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Final Report on the Safety Assessment of Quaternium-22[1]

Abstract: The quaternary ammonium salt Quaternium-22 is used as a film former, hair conditioning agent, and antistatic agent in a wide variety of cosmetic products. This ingredient has reportedly also been used as an emollient and skin conditioner. It is supplied in water with 60% solids (Quaternium-22). Impurities include 3-dimethylaminopropylamine (DMAPA) at concentrations up to 2.45%, and ethylene chlorohydrin (ECH) up to 0.097%. The maximum concentration of Quaternium-22 in formulations is 5.0%. An acute oral toxicity study in rats using 6% Quaternium-22 failed to kill any of the animals. Exposure to 0.5% Quaternium-22 was a slight irritant in a 28-day dermal toxicity study in rabbits; no other adverse reactions related to the test substance were found. Ocular exposure to 8.5% Quaternium-22 produced minimal conjunctival irritation, but 6% did not. Intracutaneous injections of 6% Quaternium-22 did not produce irritation or sensitization in Guinea pigs. No evidence of mutagenesis was seen in the Ames test. Clinical data revealed no irritation or sensitization, nor was there any evidence of photosensitization. While there was some concern over the toxicity of the DMAPA and ECH impurities, the absence of any toxicologic or mutagenic findings on exposure to material containing these impurities suggested there were no adverse effects associated with either the ingredient or any impurities. In order that exposure to these impurities be kept low, however, it was recommended that the concentration of this ingredient in cosmetic products should be limited so that the concentration of DMAPA not exceed 0.2% and that of ECH not exceed 0.008%—this is consistent with the expected use of Quaternium-22 at ≤5% solids. Accordingly, it was concluded that the cosmetic ingredient Quaternium-22 is safe in the present practices of use. **Key Words:** Quaternium-22—Rat—Guinea pig—3-Dimethylaminopropylamine—Ethylene chlorohydrin.

Quaternium-22 is a quaternium ammonium salt that is used as a film former, hair conditioning agent, and an antistatic agent in cosmetic products. The safety of Quaternium-22 in cosmetics is evaluated in this report.

CHEMISTRY

Chemical and Physical Properties

Quaternium-22 (CAS Numbers: 51812-80-7 and 82970-95-4) is the quaternium ammonium salt that conforms to the formula (Wenninger and McEwen, 1993):

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

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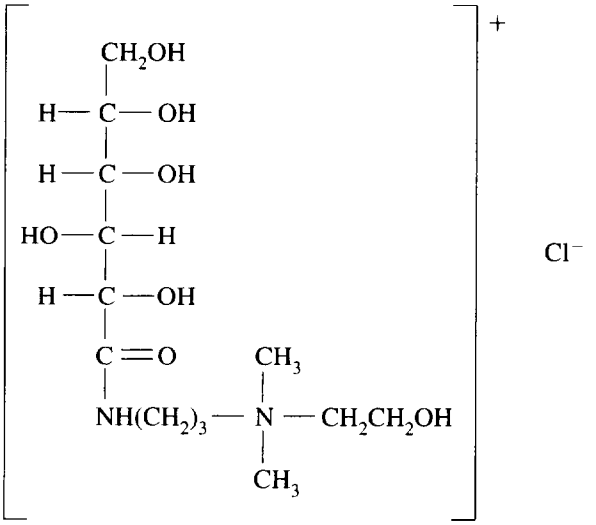

Other names for this chemical are as follows: γ-Gluconamidopropyl Dimethyl 2-Hydroxyethyl Ammonium Chloride; 3-(D-Gluconoylamino)-*N*-(2-Hydroxyethyl)-*N*,*N*-Dimethyl-1-Propanaminium Chloride; and 1-Propanaminium, 3-(D-Gluconoylamino)-*N*-(2-Hydroxyethyl)-*N*,*N*-Dimethyl-, Chloride (Wenninger and McEwen, 1993).

Quaternium-22 is a clear, light amber liquid with the following specifications: solids (58–62%), water (38–42%), ionic chloride (5.8–6.2%), pH (4.0–5.0), and specific gravity at 25°C (1.170–1.210). It is soluble in water, 70% ethanol, glycerine, propylene glycol, and 70% sorbitol and is insoluble in ethanol (≥95%), propylene glycol 2025, isopropyl myristate, and mineral oil (Van Dyk and Company, 1989). Quaternium-22 is supplied as a 60% solids (i.e., 60% Quaternium-22) solution (ISP, 1994).

Methods of Production

Quaternary compounds are normally synthesized by reacting a tertiary amine with an alkyl chloride or sulfate (Hunting, 1983).

Impurities

A gas chromatographic method was used in the identification and quantification of impurities that are present in Quaternium-22. This method was intended for the analysis of 3-dimethylaminopropylamine (DMAPA) and ethylene chlorohydrin (ECH); four different batches of Quaternium-22 were analyzed. Specifically, the impurities were separated using a gas chromatographic column equipped with an automatic injector and flame ionization detector. The results for the four batches analyzed were as follows: Batch 1 (2.41% DMAPA and 0.079% ECH), Batch 2 (2.39% DMAPA and 0.097% ECH), Batch 3 (2.45% DMAPA and 0.062% ECH), and Batch 4 (1.99% DMAPA and 0.052% ECH) (ISP, 1993).

USE

Purpose in Cosmetics

Quaternium-22 is used as a film former, hair conditioning agent, and an antistatic agent in cosmetic products (Wenninger and McEwen, 1992). Other cosmetic uses that have been reported include both an emollient and skin and hair conditioner (ISP, 1993).

Scope and Extent of Use in Cosmetics

The product formulation data submitted to the Food and Drug Administration (FDA) in 1994 indicated that Quaternium-22 was used in as many as 80 cosmetic product formulations (Table 1) (FDA, 1994).

Current information indicates that the maximum concentration of Quaternium-22 in the finished cosmetic product is 5.0% solids (i.e., 5% Quaternium-22) (ISP, 1994).

International Use

Quaternium-22 is not included in the CTFA List of Japanese Cosmetic Ingredients that are known to be approved for cosmetic use in Japan. The inclusion of any ingredient in the CTFA List neither guarantees that the ingredient is safe for use as a cosmetic ingredient nor that the use of the substance as a cosmetic ingredient complies with the laws and regulations governing such use in Japan. Quaternium-22 also is not included in the CTFA list of substances that are prohibited from use in cosmetics that are manufactured in or imported into Japan (Rempe and Santucci, 1992).

TABLE 1. *Product formulation data on Quaternium-22*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Bubble baths	208	2
Other bath preparations	111	3
Mascara	178	34
Hair conditioners	597	4
Hair sprays (aerosol fixatives)	294	1
Shampoos (non-Coloring)	845	17
Tonics, dressings, and other hair grooming aids	494	2
Other hair preparations	356	2
Bath soaps and detergents	335	5
Other personal cleanliness products	296	1
Cleansing	702	1
Moisturizing	806	1
Other skin care preparations	745	1
No. of uses listed under tradename		6
1994 Totals		80

Quaternium-22 is not included among the ingredients listed as prohibited from use in cosmetic products marketed in the European Union (formerly called European Economic Community) (EEC, 1993).

Surfaces to Which Applied

Cosmetic products containing Quaternium-22 are applied to the skin and hair, and may come in contact with the ocular and nasal mucosae.

Frequency and Duration of Application

Product formulations containing Quaternium-22 may be used daily or on a monthly basis. Many of the products may be expected to remain in contact with body surfaces for as briefly as a few minutes to as long as a few months. Each product has the potential for being applied many times over a period of several years.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity of Quaternium-22 (6.0% solids) was evaluated using six groups of five fasted albino rats (male and female; 200–300 g). The test substance was placed in a glass syringe and introduced into the stomach with a stainless steel dosing needle; doses ranged from 2.0 to 64.0 cc/kg. Animals were then observed daily for 2 weeks. Neither postmortem nor histopathologic examinations were performed. Feed consumption and behavior were normal throughout the study and none of the animals died (Bio-Toxicology Laboratories, 1972*a*).

Subchronic Dermal Toxicity

The cutaneous and systemic toxicity of Quaternium-22 were evaluated in a 91-day study using New Zealand White rabbits of the HRA:(MZW) SPF strain. The body weights for male rabbits ranged from 2.14 to 2.43 kg and female body weights ranged from 2.14 to 2.51 kg. The first experimenal group consisted of five male and five female rabbits. Initially, 1% aqueous Quaternium-22 (dose volume 2 ml/kg) was applied with a syringe to intact dorsal skin (right lateral region) of each animal daily for 4 days. A restraining collar was placed on each rabbit in order to prevent ingestion of the test substance. The test substance remained in contact with the skin for ~7 h each day; test sites were rinsed with tap water after each 7-h exposure. Because extreme dermal irritation (phonation and sensitivity to application reported) was noted in all animals on day 4, the test substance was not applied on day 5 and the test concentration was reduced to 0.5% w/v in distilled water. Beginning with the next exposure (day 8), 0.5% aqueous Quaternium-22 was applied 5 days per week (7 h/day) throughout the remainder of the 91-day study. Negative controls (five males, five females) were dosed with distilled water (2 ml/kg) according to the same procedure. Only three male rabbits

died during the study and none of the deaths were related to administration of the test substance. Signs that were observed in these animals prior to death included the following: anorexia, little or no feces, and/or languid and prostrate behavior. Gross lesions considered causally related to death of the animals involved the stomach and small intestine. Other gross findings included lesions of the penis and lungs in one animal. Histopathologic findings in animals that died were noted in the following tissues: intestine, lungs, heart, liver, mesenteric lymph node, epididymis, and thymus. Gross lesions in the remaining rabbits (experimentals and controls) killed at the end of the study were considered incidental to treatment, in that the findings occurred in only one treated animal or in both control and treated animals; the same was true for histopathologic changes. All significant hematologic findings were considered incidental because the effects were of low magnitude and similar or greater effects were observed in individual control animals. Dermal reactions that were observed in the experimental animals were classified as follows: erythema, edema, atonia, desquamation, and fissuring. Irritation scores ranged from none or normal to moderate. After the concentration of Quaternium-22 was reduced from 1% to 0.5% aqueous, the dermal responses began to diminish in severity. By day 23, no further evidence of skin irritation was evident. Gross lesions did not include any lesions of treated skin sites in animals that died during the study or were killed at the end of the study. There were no signs of dermal irritation in control rabbits (Hazleton Laboratories America, Inc., 1990).

Because three deaths were noted in the preceding experiment, a second 91-day experiment was conducted using five experimental and five negative control male rabbits (weights 2.13 to 2.34 kg). Additionally, the ten control rabbits from the preceding experiment served as negative controls. A different lot of Quaternium-22, diluted with distilled water to a concentration of 0.5% w/v, was applied to experimental animals according to the procedure in the preceding experiment. The dose volume per application was 2 ml/kg, and applications were made 5 days per week (7 h/day). Similarly, control rabbits were dosed with distilled water throughout the study. Gross lesions (treated skin included) were not observed in experimental or control rabbits. Histopathologic findings were considered incidental to treatment, in that all of the alterations were noted in at least one or only in control animals, and, therefore, were not considered treatment-related. Microscopic findings were reported for the following tissues: brain, thyroid, lungs, liver, kidneys, pancreas, and treated skin. Changes in hematologic findings were considered spurious and incidental to application of the test substance. Slight to moderate desquamation was observed on days 8 through 18 of the study, and isolated occurrences of slight edema were noted only seven times over a 46-day period. Neither desquamation nor any other type of dermal reaction was observed in control rabbits. In both 91-day dermal toxicity studies, the authors concluded that both lots of Quaternium-22, diluted to a concentration of 0.5% w/v in distilled water, were slightly and reversibly irritating when applied to intact skin of New Zealand White rabbits over a period of 91 days. Furthermore, there were no discernible pathologic changes that were related to treatment (Hazleton Laboratories America, Inc., 1990).

Ocular Irritation

The ocular irritation potential of 8.5% Quaternium-22 was evaluated using three albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of each animal, and the upper and lower lids were held together for 1 s. Eyes were not rinsed after instillation. Fluorescein (2.0%) was also instilled into the eye of each animal at least once during the study. Ocular reactions were scored at 1 h, 24 h, and up to day 7 post-instillation according to the Draize scale. Conjunctival hyperemia (Draize score for conjunctiva = 1) was observed in two rabbits. The total Draize score for ocular irritation was 2 (Draize scale = 0 to 110). When 6.0% Quaternium-22 was tested according to the same procedure in a second experiment, ocular reactions were not observed in any of the three rabbits tested (Bio-Toxicology Laboratories, 1973).

The ocular irritation potential of Quaternium-22 (diluted to a 6.0% gravimetric solution in deionized water) was evaluated using nine New Zealand rabbits (weights = 1.8 to 2.4 kg). The test substance (0.1 ml) was instilled into the right eye of each animal; untreated eyes served as controls. Only three rabbits were subjected to ocular rinsing. Ocular reactions were scored on days 1, 2, 3, and up to day 7 post-instillation according to the Draize scale (0 to 110). Ocular irritation was not observed in any of the animals tested (Van Dyk and Company, 1978).

In another study, the ocular irritation potential of Quaternium-22 (2.0% solids) was evaluated using three albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of each animal, and the upper and lower lids were held together for 1 s. Eyes were not rinsed after instillation. Fluorescein (2.0%) was also instilled into the eye of each animal at least once during the study. Ocular reactions were scored at 1 h, 24 h, and up to day 7 post-instillation according to the Draize scale (0 to 110). Ocular irritation was not observed in any of the animals tested (Bio-Toxicology Laboratories, 1972*b*).

Skin Irritation

The skin irritation potential of Quaternium-22 (diluted to 6.0% gravimetric solution in deionized water) was evaluated according to the method of Draize (1944) using six New Zealand albino rabbits. The test substance (0.5 ml) was applied to an abraded and intact skin site (clipped free of hair), respectively, on each animal. Both sites were covered with an occlusive patch and the trunk was wrapped with an impermeable occlusive wrapping. Reactions were scored at 24 h and 72 h post-application according to the grades: 1 (very slight erythema) to 4 (severe erythema); 1 (very slight edema) to 4 (severe edema, raised >1 mm and extending beyond the area of exposure). None of the animals had reactions, and the test substance was classified as a nonirritant (Van Dyk and Company, 1978).

In another study, the skin irritation potential of Quaternium-22 (6.0% solids) was evaluated using three albino rabbits according to the method of Draize et al. (1944). Controls were not included in the current study protocol. The test substance (0.5 ml) was applied to abraded and intact sites (clipped free of hair) on the back of each animal. The sites were covered with occlusive patches consisting of two layers of light gauze. Each patch was secured with thin bands of adhesive

tape, and the trunk of each animal was wrapped with a clear plastic trunk band. The animals were immobilized during the 24-h application period; reactions were scored at 24 h and 72 h post-application. Skin irritation was not observed in any of the animals tested (Bio Toxicology Laboratories, 1972*c*).

Skin Sensitization

The skin sensitization potential of Quaternium-22 (6.0% solids) was evaluated using 10 white male guinea pigs (weights 300–500 g). The back of each animal was shaved, and a 0.1% solution of the test substance was injected intracutaneously three times weekly for a total of ten injections. The first injection delivered 0.05 ml of test solution, and the remaining nine delivered 0.1 ml each. An eleventh, challenge injection (0.05 ml test solution) was made 2 weeks after the tenth injection. Distilled water served as the control and was administered according to the same procedure. Reactions were scored 24 h after each injection according to the following scales: 1 (very slight erythema) to 4 (severe erythema to slight eschar formation) and 1 (very slight edema) to 4 (severe edema, raised >1 mm and extending beyond area of exposure). Reactions were not observed in any of the animals during induction or challenge, and the test substance was classified as a nonsensitizer (Bio-Toxicology Laboratories, 1972*d*).

Mutagenicity

The mutagenicity of Quaternium-22 in strains TA97, TA98, and TA100 of *Salmonella typhimurium* was also evaluated in quantitative mutagenicity tests according to the procedure by Maron and Ames (1983). Tests were conducted with and without metabolic activation. In the plate incorporation assay without metabolic activation, each strain was incubated with Quaternium-22 (10 μl/plate) for 72 h at a temperature of 37°C. Untreated cultures served as negative controls and 4-nitroquinoline *N*-oxide (10 μg) served as the positive control. In the two-plate incorporation assays with metabolic activation, each strain was incubated with Quaternium-22 (doses 0.1–10.0 μg/plate) for 72 h at a temperature of 37°C. Untreated cultures served as negative controls and 2-aminofluorine served as the positive control. Quaternium-22 was not mutagenic either with or without metabolic activation. Both positive controls were mutagenic (Bio-Science Research Institute, Inc., 1992).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation and Sensitization

The cumulative skin irritation potential of Quaternium-22 (1% in each of two formulations) was evaluated using 50 female volunteers. Facial use and patch tests were conducted concurrently over a period of 3 weeks. In patch tests, 0.1 ml or 0.1 g of each of the two formulations was applied (under separate occlusive patches) to the volar aspect of the forearm of each subject. Distilled water and 0.1% sodium lauryl sulfate in water served as negative and positive controls, respectively. Fifteen consecutive patches were applied to the same test site every

24 h (72 h on weekends) on Monday through Friday. Reactions were scored prior to application of the next patch according to the following scale: 0 (no erythema) to 4 (intense erythema with edema and vesicular erosion). If a score of 3, intense erythema with edema (elevated lesion) at the application site, or greater, was reported, the test substance was not reapplied. At the conclusion of the study, erythema scores were added in order to determine a cumulative irritation score for each subject. In facial use tests, 25 subjects were instructed to apply one of the two products to the face and neck once every morning and once every evening for 3 weeks. The remaining 25 subjects were instructed to apply the other product according to the same procedure. All of the subjects were examined by the study investigator at baseline and at weekly intervals, and were asked to respond with comments and/or complaints. Only one of the volunteers withdrew from the study, and the reasons for withdrawal were not related to application of the test substance. Reactions on the face were observed in eight subjects. In four of the eight subjects, reactions ranged from what was described as "breaking out" a little on the forehead to inflammatory papular acne lesions on the face. All of these lesions had healed by the third week or within 7 days after the end of the study. Reactions that were described as either acne or pimples were observed in the remaining four subjects. Patch test reactions were observed in one subject; there were no reactions on the face. Multiple pruritic, erythematous papules at both patch test sites (one per formulation) were observed in this subject on day 17. Patch applications to this subject were discontinued, and, without treatment, the papular reaction cleared within 5 days. Two challenge patches containing each formulation, respectively, were subsequently applied to this subject and removed 72 h later. Reactions were neither observed immediately after patch removal or 24 h later; thus, the formulations did not induce a delayed contact hypersensitivity reaction. The two formulations containing 1% Quaternium-22 did not cause significant irritation in human skin. The mean cumulative irritation scores for the two test formulations were 4.8 and 5.4, and the scores for sodium lauryl sulfate and distilled water were 7.1 and 4.3, respectively (Procter and Gamble, 1994*a*).

The skin sensitization potential of three product formulations (one blue viscous liquid and two white creams) containing 1.0% Quaternium-22 was evaluated using 110 volunteers (ages between 18 and 73 years). The number of volunteers over 65 years of age did not exceed 25% of the test population. A total of 106 subjects completed the study; withdrawal from the study (four subjects) was not related to the administration of test materials. During the induction phase, nine consecutive patch applications (occlusive patches) of the test material were made to the infrascapular area of the back. The subjects received patch applications of each of the three test materials simultaneously at different sites on the back. The subjects were instructed to remove the patches approximately 24 h after application, and return to the test facility at 48 h intervals for test site evaluation and patch reapplication. Patches that were applied on Friday were removed by the subjects after 24 h and test sites were evaluated on the following Monday. After the first five induction applications of the blue liquid, the test concentration of this product was reduced to a 3.0% aqueous v/v solution (effective test concentration of Quaternium-22 0.03%), and was tested as such for the remainder of the study. The reason

for reducing the test concentration of this product after initiation of the study was not stated. The white cream products were not diluted at any time during the study. After a 2-week nontreatment period, the challenge phase was initiated during the sixth week. Patches were applied to new test sites and removed by the subjects at 24 h; reactions were scored at 48 and 72 h post-application. During induction and challenge phases, reactions were scored according to the following scale: – (no reaction) to + + + (definite erythema; definite edema and vesiculation). A doubtful response was defined as barely perceptible erythema, only slightly different from the surrounding skin. Doubtful reactions were observed in nine subjects during the induction phase; two of the subjects also had a + reaction (definite erythema and no edema) during the challenge phase. A tenth subject had reactions, classified as doubtful, only during the challenge phase. There was no evidence of sensitization to any of the three products containing 1% Quaternium-22 that were evaluated (Procter and Gamble, 1994*b*).

Phototoxicity

The phototoxicity of two white cream products containing 1% Quaternium-22 was evaluated using twelve volunteers (≥18 years old). Each of the two products was applied to occlusive patches that were placed on duplicate sets of sites on the infrascapular region of the back. The patches were removed at 24 h post-application and one site per product was irradiated with UVA light (320–400 nm; 20 J/cm^2). A xenon arc simulator (150 W) with a continuous emission spectrum in the UVA–UVB range (290–400 nm) served as the light source. A UVB absorbing filter was used to eliminate erythemogenic wavelengths (below 320 nm). The second application site for each product was not exposed to UV light. An additional irradiated site in the infrascapular region served as the irradiated control. Reactions were scored at 24 h and 48 h post-irradiation for both degree of erythema and edema. The erythema scale ranged from no reaction to marked/severe erythema. The edema scale ranged from minimal/doubtful edema to definite edema with erosion/vesiculation. The following results were the same for both products. At 24 h post-irradiation, mild but definite erythema was observed at irradiated test sites on 8 of 12 subjects. Identical reactions were reported for the irradiated control sites on each of the eight subjects. At 48 h post-irradiation, the incidence of positive reactions at irradiated sites was reduced to two of 12 subjects; three subjects had a positive reaction at the irradiated control sites. Reactions were not observed at nonirradiated test sites on any of the subjects throughout the study. It was concluded that both products containing 1% Quaternium-22 were not phototoxic (Procter and Gamble, 1994*c*).

Photoallergenicity

The photoallergenicity of two white cream products containing 1% Quaternium-22 was evaluated using 31 volunteers (≥18 years old). Twenty-six of the 31 volunteers completed the study; withdrawal from the study was not related to application of either product. During induction, the products were applied (occlusive patches) twice weekly on Mondays and Thursdays for a total of six induction

applications. Applications of each product were made to two sets of sites (irradiated and nonirradiated test sites) on the right and left lumbar area of the back. At 24 h after the initial patch applications of each product, one set of sites and an additional site were irradiated with three times the minimal erythema dose (MED). A xenon arc solar simulator (150 W) with a continuous emission spectrum in the UVA–UVB range (290–400 nm) served as the light source. During the remainder of the study, irradiated sites were exposed to twice the MED at 24 h after patch application; sites remained uncovered until application of the next patch. The third week of induction involved patch applications and irradiation on Thursday and Friday, respectively. On Monday and Tuesday of the fourth week, the sixth and final induction patches were applied and sites were irradiated after patch removal. Induction reaction scores were not reported. The challenge phase was initiated 12 days after the sixth irradiation. Duplicate sets of occlusive patches containing each product, respectively, were applied for 24 h to new test sites on the back. After patch removal, duplicate test sites were irradiated with UVA light (4 J/cm^2); a UVB-absorbing filter was used to eliminate erythemogenic wavelengths (below 320 nm). Other duplicate sets of test sites per product served as nonirradiated treated controls, and an adjoining site (irradiated untreated control) was irradiated with UVA light (4 J/cm^2). Challenge reactions at irradiated and nonirradiated test sites and irradiated control sites were scored for erythema and edema at 24, 48, and 72 h after irradiation. At irradiated sites, challenge reactions to one of the products at 24 h included one subject with mild, but definite erythema and five subjects with minimal or doubtful erythema, barely perceptible compared with surrounding skin. Two of the subjects with doubtful challenge reactions also had this type of reaction at irradiated control sites 24 h after irradiation. Five subjects had doubtful reactions to the second product at irradiated sites; two of the five also had a doubtful reaction at the irradiated control site. There were no reactions to either of the two products at 48 or 72 h post-irradiation. Reactions at nonirradiated test sites were not observed at any time during the challenge phase. Both products containing 1% Quaternium-22 were not photoallergenic (Procter and Gamble, 1994*d*).

SUMMARY

Quaternium-22 is a water-soluble ingredient that is used as a film former, hair conditioning agent, and antistatic agent in cosmetic products. Quaternium-22 is commercially supplied as a 60% solids solution. Other cosmetic uses that have been reported include use as an emollient and skin and hair conditioner.

Quaternary compounds are normally synthesized by reacting a tertiary amine with an alkyl chloride or sulfate. The impurities 3-dimethylaminopropylamine and ethylene chlorohydrin have been detected in Quaternium-22 at concentrations up to 2.45 and 0.097%, respectively.

Product formulation data submitted to the FDA in 1993 indicate that Quaternium-22 was used in 78 cosmetic products. Concentration of use values are no longer reported to the FDA by the cosmetics industry. However, in 1984, the maximum use concentration of Quaternium-22 that was reported to FDA was 5.0%.

In an acute oral toxicity study involving rats, Quaternium-22 (6.0% solids) was nontoxic. The LD_{50} was not achieved at a dose of 64.0 cc/kg, the highest dose tested.

In a 91-day dermal toxicity study involving male and female rabbits, 1% aqueous Quaternium-22 induced extreme dermal irritation on day 4, and the test concentration was reduced to 0.5% aqueous for the remainder of the study. Quaternium-22 (0.5% aqueous) was classified as a slight irritant. A different lot of 1% aqueous Quaternium-22 (diluted to 0.5% aqueous solution) was also classified as a slight irritant when the 91-day study was repeated using male rabbits only. In both experiments, histopathologic findings were considered unrelated to test substance administration.

Quaternium-22 (8.5%) induced minimal conjunctival irritation in two of three albino rabbits. Quaternium-22 (6.0% in deionized water) and Quaternium-22 (2.0% solids) did not induce ocular irritation in albino rabbits.

In occlusive 24-h patch tests involving albino rabbits, Quaternium-22 (6.0% gravimetric solution in deionized water) and Quaternium-22 (6.0% solids) were not irritating to intact or abraded skin.

Repeated intracutaneous injections of a 0.1% solution of Quaternium-22 (6.0% solids) did not induce irritation or sensitization reactions in white male guinea pigs.

In the Ames test, Quaternium-22 was not mutagenic to strains TA97, TA98, and TA100 of *Salmonella typhimurium*, the only bacterial strains tested.

Two formulations containing 1% Quaternium-22 were not classified as skin irritants in a 21-day cumulative skin irritation study involving 50 volunteers. Facial use and patch tests were conducted concurrently over a period of 3 weeks.

In a repeated insult patch test, three product formulations containing 1% Quaternium-22 did not induce sensitization in a population of 106 volunteers. One of the products was diluted to a concentration of 0.03% during the induction phase, and was tested at this concentration for the remainder of the study.

Products containing 1% Quaternium-22 were not phototoxic when tested on twelve volunteers and also were not photoallergenic in a group of 26 volunteers.

DISCUSSION

Quaternium-22 (commercially supplied as a 60% solids solution) is used in cosmetic products at concentrations up to 5% solids. Based on its chemical structure, the Expert Panel believes there would be either no absorption or an extremely slow rate of absorption. The Expert Panel is aware of the presence of 3-dimethylaminopropylamine ($\leq$2.45%) and ethylene chlorohydrin ($\leq$0.097%) as impurities in commercial samples of Quaternium-22, and is concerned with the toxicity of these chemicals. However, the negative results reported in acute oral toxicity, subchronic dermal toxicity, and Ames bacterial mutagenicity assays suggest that there are no toxic effects of Quaternium-22 that may be due to the presence of these impurities.

As a precautionary measure, the Expert Panel recommends that the concentrations of 3-dimethylaminopropylamine and ethylene chlorohydrin in Quater-

nium-22 not exceed 0.2% and 0.008%, respectively, in the finished cosmetic product. These limitations were established, taking into consideration the maximum concentration of each impurity in the raw material (60% solids) and that the maximum use concentration of Quaternium-22 in cosmetic products is expected to be 5% solids.

CONCLUSION

Based on the animal and clinical data included in this report, the CIR Expert Panel concludes that Quaternium-22 is safe in the present practices of use.

Acknowledgment: This report was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst and Writer.

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