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Final Report on the Safety Assessment of Polyquaternium-7[1]

Abstract: The quaternary ammonium compound Polyquaternium-7 is used as an antistatic agent, film former, and hair fixative in a wide variety of cosmetics. This ingredient is formed by the polymerization of acrylamide with dimethyl dialylammonium chloride; residual acrylamide monomer can be found at levels as high as 10 ppm. An 8% aqueous solution of Polyquaternium-7 is typically supplied and this solution may be used in cosmetic formulations at a concentration as high as 5%. Most uses are at lower concentrations. Rats were fed up to 50,000 ppm of an 8% aqueous solution for 30 days; a decrease in organ weight was noted in the higher exposure groups. Dermal exposure of rats to 2.25 ml/kg per day for 14 weeks was nonirritating to both intact and abraded skin. Dermal exposure of rabbits to an 8% solution produced no irritation, and ocular exposure showed mild irritation that cleared after 24 h. Polyquaternium-7 was not mutagenic in an Ames test. Repeated insult patch test data suggest that 8% Polyquaternium-7 is at best a mild cumulative irritant, but not a sensitizer. Clinical tests with an 8% solution indicated that Polyquaternium-7 is not a photosensitizer. Given its structure, this material is considered not likely to be significantly absorbed in the skin and therefore is unlikely to produce general toxicity, developmental toxicity, or mutagenic/carcinogenic effects under use conditions. The presence of unreacted acrylamide monomer is considered sufficiently low so as to have no toxicologic significance. Based on the available data, it is concluded that Polyquaternium-7 is safe for use in cosmetic formulations. **Key Words:** Polyquaternium-7—Rat—Rabbit—Ocular irritation.

The following is a summary of data available to CIR concerning the chemistry, cosmetic use, and toxicity on Polyquaternium-7.

CHEMISTRY

Definition

Polyquaternium-7 (CAS No. 26590-05-6) is a copolymer consisting of acrylamide and dimethyl diallyl ammonium chloride monomers (Wenninger and McEwen, 1993). The structure of the two monomers are as follows (STN International, 1994):

[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.
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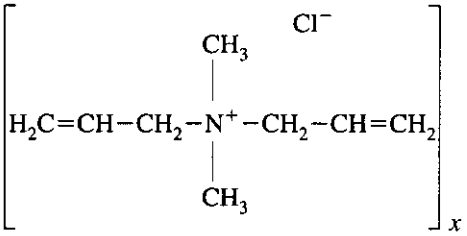
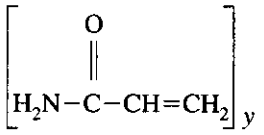


dimethyl diallyl ammonium chloride



acrylamide

It is difficult to assign a structure to the Polyquaternium-7 polymer as each functional group on the monomers can react in numerous ways with the others. By controlling the ratio of the two monomers and altering the catalyst system and experimental conditions different polymers can be created. For example, the two diallyl functional groups on the ammonium chloride monomer can cross-link with each other or they can react with acrylamide such that the ammonium chloride monomer becomes either a 5- or 6-membered ring. As a result, Polyquaternium-7 polymers produced by various manufacturers can differ from each other either in chain length, in the sequential arrangement of the two monomers, or in the types of bonds found between the monomers (Akerson, 1994).

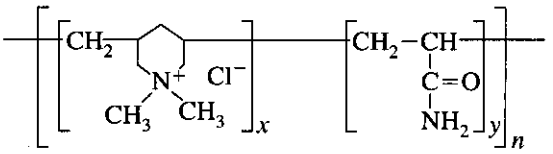
Polyquaternium-7 is also known as Quaternium-41; *N,N*-Dimethyl-*N*-2-Propenyl-2-Propen-1-ammonium Chloride, Polymer with 2-Propenamide; and 2-Propen-1-ammonium, *N,N*-Dimethyl-*N*-2-Propenyl-, Chloride, Polymer with 2-Propenamide (Wenninger and McEwen, 1993).

Chemical and Physical Properties

Polyquaternium-7 is supplied by one manufacturer as an 8% aqueous solution with 0.1% methylparaben and 0.02% propylparaben. The manufacturer reports a molecular weight for the solution of 1×10^6–10^7. This solution appears as a clear, colorless to pale yellow liquid with a molecular weight of approximately 1×10^6–10^7 and a pH of 6.5–7.5. The viscosity of the solution at 25°C is 7,500–15,000 cps. An ultraviolet absorption analysis of a 1.0% dilution of the 8% aqueous Polyquaternium-7 solution had absorbance peaks at 250–260 nm and 290–300 nm. The first peak was attributed to the paraben preservative system; the second peak to sodium salicylate impurities (Calgon, 1992*a*, 1992*b*).

Method of Manufacture

Calgon reports synthesizing Polyquaternium-7 by radical polymerization of equal amounts of acrylamide and dimethyl dialylammonium chloride (Calgon, 1992a). Under these conditions the following polymer is the predominant reaction product (Bozo Research Center, 1979):



As the majority of data presented in this review was supplied by this manufacturer, the structure of the Polyquaternium-7 polymer is consistent among the studies.

Impurities

Concentrations of reported impurities using the above-described method of manufacture are as follows: catalyst system, 0.6%; sodium salicylate, 0.04%; dimethyl diallylammonium chloride, 0.68–1.42%; and acrylamide, <5 ppm (Calgon, 1992*b*). A separate source cites that for "one company" the amount of acrylamide impurity is a maximum of 10 ppm (CTFA, 1992).

USE

Cosmetic

Polyquaternium-7 is a quaternary ammonium compound that is used as an antistatic agent, film former, and hair fixative (Wenninger and McEwen, 1992).

Table 1 reports the 1994 FDA voluntary submission data on formulations containing Polyquaternium-7 (FDA, 1994). Concentrations of use are no longer re-

TABLE 1. *Product formulation data for Polyquaternium-7*

Product category	Total no. of formulations in category	Total no. of formulations containing Polyquaternium-7
Baby shampoos	19	2
Other baby products	23	1
Bubble baths	214	2
Other bath preparations	132	4
Other fragrance preparations	136	2
Hair conditioners	614	16
Permanent waves	387	4
Rinses (non-coloring)	58	1
Shampoos (non-coloring)	852	37
Tonics, dressings and other grooming aids	563	19
Other hair preparations	376	3
Hair shampoos (coloring)	15	3
Bath soaps and detergents	343	26
Other personal cleanliness products	321	3
Aftershave lotion	229	1
Shaving cream	147	4
Cleansing	746	8
Other skin care preparations	790	1
Other suntan preparations	61	1
1994 Total		138

ported to FDA (Federal Register, 1992). However, in 1992 one cosmetic manufacturer reported the concentration of use of Polyquaternium-7 to be 0.04 to 0.17% (CTFA, 1992). Calgon (1992*b*) also reported typical concentration of use of their 8% aqueous solution in some formulation types: shampoo, 5.0%; creams/lotions, 2.0%; bar soap, 2.0% (active); liquid soap, 5.0%; sunscreens, 2.0%.

International

Polyquaternium-7 is approved by Japan for use in cosmetics (Rempe and Santucci, 1992).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Polyquaternium-7, as supplied by one manufacturer in an 8% aqueous solution, has an oral LD_{50} of >39.8 g/kg (Calgon, 1992*b*). The details were not reported.

A dose of 25 ml/kg of the 8% aqueous solution of Polyquaternium-7 was orally administered by gastric intubation to five male and five female Charles River rats, CRCD strain. Feed had been withheld for 24 h prior to administration. No animals died during the 2-week observation period that followed and all had normal body weight gain (Merck, Sharp and Dohme Research Laboratories, 1978).

Dermal

The dermal LD_{50} of Polyquaternium-7 (8% aqueous) is >21.5 g/kg (Calgon, 1992*b*). The details were not reported.

An undiluted solution of 8% aqueous Polyquaternium-7 was applied as a 5 g/kg dose to the shaved back of four male and four female albino New Zealand rabbits (2.80–3.40 kg body weight). The skin of four animals (two of each sex) was abraded; the skin of the other four was left intact. Occlusive dressings were applied to maintain 24-h contact. When the dressings were removed 2 of 4 abraded sites showed very slight erythema and edema; the condition disappeared by the next day. No other irritation was noted during the 2-week observation period (Merck, Sharp and Dohme Research Laboratories, 1978).

Short-Term Toxicity

Oral

A 30-day feeding study of Polyquaternium-7 (8% aqueous) was performed using CD-CRJ (SD) rats, 10 male and 10 female per group (Bozo Research Center, 1979). Dose groups were 1,650; 5,000; 16,500, and 50,000 ppm. Body weight, feed consumption, and water consumption were measured every other day. Urine was collected. At the end of the dosing period, the animals were fasted 1 day, anesthetized, and bled. Hematology assays (red blood cell, leucocyte, hemoglobin, hematocrit, and leucocytes percent) and clinical chemistry assays (GOT, GPT,

AIP, total protein, A/G, total cholesterol, blood sugar, urea nitrogen, sodium, and potassium) were performed. All of the animals survived to the end of the study. The following organs were weighed and examined microscopically: brain, pituitary gland, thyroid gland, heart, lungs, liver, spleen, kidneys, adrenal glands, testes, and ovaries. In addition, the following organs were also grossly examined for anatomic changes: the salivary glands, thymus, pancreas, stomach, mesentery lymph nodes, and the small and large intestines.

The 50,000 ppm–dosed group had decreased body weight gains; it was minor in the males and significant in the females. Males of the 50,000 ppm group had a small decrease in feed intake. The males of the 5,000 ppm group had incidental decrease and females of the 5,000 ppm group had incidental increase of water consumption. Otherwise, feed and water consumption in dosed animals were comparable with controls.

No differences in hematologic parameters were observed between test and control groups. There were no significant differences between test and control groups in any of the urine assays.

Changes in internal organ weights compared with controls were noted. In males, the thyroid gland weight was decreased in the 16,500 ppm group by an average of 20% and in the 50,000 ppm group by 26%; the heart weight was decreased by 13% in the 50,000 ppm group; the kidney weight (left) was increased in the 1,650 ppm group by 8%; and the weight of adrenal glands was decreased in the 5,000, 16,500, and 50,000 ppm groups by an average of 11%. In females, the liver weight was decreased in the 16,500 and 50,000 ppm groups by 11 and 9%, respectively; the spleen was decreased by 13% in the 50,000 ppm group. No other organ weight changes were noted in females.

Incidental bleeding of the thymus was observed in some animals and was the only anatomic abnormality noted.

Pathologic changes were noted in some of the animals; these changes were not significantly correlated with the dosing of Polyquaternium-7. Of note, a decrease of the follicle colloid of the thyroid gland was observed in some male animals. Circumscribed inflammatory cell infiltration in the heart was observed in one dosed (5,000 ppm) and one control male. Partial apneumatosis and partial pulmonary emphysema was seen in both dosed and control groups. Some animals had lymphocyte infiltration of Glisson's capsule of the liver. Chronic lipopexia was observed in some female animals. One male (50,000 ppm) had a granuloma in the liver. In the kidneys, lymphocyte infiltration was observed. An increase in cortex lipid of the adrenal glands was observed in some test and control animals.

Subchronic Toxicity

Dermal

A 14-week dermal toxicity study was performed using New Zealand albino rabbits. Groups of 4 animals of each sex received a dose of 0.25, 0.75, or 2.25 ml/kg per day of (8% aqueous) Polyquaternium-7 or physiologic saline. Four animals of each group—two male and two female—had treatment sites abraded during the first day of each week of the study. Doses were spread evenly every

day throughout the study (89 to 92 days). After 4–5 h of dermal contact, the excess material was removed. A control group of animals had saline applied to abraded and intact sites following the same schedule as described for the treated animals. Animals were examined daily for gross changes and weighed weekly. Ophthalmic examinations, hematologic and serum analyses, serum glutamic oxaloacetic transaminase (SGOT) tests, and alkaline phosphatase tests were performed at regular intervals. At the end of the study the animals were killed and necropsy and microscopic examinations were performed. All but one rabbit (a control) survived to the end of the study. Organs examined and weighed at necropsy included: heart, liver, kidneys, brain, adrenal glands, and testes.

In all treated groups except the 0.25 ml/kg per day on nonabraded skin there was a small but significant suppression of body weight gain as compared with saline controls; abrasion had no significant impact on this trend. The researchers attributed the loss of body weight to the stress caused by greater handling of treated animals, which was necessary to remove the hardened test substance off the skin between each daily exposure. No ophthalmic changes attributable to the test compound were observed. While there was a statistically significant decrease in serum alkaline phosphatase activity (in the 0.75 ml/kg, intact group) and an increase in SGOT activities (in drug weeks 7 and 11 in the 2.25 ml/kg groups), a treatment linked relationship could not be established. In fact, a decrease in serum alkaline phosphatase activity was observed in all groups including controls as compared with prestudy values and was a normal response to aging. Hematologic changes seen in two animals (slight anisocytosis in one animal, slight polychromasia in another) were deemed to be unrelated to the treatment. Nasal discharge was observed in some treated and control rabbits throughout the study.

Slight erythema but no edema was seen in animals with abraded skin after day 5. In 4 of 12 animals with abraded skin, there was a slight crust formation. Very slight to slight scabbing and redness were observed in control and treated groups with abraded skin. Of those treatment groups with abraded skin focal epidermal hyperplasia was noted in four animals; focal ulceration in one; and focal dermal cellular infiltration in three. Treatment with Polyquaternium-7 was considered essentially nonirritating to abraded skin and inert on intact epidermis (Merck, Sharp and Dohme Research Laboratories, 1978).

Dermal Irritation

A primary skin irritation study was conducted using six albino New Zealand rabbits (three of each sex) using 0.5 ml of a solution containing 8% Polyquaternium-7 in water. The test solution was applied to intact and abraded sites on shaved backs. The sites were covered to maintain contact for 24 h. Observations were made daily for 2 weeks following removal of the dressing and no evidence of irritation was found (Merck, Sharp & Dohme Research Laboratories, 1978).

Ocular Irritation

A dose of 0.1 ml of undiluted Polyquaternium-7 was instilled into the conjunctival sac of the left eye of three male and three female albino New Zealand rabbits.

The eyelids were held together for 1 min and then released. The eyes were not rinsed. The right eye of each animal served as a control. At 15 min and 2 h, a slight clear discharge was seen coming from all eyes that were treated and three of the treated eyes had a slight conjunctival injection. By 24 h all of the treated eyes appeared normal and no further irritation was noted during the 2-week observation period (Merck, Sharp & Dohme Research Laboratories, 1978).

MUTAGENICITY

Polyquaternium-7 in concentrations up to 0.1 ml/plate did not cause a significant increase in the number of revertants in *Salmonella typhimurium* strains TA92, TA98, TA100, and TA1537 regardless of S9 metabolic activation (Merck, Sharp & Dohme Research Laboratories, 1978).

CLINICAL ASSESSMENT

Irritation and Sensitization

A modified Shelanski repeated insult patch test (RIPT) was performed on two groups of volunteers (Product Investigations, Inc., June 1981). Induction occurred by applying 24-h occlusive patches containing 0.2 ml of Polyquaternium-7 (8% aq) to a specified area of the back 12 times over the course of 3 weeks. Panelists were checked for reactions at the time following removal of one patch and prior to application of a subsequent one. Induction was followed by a 2-week nontreatment period. Then, during the final week, four patches were administered to a new site. Reactions were graded after 24 h. There was no reaction in any of the 106 panelists to the initial application. During the induction period four panelists had irritation reactions to the treatment. In 3 of 4, the test material was determined to be a primary irritant of the cumulative type and in the remaining individual the response could not solely be attributed to the test material. During the challenge phase, five panelists had sensitization reactions to the treatment. Four of the five had reactions scored as 1; the fifth had a reaction scored as 3. This fifth responder was rechallenged with the test material and had reactions with a maximum score of 1 on three of four observation days following reapplication. The formulation, containing 8% Polyquaternium-7, was considered a very mild cumulative irritant.

A second RIPT was conducted, again by Product Investigations (January 1994). The protocol followed was identical to that used in the earlier RIPT except that there was only 1 week of nontreatment between induction and challenge. Of the 155 panelists who completed induction, two responded with faint erythema that disappeared within 24 h of detection. No adverse effects were observed in any of the 150 panelists who completed the study.

Photosensitization

A study to determine the photoallergic potential of Polyquaternium-7 was performed (Hill Top Research, Inc., December 1982). A pretest was conducted in which approximately 0.3 ml of an 8% aqueous solution of Polyquaternium-7 was

administered in a single-dose 24-h closed patch. Subsequently, eight patches were administered in a 3-week period. After each patch was removed the site was exposed to 30–40 min of sunlight between the hours of 11:00 a.m. and 4:00 p.m. A 2-week nontreatment period followed. The challenge phase consisted of two patches. After 24 h, one challenge site was exposed to sunlight as during induction. Responses were graded after 24 and 72 h. None of the 29 panelists who completed the study exhibited irritation, sensitization, or photosensitization to the treatment.

SUMMARY

Polyquaternium-7 is a copolymer of acrylamide and dimethyl diallyl ammonium chloride monomers. It is typically supplied as an 8% aqueous solution. It is used in cosmetic formulations as an antistatic agent, film former, and hair fixative at concentrations reported to be equal to or below 2%.

As supplied in an 8% solution, Polyquaternium-7 has an oral LD_{50} of >39.8 g/kg and a dermal LD_{50} of >21.5 g/kg. A single occlusive patch dose of 5 g/kg to the shaved backs of rabbits was nonirritating.

In a 30-day feed study using doses of Polyquaternium-7 (8%) up to 50,000 ppm, no significant differences between dosed and control rats were found in feed and water consumption and hematologic and urine parameters. Organ weights were decreased in males and females of the higher-dosed groups. No lesions were found in treated animals.

The results of a 14-week dermal study in rats using doses of 8% Polyquaternium-7 up to 2.25 ml/kg per day indicated that Polyquaternium-7 was essentially nonirritating to abraded skin and inert on intact skin. A single 24-h dermal exposure to 8% Polyquaternium-7 produced no irritation in rabbits.

Slight ocular irritation was noted in rabbits at 15 min and 2 h post-instillation of 0.1 ml of undiluted Polyquaternium-7; the irritation cleared by 24 h.

Polyquaternium-7 was nonmutagenic in an Ames assay.

Two RIPTs were performed. In one study the 8% Polyquaternium-7 solution was a mild cumulative irritant; in the other study, adverse reactions were not found in any panelist. Polyquaternium-7 as an 8% solution did not induce photosensitization in any of 29 panelists tested.

DISCUSSION

Although the results of only one mutagenicity assay are available in this review, the CIR Expert Panel decided that an additional mammalian genotoxicity assay was not necessary as the structure of Polyquaternium-7 suggests that it will not be significantly absorbed. Further, the results of the animal 14-week dermal study showed that whatever Polyquaternium-7 was absorbed had no effect. The Panel acknowledged the presence of acrylamide as an impurity but the reported maximum concentration of 10 ppm is sufficiently small so that is has no toxicologic significance. The Panel therefore issued a safe as used conclusion.

CONCLUSION

Based on available data, the CIR Expert Panel concludes Polyquaternium-7 to be safe as used in cosmetic formulations.

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* Available for review from the Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036 U.S.A.