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Final Report of the Safety Assessment of Polyamino Sugar Condensate

Polyamino Sugar Condensate (PSC) is the product of a condensation reaction between amino acids and sugars. It appears in over 100 cosmetic preparations at concentrations up to 1%.

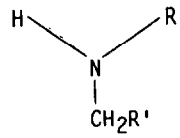
PSC has an acute oral toxicity greater than 5 g/kg in rats. In tests on rabbits, undiluted PSC was not a primary irritant and produced only mild irritation in some animals. Subacute skin irritation was not observed in rabbits when PSC (undiluted) was applied. Human safety data indicate that PSC is nonsensitizing and, at worst, a mild irritant. PSC is also nonphototoxic.

On the basis of the available animal data and limited human experience, it is concluded that Polyamino Sugar Condensate is safe for topical application to humans.

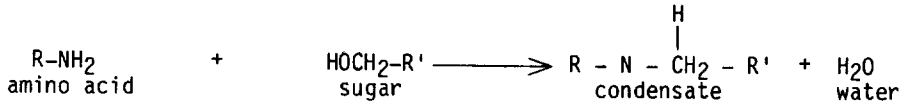
CHEMICAL AND PHYSICAL PROPERTIES

Structure

POLYAMINO Sugar Condensate (PSC) is a sugar-amino acid condensation product which conforms to the following structure:[1]



where R is an amino acid alkyl group and R′ is a monosaccharide ring.
Three patients describe the extraction and/or preparation of the condensate.[2-4] It is prepared commercially by reacting water soluble salts of amino acids with ribose, fructose, and glucose to form N-glycosides at temperatures limited to 63°C. The mixture of amino acids includes alanine, glycine, leucine, proline, serine, threonine, tyrosine, valine, aspartic acid, glutamic acid, arginine hydrochloride, histidine hydrochloride, lysine hydrochloride, and pyroglutamic acid. A typical condensation reaction would proceed as follows:



where R and R′ are as defined above.
Lactic acid is added to form a condensation mixture. Free amino acids, urea, potassium chloride, calcium chloride, and sodium chloride are then added to form the final product.[5]

Polyamino Sugar Condensate was analyzed for sugar, nitrogen and water content. The results are summarized in Table 1.[5]

TABLE 1.[a]

Substance analyzed for	*Content in PSC*
Sugar	8–13%
Nitrogen	7.5–10.5 μmol/mg
Alpha-amino nitrogen	3.0–6.0 μmol/mg
Water (and volatiles)	10–20%

From Ref. 5.

Physical Properties

PSC is a water soluble, brown semisolid with a pH range of 3.9 to 4.3[6,7] No other data describing the compound's physical characteristics have been reported.

Impurities

Impurities in a random lot analysis of PSC were: heavy metal (as Pb), 3.5 ppm; arsenic, 0.01 ppm and mercury, 0.0003 ppm.[6] When a method with a detection limit of 0.1 ppm was used, no nitrite impurities were found in PSC;[8] nitrosodiethanolamine was not present (detection limit = 0.028 ppm) in either a one-year-old or three-year-old sample of PSC.[9] With regard to trace amounts of pyrazines and/or volatile N-nitrosamines in PSC, no analytical data verifying their presence or absence were available.

USE

Purpose in Cosmetics

PSC is a moisturizing agent in cosmetic products, especially makeup and skin care formulations.[1]

Scope and Extent of Use in Cosmetics

According to industry's voluntary submissions to the Food and Drug Administration in 1976, PSC was used in over 100 formulations up to concentrations of 1% (Table 2). It is estimated that over 40,000,000 units containing this ingredient have been distributed in the last 10 years.[7]

BIOLOGICAL PROPERTIES

General Effects

Discussion of the Maillard reaction is included here because of its possible relationship to the production of PSC. The Maillard reaction, a process which occurs during the browning of foods, involves a complexing of amino acids with reducing sugars to form glycosylamino products, rearrangements of which result in stable Amadori compounds. Nutritional and toxicological studies focus on the problems associated with such compounds.[11-15]

Studies have shown products of the Maillard reaction have a particular tendency to nitrosate in the presence of sodium nitrite.[16-18] Heyns[19] found that nitrosopiperdine could be formed when D-glucose and D-lysine react at 105°C in the presence of sodium nitrite. While Devik[16] suggests that dimethylnitrosamine may form upon heating various amino acid-glucose combinations to 104°–105° C, two subsequent studies failed to confirm this.[17,18] Shinohara et al.[20] reported that

TABLE 2. PRODUCT FORMULATION DATA.[a]

Ingredient	*Cosmetic product type*	*Concentration (percent)*	*Number of product formulations*
Polyamino sugar condensate	Other eye makeup preparations	≤0.1	1
	Shampoos (noncoloring)	≤0.1	1
	Blushers (all types)	≤0.1	6
	Face powders	≤0.1	2
	Foundations	>0.1-1	3
		≤0.1	5
	Leg and Body paints	>0.1-1	1
	Lipstick	>0.1-1	1
	Makeup bases	>0.1-1	2
		≤0.1	3
	Rouges	≤0.1	4
	Makeup Fixatives	≤0.1	1
	Other makeup preparations	≤0.1	1
	Cuticle softeners	>0.1-1	1
	Nail creams and lotions	≤0.1	1
	After shave lotions	>0.1-1	1
		≤0.1	
	Cleansing (cold creams, cleansing lotions, liquids, and pads)	>0.1-1	6
	Face, body, and hand (excluding shaving preparations)	>0.1-1	11
		≤0.1	1
	Moisturizing	>0.1-1	19
		≤0.1	7
	Night	>0.1-1	6
		≤0.1	14
	Paste masks (mud packs)	>0.1-1	1
		≤0.1	2
	Skin fresheners	>0.1-1	1
	Other skin care preparations	>0.1-1	5
		≤0.1	3
		Total	111

[a]From Ref. 10.

heating a mixture of glucose and lysine at 100°C for 10 h resulted in a browning product which was mutagenic to *S. typhimurium* TA 100.

Using the Ames test, nitrosated Amadori compounds were determined to be mutagenic in the presence of sodium nitrite or under prolonged heating.[21,22]

In general, the Maillard reaction is favored by specific reaction conditions; these include high temperatures (greater than 100°C), lack of moisture, and high pH, which in general are not expected to occur during the manufacture of PSC.[11]

In the preparation of PSC, the reaction is kept at or below 63°C and in aqueous solution at all times. Lactic acid is added in the final stages of PSC preparation, so that the pH of the product is adjusted between 3.8 and 4.3.[7]

The formation of nitroso compounds from Maillard products requires either heating to a temperature higher than 100°C or those products being in the presence of nitrosating agents. The preparation of PSC is limited to temperatures below 63°C, and analyses indicate that even in material stored up to three years, nitrite (<0.1 ppm) and N-nitrosodiethanolamine (<0.02 ppm) are absent.[8,9]

Absorption, Metabolism, and Excretion

When administered intravenously to humans, heat sterilized glucose–amino acid complexes were completely excreted in the urine; the complexes were not resorbed from the glomerular filtrate. When they were administered by gastric tube, these same substances were not detected in the subjects' blood or urine, indicating a lack of absorption.[13]

An amino acid–glucose mixture was browned at 37°C, stored for one month and then fed to an unspecified number of weanling Sprague–Dawley rats for 22 days. As a result of the unavailability of essential and nonessential amino acids as a nitrogen source for protein building, these rats experienced no weight gain. Moreover, during the experiment the animals also experienced decreased utilization of plasma amino acids; not only was the incorporation of free amino acids into proteins affected, but also the catabolic rates of some amino acids may have been decreased.[23,24]

Animal Toxicology

Acute Oral Toxicity

When administered by gastric intubation, the acute oral LD50 of PSC was determined to be >5 g/kg. This dosage (5 g/kg) was administered to 10 rats, and observations were made at 1, 3, and 6 h and daily for two weeks. During this period, no toxic effects were reported. It was concluded that under these conditions PSC is nontoxic.[25]

Acute Skin Irritation

Two studies used the Draize method to test the potential irritancy of PSC on rabbit skin. In these tests, 0.5 g undiluted PSC was applied under occlusive patches both to intact and to abraded skin of six rabbits. Patches remained in place for 24 h, during which time the animals were immobilized. Evidence of irritation was scored at 24 and 72 h. In neither study were there any signs of irritation to either intact or abraded skin (Primary Irritation Indices = 0). Consequently, PSC was not considered to be a primary skin irritant.[26,27]

Eye Irritation

Three studies, also using the Draize method, reported on the potential irritancy of undiluted PSC to the eyes of rabbits.

One of the six rabbits tested in the first study exhibited conjunctival redness at 24 h, resulting in a mean irritation score of 0.33 (where the maximum possible score is 110). All eyes appeared normal at 48 and 72 h. Thus this study concluded that undiluted PSC caused "insignificant irritation."[28]

In the second study, conjunctival redness was observed in the same four of six rabbits at 24, 48, and 72 h. Mean scores for these observation periods were 3.33, 1.67, and 1.67, respectively (where the maximum possible score is 110). At seven days no irritation was observed in any animal. In this test, PSC was determined to be mildly irritating.[29]

In the final study, the eyes of half of the six animals tested were washed with 20 ml warm water four seconds after instillation of PSC. At no time was any irritation observed in either washed or unwashed eyes. PSC was considered to be nonirritating under the test conditions.[30]

Subchronic Skin Irritation

PSC was tested in eight rabbits for subchronic skin irritation. Animals were depilated on the back and flanks, and half the skin site abraded in each rabbit. Four dose levels were assigned, with two animals per dose; doses were applied daily for 20 days. The animals were checked daily for changes in body weight, behavior, and food consumption, as well as for signs of skin irritation. Likewise, urine and blood were analyzed for abnormalities. Undiluted PSC was applied to each group of rabbits in doses of 0, 0.5, 1.0, or 1.5 g/kg. No irritation developed in either intact or abraded skin, and no physiological abnormalities were observed. It was concluded that undiluted PSC caused no systemic toxicity by percutaneous absorption.[31]

Sensitization

A gel makeup containing 0.10% PSC and a cleansing cream containing 0.12% PSC were tested on groups of 10 and six guinea pigs, respectively, for potential sensitization. Guinea pigs were

depilated, and 0.1 ml of a 1% suspension (in saline) was injected intracutaneously. Injections were made every other day, until there was a total of 10 injections per animal. Two weeks after the last sensitizing injection, 0.05 ml of the suspension was injected in a fresh skin site as a challenge. Observations were made 24 h after each injection and a comparison made between challenge and sensitizing reactions. Each study showed no appreciable differences between the two types of reactions. The cosmetic products containing 0.10 and 0.12% PSC were found to be nonsensitizing.[32,33]

Clinical Assessment of Safety

Skin Irritation and Sensitization

Single insult patch test

A single insult patch test was performed on 55 subjects; 0.5 ml of undiluted PSC was applied to their skin. Observations made at 24 and 48 h revealed no irritation in any subject caused by the application of PSC (though one case of adhesive tape dermatitis did arise).[34]

Repeat insult patch test

Four studies tested PSC and products containing PSC for potential irritation and sensitization on human skin. In these tests, various concentrations of PSC were placed under occlusive patches, left in place for 24 h, and then removed. Twenty-four hours later, sites were scored and a new patch was applied; this procedure was repeated until 10 induction patches had been applied. Ten to 14 days after the final induction patch had been removed, a challenge patch was placed on the original test site and/or to a fresh site adjacent to that. Sites were scored 24 and 48 h after these challenge patch applications. Results of these tests appear in Table 3.[35,36]

A moisturizing lotion containing 0.24% PSC and a solution of 10% PSC were tested on 201 and 51 subjects, respectively. Concentrations of up to 10% PSC did not result in any reactions.[35,36]

A solution containing 30% PSC caused a single reaction in two of 54 subjects tested. One subject experienced slight erythema after the third exposure, while erythema and edema were observed in another subject after the second exposure. These people did not have any reactions to the other patches.[36]

On 10 occasions a hand lotion containing 3.0% PSC was applied to 51 subjects. Four subjects experienced irritation which ranged from slight erythema (1+ reaction) to moderate erythema, edema, and vesicle formation (3+ reaction). Irritation occurred after a single exposure and then disappeared, except in one case when a 1+ (erythema) reaction was observed after exposure to patches 2, 6, 7, and 9.[36]

Overall, the skin irritation and sensitization tests indicated that a 10% PSC solution (aqueous) and a cosmetic lotion containing 0.24% PSC were nonirritating, while a 30% PSC solution (aqueous) and a cosmetic lotion containing 3% PSC were mildly irritating. In none of the studies were there any reactions to challenge patches; thus, these tests determined that PSC was nonsensitizing at test concentrations.[35,36]

TABLE 3. REPEAT INSULT PATCH TESTS USING PSC.[a]

Product/ Ingredient	*PSC Conc.*	*No. of subjects*	*M/F*	*Age range*	*No. of Reactions*		*Comments*
					Patches 1–10	*Challenge Patch*	
Moisturizing lotion	0.24%	201	57/144	8–73	"No untoward effects"		Nonirritant
PSC	10.0% (aq)	51	11/40	12–70	0	0	Nonirritant
PSC	30.0% (aq)	54	12/42	12–70	2	0	1+, 2+
Hand lotion	3.0%	51	11/40	12–70	4	0	1+–3+

[a]Data from Refs. 35 and 36.

Phototoxicity

A 30% (aqueous) solution of PSC (0.2 ml) was applied to 10 subjects. Patches were left in place for 24 h and then removed. One site was used as a control, while the other was irradiated at 4400 $\mu W/cm^2$ through the use of four f4BL black-light tubes having a peak output of 360 nm. Observations made at 24, 48, and 96 h and at seven days revealed one subject with mild erythema at both control and irradiated sites. PSC (30%) did not produce phototoxicity in the subjects who were studied.[37]

SUMMARY

Polyamino Sugar Condensate (PSC) is the product of a condensation reaction between amino acids and sugars. It appears in over 100 cosmetic preparations at concentrations up to 1%.

Many nutritional and toxicological studies have dealt with the Maillard reaction, a process that occurs when foods are browned. This reaction appears to be unrelated to the production of PSC; however, specific analytical data are unavailable to confirm this statement. Data regarding the absence in PSC of traces of mutagenic agents and volatile N-nitrosamines are also unavailable.

PSC has an acute oral toxicity greater than 5 g/kg in rats. When it was applied undiluted to rabbit skin, it was found not to be a primary irritant. Application of PSC to the eyes of rabbits produced mild irritation in some animals; this usually appeared as conjunctival redness. Subacute skin irritation was not observed in rabbits when PSC (undiluted) was applied.

No data were available on the teratogenicity, mutagenicity or carcinogenicity of PSC.

In a single-insult patch test, undiluted PSC applied to 55 subjects did not cause irritation. In a number of repeated insult patch tests, an aqueous solution containing 10% PSC and a moisturizer containing 0.24% PSC caused no irritation in 51 and 201 subjects, respectively. To test an aqueous solution of 30% PSC, a total of 594 patches were applied to 54 subjects; two subjects experienced single reactions. A hand lotion containing 3% PSC resulted in four reactions in the 51 tested subjects, to whom a total of 561 patches were applied. In all tests, there were no reactions to challenge patches. Thus, human safety data indicate that PSC is nonsensitizing and, at worst, a mild irritant. PSC is also nonphototoxic.

CONCLUSION

On the basis of the available animal data and limited human experience presented in this report, the Panel concludes that in the present practices of use and concentration, Polyamino Sugar Condensate is safe for topical application to humans.

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Mr. Kevin Fisher, Scientific Analyst and writer prepared the Technical Analysis used by the Expert Panel in developing this report.

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