However, in absorption studies, cosmetic formulations containing Polyacrylamide were not readily absorbed because of the large size of the polymers.

Acrylamide monomer, a residual of the polymerization that results in the formation of Polyacrylamide, is an impurity that is of concern. Based on a report by WHO,[13] the Expert Panel stated that Polyacrylamide formulations could be considered safe, provided they did not expose an individual to more than 0.8 mg/day acrylamide.

CONCLUSION

On the basis of data presented in this report, the CIR Expert Panel concludes that Polyacrylamide, with less than 0.01% acrylamide monomer content, is safe as a cosmetic ingredient as currently used.

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