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Final Report on the Safety Assessment of Steapyrium Chloride and Lapyrium Chloride

Steapyrium Chloride and Lapyrium Chloride are quaternary ammonium salts used in cosmetic products as biocides or as antistatic agents at concentrations equal to or less than 5.0%.

The oral LD_{50} of Steapyrium Chloride was estimated to be 8.2 g/kg. Subchronic studies in rats established a no-effect dose of 100 mg/kg.

Only a very slight dermal irritation was produced on abraded or intact rabbit skin by 1.0% Steapyrium Chloride. A 50% solution of Lapyrium Chloride produced slight to moderate erythema under occluded conditions. Very slight ocular irritation was produced in the eye of the rabbit by a solution containing 1.0% Steapyrium Chloride. Steapyrium Chloride was nonmutagenic when tested in a *Salmonella*/microsome assay, both with and without activation.

Steapyrium Chloride was neither an irritant nor sensitizer when tested at 100% concentration in a repeat insult occluded patch test on 164 individuals. Steapyrium Chloride does not absorb light in the UVA or UVB range and, therefore, would not be expected to be a phototoxic agent.

Only limited formulation safety test data were available for Lapyrium Chloride. However, the structural characteristics of Lapyrium Chloride and Steapyrium Chloride are very similar. Therefore, the safety test data on Steapyrium Chloride were used for the safety evaluation of both compounds. On the basis of the available data in this report, it is concluded that Steapyrium Chloride and Lapyrium Chloride are safe as cosmetic ingredients.

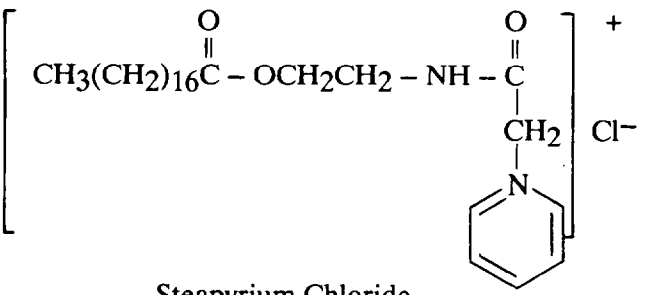
INTRODUCTION

Steapyrium Chloride and Lapyrium Chloride are quaternary ammonium salts used in a variety of cosmetic formulations as antistatic agents or as biocides.

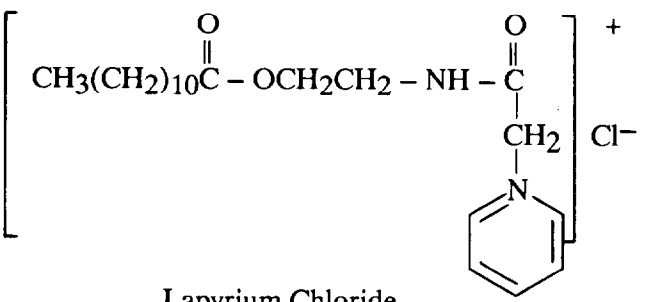
CHEMICAL AND PHYSICAL PROPERTIES

Steapyrium Chloride (CAS Nos. 1341-08-8, 14492-68-3, 42566-92-7) and Lapyrium Chloride (CAS No. 6272-74-8) are the quaternary ammonium salts that conform

generally to the following chemical formulas[1]:



Steapyrium Chloride



Lapyrium Chloride

The compounds differ only in that Steapyrium Chloride is an ester of stearic acid and Lapyrium Chloride is an ester of lauric acid.

Steapyrium Chloride is also known as Emcol E-607S, 1-[[(2-hydroxyethyl) carbamoyl]methyl]pyridinium chloride stearate, 1-[2-oxo-2-[[2-[(1-oxooctadecyl) oxy]ethyl] amino]ethyl]pyridinium chloride, quaternium-7, and N-(stearoyl colamino formyl methyl) pyridinium chloride.[1]

Lapyrium Chloride is also known as Emcol E-607L, 1-(2-hydroxyethyl)-carbamoyl methyl pyridinium chloride laurate, N-(lauryl colamino formyl methyl) pyridinium chloride, and 1-[2-oxo-2-[[2-(1-oxododecyl)-oxy]ethyl]amino]ethyl] pyridinium chloride.[1]

Steapyrium Chloride is a white to light cream-colored powder. It is soluble in water. Steapyrium Chloride, for use as an ingredient in cosmetics, typically contains a minimum of 90% Steapyrium Chloride, has a total chloride content of 7.4 to 8.1%, and contains a maximum of 3.0% free fatty acids as stearic acid and a maximum of 0.5% hydrochloric acid. The pH of a 1% aqueous solution is 3.3 to 3.5.

IMPURITIES

The results of a gas chromatographic analysis of a Steapyrium Chloride sample are shown in Table 1.[2] Steapyrium Chloride can be identified positively by a close match to a standard IR spectrum with no indication of foreign materials.[3] Steapyrium Chloride does not absorb UVA(315–340 nm) or UVB(280–315 nm) light.[4]

Lapyrium Chloride is a powder. It has a molecular weight of 398.97.[5]

COSMETIC USE

Lapyrium Chloride has been used as a cationic emulsifier, a deodorant, a detergent-germicide, and an antistatic agent in products other than cosmetics.[5]

Cosmetic products containing Steapyrium Chloride or Lapyrium Chloride may be applied to or may come in contact with hair, skin, eyes, and mucous membranes. Product formulations containing Steapyrium Chloride or Lapyrium Chloride may be applied as many as several times a day and may be used over many years. They may remain in contact with the hair and skin for variable periods following application (Table 1).[6]

Product types and the number of product formulations containing Steapyrium Chloride or Lapyrium Chloride and reported voluntarily to the Food and Drug Administration (FDA) in 1986 are presented in Table 2. Voluntary filing of this information by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations (21 CFR 720.4).[7] Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the true concentration of the finished product. The actual concentration in such a case would be a fraction of that reported to FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. In 1986, Steapyrium Chloride and Lapyrium Chloride were reported as ingredients at concentrations up to 5% in 36 and 38 cosmetic formulations, respectively.[6]

ANIMAL TOXICOLOGY

Acute Oral Studies

Steapyrium Chloride was administered by gavage as a 30% "ground suspension" in corn oil to 46 albino rats ranging in weight from 90 to 205 g, and the rats were observed

TABLE 1. IMPURITIES IN STEAPYRIUM CHLORIDE[2]

Impurities	*Concentration (ppm/wt)*
Methyl dodecanoate	10
Lauric acid	100
Methyl myristate or a C_3 dodecanoate	8
Methyl hexadecanoate	290
Methyl heptadecanoate	10
Methyl octadecanoate	290
Pyridine	3
11 Unknown GS/MS peaks	—

TABLE 2. PRODUCT FORMULATION DATA[6]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)	
			>1–5	>0.1–1
Steapyrium Chloride				
Baby shampoos	35	1	—	1
Hair conditioners	478	8	1	7
Hair rinses (noncoloring)	158	5	1	4
Hair shampoos (noncoloring)	909	1	—	1
Hair dyes and colors (all types requiring caution statement and patch test)	811	1	1	—
Aftershave lotions	282	2	—	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	2	—	2
Face, body, and hand skin care preparations (excluding shaving preparations)	832	7	—	7
Moisturizing skin care preparations	747	3	1	2
Night skin care preparations	219	2	2	—
Suntan gels, creams, and liquids	164	3	—	3
Other suntan preparations	28	1	—	1
1986 Totals		36	6	30

			>1–5	>0.1–1	≤0.1
Lapyrium Chloride					
Baby lotions, oils, powders, and creams	56	2	—	2	—
Colognes and toilet waters	1120	5	—	5	—
Hair conditioners	478	3	—	3	—
Tonics, dressings, and other hair grooming aids	290	1	—	1	—
Wave sets	180	1	—	—	1
Other makeup preparations (not eye)	530	1	—	1	—
Deodorants (underarm)	239	5	—	5	—
Other personal cleanliness products	227	7	1	6	—
Aftershave lotions	282	2	—	2	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4	—	3	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	4	2	1	1
Moisturizing skin care preparations	747	2	—	2	—
Skin fresheners	260	1	—	1	—
1986 Totals		38	3	32	3

for 6 days.[8] The estimated LD_{50} was 8.2 g/kg. Growth suppression for 2 to 3 days following dosing was observed in rats given more than 6 g/kg Steapyrium Chloride. Rats that survived for 6 days recovered the lost weight and grew at a normal rate. At necropsy, distended stomachs filled with undigested material and marked hyperemia of the digestive tract were observed in the animals that died. In animals that survived, no gross lesions were observed at necropsy except for 1 that had slight hyperemia of the digestive tract.

The acute oral toxicity of a lotion containing 0.13% Steapyrium Chloride was determined in Sprague-Dawley rats.[9] Four groups of 5 male and 5 female rats were fasted for 16 h before treatment, were given 27.6 to 65.4 g/kg undiluted lotion by oral intubation, and were observed until death or for 14 days. All rats were necropsied. The acute LD_{50} for the undiluted lotion was 48.3 g/kg. Salivation, diarrhea, polyuria, hematuria, nasal discharge, discoloration of stomach and intestinal contents, discoloration of the liver and kidneys, empty stomach, stomach distended with gas, discoloration of the serosal blood vessels prominent on the entire gastrointestinal tract, and variations of these findings were observed in some rats that received 36.8 g/kg or more of the lotion. These findings may have been related to the administration of the lotion.

The acute oral toxicity of a conditioner containing 0.5% Steapyrium Chloride was determined in Sprague-Dawley rats that had been fasted overnight.[10] Ten rats were given 15 ml/kg conditioner by intubation and were observed for 14 days. All animals were killed and necropsied at the termination of the observation period. All of the rats survived for 14 days and appeared to be normal. No abnormalities were observed in organs of the thorax and abdomen. The LD_{50} of the conditioner for rats was greater than 15 ml/kg.

Emulsept, a lauric (Lapyrium Chloride) and myristic acid ester of colaminoformylmethylpyridinium chloride (unspecified proportions of each), was administered in the drinking water at a 0.1% concentration to groups of 6 to 16 male and 7 to 9 female Sprague-Dawley rats in a three generation study.[11] The male rats received the Emulsept solution for 4 to 25 weeks, and the female rats received the solution for 4 to 7 weeks. Groups of control rats received tap water. All rats were necropsied at the end of the experiment. The body weight gains of all treated rats were comparable to the controls, and diarrhea was not observed. In all cases, treated females gave birth to an "average litter of rats." The appearance of these rats was normal. No gross or microscopic lesions were found in the liver, kidneys, and gastrointestinal tract of treated rats.

Subchronic Oral Toxicity

A 90-day oral toxicity study was conducted on groups of 20 male and female rats using Steapyrium Chloride.[12] The test material was administered by gavage at varying concentrations in deionized water, 5 times per week for 13 weeks. Preliminary range-finding studies revealed an increase in toxicological signs at 500 and 1000 mg/kg doses. Therefore, the 1010 mg/kg dose was selected as the high dose, and 100 mg/kg and 10 mg/kg as the mid and low doses, respectively. The control group of 20 male and 20 female rats received 10 mg/kg water. The potential human exposure was estimated to be 2 to 3 mg. There were no apparent effects due to the administration of Steapyrium Chloride at the 10.0 and 100 mg/kg doses for any of the following parameters: weight gain, feed consumption, hematology, clinical chemistry, organ weights or organ/body weight ratios, ophthalmology, necropsy observations, or results of microscopic exam-

ination. There was 1 death in the males treated with 100 mg/kg. Four male and 1 female animals died in the 1010 mg/kg test groups. There were significant differences between the controls and the high-dose group (1010 mg/kg) but not in the 100 mg/kg dose groups for the following parameters: body weight, feed consumption, hematology, organ weights and organ/body weight ratios, mortality, and the presence of lesions. The high-dose males, 14 of 15 examined, and 18 of 18 of the high-dose females had lesions in the nonglandular portion of the stomach. The decrease in body weight and feed consumption in the high-dose group was attributed to the gastric lesions. The no-effect level for Steapyrium Chloride, under the conditions of the study, was 100 mg/kg body weight.

Skin Irritation

The backs of 6 New Zealand white rabbits were clipped and abraded on one side.[13] A 0.5 ml volume of a 1.0% (w/v) aqueous solution of Steapyrium Chloride was applied beneath gauze to one intact and one abraded test site on each rabbit. The trunks of the rabbits were wrapped in impervious material for 24 h. The sites were observed at 24 and 72 h following treatment. Erythema and eschar formation were scored on a 0 to 4 scale. The mean scores for intact and abraded sites at 24 and 72 h were 0.54 for erythema and eschar formation and 0.59 for edema formation. Erythema and edema were very slight. A dermal irritation score was calculated by summing all the mean scores and dividing by 4. The dermal irritation score was 1.13 of a possible maximum of 8.0. There was very slight dermal irritation. No ulceration, necrosis, or other signs of dermal defects or irritation was observed. All rabbits were in good health throughout the study. No pharmacological or toxicological effects were observed.

The backs and sides of the trunks of 3 male and female New Zealand white rabbits were clipped, and 1 side of each animal was abraded.[14] A 1.0 ml volume of a 50% (w/v) aqueous solution of Lapyrium Chloride was applied to 1 intact and 1 abraded site on each rabbit. The sites were covered with gauze, and the entire trunk of each animal was wrapped with an impervious material for 24 h. Erythema and eschar formation and edema formation were each scored on a scale of 0 to 4, 24 and 72 h following compound application. The mean scores for intact and abraded sites at 24 and 72 h were 2.09 for erythema and eschar formation and 2.79 for edema formation. Erythema and edema were slight to moderate. A dermal irritation score was calculated by summing all the mean scores and dividing by 4. The dermal irritation score was 4.88 of a possible maximum of 8.0. There was slight to moderate dermal irritation. No ulceration or necrosis or other signs of dermal defects or irritation were observed. All rabbits were in good health throughout the study. No pharmacological or toxicological effects were observed.

A conditioner containing 0.5% Steapyrium Chloride was applied to an intact and an abraded site on the skin of 6 rabbits for 4 h, and the skin was rinsed.[10] Sites were scored for erythema and edema at 24 and 72 h using the Draize grading system.[15] No edema was observed at intact or abraded sites at any time. The primary skin irritation score was 1.62 of a possible maximum of 8.0. The conditioner was mildly irritating.

A 0.5 ml volume of roll-on antiperspirant containing 0.5% Lapyrium Chloride was applied to an intact and an abraded site on the clipped back and flanks of 3 male and 3 female New Zealand white rabbits, and the sites were occluded for 24 h.[16] Sites were scored for erythema and edema at 24 and 72 h using the Draize grading system.[15] The

primary skin irritation score was 2.0 of a possible maximum of 8.0. The antiperspirant was mildly irritating.

Eye Irritation

A 0.1 ml volume of a 1.0% aqueous solution of Steapyrium Chloride was placed into the conjunctival sac of one eye of each of 6 New Zealand white rabbits, and the lids were held together for 1 sec.[17] The untreated eyes served as controls. The eyes were examined at 24, 48, and 72 h, and at 4 and 7 days following treatment. Very slight ocular irritation was observed. Steapyrium Chloride was considered a nonirritant.

A 0.01 ml volume of a no greater than 6% (w/v) aqueous solution of Steapyrium Chloride and a no greater than 6% (w/v) aqueous solution of Lapyrium Chloride were applied directly to the corneas of two groups of 6 New Zealand albino rabbits, respectively.[18,19] Eye injury was scored at 24, 48, and 72 h using the Draize scale.[15] The researchers did not report the Draize scores observed for these cationic surfactants but instead used the results to predict the concentrations of Steapyrium Chloride and Lapyrium Chloride that would produce Draize scores of 20 of a possible maximum of 110. This Steapyrium Chloride concentration was 28.8%, and this Lapyrium Chloride concentration was 6.1%.

A 0.1 ml volume of an undiluted lotion containing 0.13% Steapyrium Chloride was placed in the conjunctival sac of one eye of each of 9 male New Zealand white rabbits.[20] The eyes of 3 rabbits were rinsed 30 sec later with 20 ml water. The eyes were examined and ocular reactions were scored at 24, 48, and 72 h, and at 4 and 7 days after treatment using the Draize scale.[15] The maximum average eye irritation score for rinsed eyes was 1.3 of a possible maximum of 110 and for unrinsed eyes was 2.0 of a possible maximum of 110. The lotion was minimally irritating.

A 0.1 ml volume of a conditioner containing 0.5% Steapyrium Chloride was instilled into the conjunctival sac of one eye of each of 9 New Zealand albino rabbits.[10] The eyes of 3 rabbits were rinsed 15 sec later with 35 ml water. The treated eyes were evaluated 1, 24, 48, and 72 h, and 7 and 14 days after treatment using the Draize scale.[15] The maximum mean irritation score for unrinsed eyes was 8.7 of a possible maximum of 110. The maximum mean irritation score for rinsed eyes was 6.7. The conditioner was minimally irritating.

MUTAGENICITY

Steapyrium Chloride was nonmutagenic when tested in a *Salmonella*/microsome assay.[21] Five strains of *Salmonella typhimurium* (TA97a, TA98, TA100, TA102, TA104) were exposed to 1, 4, 8, 10, 40, 80, 100, and 400 μg/plate, both with and without activation. Negative controls, tester strain only, and DMSO solvent plus tester strain along with positive controls were included in the assay.

CLINICAL ASSESSMENT OF SAFETY

Primary Skin Irritation

Patches containing 15% (w/w) Lapyrium Chloride were applied in vertical strips at three locations on one of the scapulae of each of 18 male volunteers on 5 consecutive

days for 6 h.[22] Para-axillary, central, and paravertebral responses were evaluated on a 13-point scale each day. The middle of the scapula was usually the most reactive, and the para-axillary region was usually the least reactive. The para-axillary mean response ranged from 0.21 on day 1 to 3.25 on day 5, the central response from 0.48 on day 1 to 3.85 on day 5, and the paravertebral response from 0.65 on day 1 to 3.27 on day 5. There was a statistically significant difference between the reactivities of the different regions of the scapula. A similar study was conducted by the same researchers with 10, 15, and 20% Lapyrium Chloride on 22 male volunteers.[23] Patches were randomized with respect to location on the scapulae and daily application times, and reactions were scored 2, 10, and 18 h following patch removal. The 2-h scores were always significantly less than the 10 and 18-h scores. There were no significant differences between the 10 and 18-h scores. Cutaneous reactivity varied significantly from day 2 and throughout the remainder of the study in regard to time of patch application and area patched. The strongest reactions to Lapyrium Chloride occurred in the middle of the scapula, and the weakest reactions were usually in the para-axillary region.

A lotion containing 0.13% Steapyrium Chloride was tested for irritation using 25 male and female volunteers.[24] The material was applied to the volar aspect of the forearm under an occlusive patch for 48 h. The lotion was nonirritating.

Occlusive patches containing 0.2 ml of a lotion containing 0.13% Steapyrium Chloride were applied for 23 h to the backs of 13 female volunteers on each of 21 consecutive days.[25] Treated sites were scored every 24 h on a scale of 0 to 3. Once a score of 3 was reached, it was used for the rest of the study. The composite total irritation score was 571 of a possible maximum of 819. With a base of 10 women, the composite total irritation score was 439.23 of a possible maximum of 630. The irritation time average was derived from the cumulative irritation score and was 6.36 days. The irritation time median is the number of days during which at least 50% of the women would be expected to have a response of less than 3; the irritation time median was 4 days. The irritation time average and median were relatively close. This would be expected if the responses of the test panel were reasonably homogeneous and were due to cumulative irritation reactions. It was concluded that under the conditions of this study, the lotion had a moderate potential for cumulative irritation. The lotion is expected to be "possibly mild in normal use."

Skin Sensitization

The skin sensitization potential of a lotion containing 0.13% Steapyrium Chloride was determined in 25 male and female volunteers with a modification of the maximization test.[24,26] Five induction patches of 0.3 g lotion were applied under occlusive patches to the volar aspect of the forearm for 48 h, 2 to 3 days apart. A 1% sodium lauryl sulfate solution was used before induction. Its use in the procedure was unspecified, but it probably was applied with a patch for 24 h prior to induction. After a 20-day nontreatment period, a challenge patch was applied under occlusion to a fresh site for 48 h. A 10% aqueous solution of sodium lauryl sulfate was used prior to the challenge. Its use was unspecified, but it probably was applied with a patch for 1 h prior to challenge. Reactions were scored on a scale of 0 to 3 24 and 48 h following removal of the challenge patch. No instances of contact sensitization were observed.

Irritation and Sensitization

A repeat insult patch test (RIPT) was conducted on 164 subjects, 18 males and 146 females.[27] The test material, approximately 0.2 g of Steapyrium Chloride, was placed on a moistened Parke-Davis Readi-Bandage occlusive patch and applied to the back of each subject. The subject removed the patch after each 24-h exposure. A 24-h nontreatment period followed the removal of the patches on Tuesday and Thursday, and a 48-h nontreatment period followed removal of the patch on Saturday. The treatment procedure was repeated every Monday, Wednesday, and Friday until nine applications of the test material were made. After a 10 to 21-day nontreatment period, a challenge patch was applied and observed 24 and 48 h later. A total of 148 of the 164 subjects completed the study. Transient, barely perceptible to mild erythema was observed on 10/148 test panelists during the induction phase of the study. No evidence of an allergic reaction was observed following application of the challenge patches. Under the conditions of the test, Steapyrium Chloride was neither an irritant nor a sensitizing agent.

SUMMARY

Steapyrium Chloride and Lapyrium Chloride are quaternary ammonium salts used in cosmetic products as biocides or as antistatic agents. Eight of the combined 74 reported uses of the two ingredients are within the concentration range of 1 to 5%. The remaining reported uses are at concentrations below 1.0%.

The oral LD_{50} of Steapyrium Chloride was estimated to be 8.2 g/kg. Subchronic studies in rats established a no-effect dose of 100 mg/kg. Substantial adverse effects were reported at 1010 mg/kg doses.

Only a very slight dermal irritation (1.13/8.0) was produced on abraded or intact rabbit skin by 1.0% Steapyrium Chloride. One milliliter of a 50% Lapyrium Chloride solution produced slight to moderate erythema under occluded conditions. The dermal irritation was calculated to be 4.88/8.0. Formulations containing either 0.5% Steapyrium Chloride or 0.5% Lapyrium Chloride produced only minimal skin irritation.

Very slight ocular irritation was produced in the eye of the rabbit by a solution containing 1.0% Steapyrium Chloride. A formulation containing 9.5% Steapyrium Chloride was minimally irritating to rabbit eyes.

Steapyrium Chloride was nonmutagenic when tested in a *Salmonella*/microsome assay, both with and without activation.

The irritation and sensitization potential of Steapyrium Chloride was evaluated in a repeat insult occluded patch test on 164 individuals. Only minimal transient irritation was produced in 10 subjects by 0.2 g of Steapyrium Chloride. The test ingredient was applied to the skin on the occlusive bandage wrap. No allergic reactions were observed in the 148 individuals who completed the induction phase and were challenged 10 to 21 days post-exposure. Under the condition of this test, Steapyrium Chloride was neither an irritant nor a sensitizer.

Steapyrium Chloride does not absorb light in the UVA or UVB range and, therefore, would not be expected to be a phototoxic agent.

DISCUSSION

Only limited formulation safety test data were available for Lapyrium Chloride. The structural characteristics of Lapyrium Chloride and Steapyrium Chloride are very similar. Consequently, the Expert Panel concluded that the safety test data on Steapyrium Chloride could be used for the safety evaluation of Lapyrium Chloride.

CONCLUSION

On the basis of the available data in this report, the CIR Expert Panel concludes that Steapyrium Chloride and Lapyrium Chloride are safe as cosmetic ingredients in the present practice of use and concentration.

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