Final Report on the Safety Assessment of Isostearamidopropyl Morpholine Lactate[1]

Isostearamidopropyl Morpholine Lactate is the lactic acid salt of isostearamidopropyl morpholine used as an antistatic agent in 20 cosmetic formulations, mostly hair preparations. The concentration of use in hair preparations is in the 1–5% range. Isostearamidopropyl Morpholine Lactate was nontoxic in acute oral toxicity studies in rats. Although Morpholine is considered a cutaneous, ocular, and mucous membrane irritant, and a sensitizer, Isostearamidopropyl Morpholine Lactate exhibits none of the sensitization and irritant reactions observed with Morpholine. Isostearamidopropyl Morpholine Lactate was minimally irritating to rabbit eyes, and mildly irritating to intact and abraded rabbit skin. Although sensitization was not seen in clinical tests, some irritancy was noted. Isostearamidopropyl Morpholine Lactate was not mutagenic in the Ames test, with or without metabolic activation, although cell killing was seen at most test concentrations. Although Morpholine is readily nitrosated to form carcinogenic nitrosamines, *N*-nitroso impurities were not detected in Isostearamidopropyl Morpholine Lactate. Mutagenicity data on Isostearamidopropyl Morpholine Lactate in a mammalian system were not available, nor were data available on skin penetration or toxicity associated with inhalation exposures. Accordingly, the safety of this ingredient in leave-on cosmetic formulations could not be determined. Based on the available data, this ingredient was considered safe for use in rinse-off cosmetic products. Additional data needed for assessing the safety of leave-on uses include: (i) skin penetration; if there is significant skin penetration, then both a 28-day dermal toxicity study to assess general skin and systemic toxicity, and a reproductive and developmental toxicity study are needed; (ii) one genotoxicity study in a mammalian system; if positive, then a 2-year dermal carcinogenesis study using National Toxicology Program (NTP) methods may be needed; and (iii) inhalation toxicity data.

INTRODUCTION

Isostearamidopropyl Morpholine Lactate is the lactic acid salt of Isostearamidopropyl Morpholine that is used as an antistatic agent in cosmetic products. The following is a review of the available safety data on this ingredient, including data on the component morpholine, which was reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in an earlier safety assessment.

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CHEMISTRY

Definition and Structure

Isostearamidopropyl Morpholine Lactate is the lactic acid salt of isostearamidopropyl morpholine (q.v.) that conforms to the formula shown in Figure 1. Other names for this ingredient include: Propanoic acid, 2-hydroxy-, compound with *N*-[3-(4-morpholinyl)propyl] isooctadecanamide (1:1) (9CI) (Wenninger and McEwen 1997; Scientific and Technical Information Network 1995). Isooctadecanamide, *N*-(3-(4-morpholinyl)propyl]-, mono(2-hydroxypropanoate) (9CI) (STN 1995). The molecular weight of Isostearamidopropyl Morpholine Lactate is approximately 500 daltons (McIntyre Group Ltd. 1996).

Method of Manufacture

Isostearamidopropyl Morpholine Lactate is produced by the condensation of one mole of isostearic acid with one mole of aminopropylmorpholine to form isostearamidopropyl morpholine and one mole of water, which is distilled out of the reaction mass. The amido functional tertiary amine is neutralized in an aqueous medium with lactic acid to prepare a 25% solution of Isostearamidopropyl Morpholine Lactate (McIntyre Group Ltd. 1996).

Impurities

The standard 25% active product has typically 0.15% unreacted aminopropylmorpholine and 0.2% unreacted isostearic acid. When assayed using high-performance liquid chromatography for the presence of *N*-nitroso compounds, polar nitrosamines were not detected. The limit of detection was 50 ppb (McIntyre Group Ltd. 1996).

UV Absorbance

Isostearamidopropyl Morpholine Lactate "has no aromatic functionality and therefore has a modest UV extinction coefficient" (McIntyre Group Ltd. 1996).

USE

Isostearamidopropyl Morpholine Lactate is used as an antistatic agent in cosmetic formulations (Wenninger and McEwen 1997). The product formulation data submitted to the Food and

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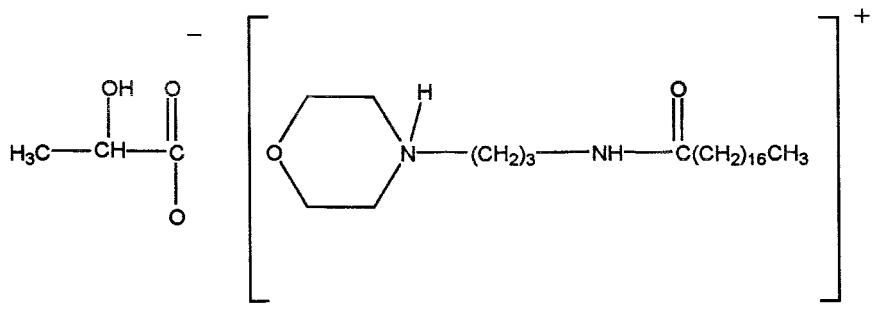

FIGURE 1
Chemical formula for Isostearamidopropyl Morpholine Lactate.

Drug Administration (FDA) in 1996 reported that Isostearamidopropyl Morpholine Lactate is used in a total of 20 formulations (Table 1) (FDA 1996). According to data submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in 1995, Isostearamidopropyl Morpholine Lactate is used at concentrations of 1–5% in hair preparations (CTFA 1995). The McIntyre Group Ltd. (1996) reported that the typical use concentration was 0.5% of the active material (25%) or 2% of the "as sold" material (not specified).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

In an acute toxicity study, five Sprague-Dawley white rats (three male, two female) were given a single oral dose of a commercial product containing 4% Isostearamidopropyl Morpholine Lactate in an aqueous solution. Animals were given 0.46 ml of the undiluted product per 100 g of body weight to produce a dose of 5 g/kg. The acute oral LD_{50} was >5.0 g/kg. No lesions were found at necropsy. In a study using 10 rats, five of each sex, the LD_{50} was >5.0 ml/kg (Pharmachem Testing Services, Inc. 1993). In an earlier study using five male and five female rats, the acute oral LD_{50} was >5 ml/kg. The rats tested appeared normal immediately after treatment and during a 2-week observation period. Organs of the thorax and abdomen appeared normal (Tox Monitor Laboratories, Inc. 1989a).

Ocular Irritation

A volume of 0.1 ml of a 16% solution of a commercial product (containing 4% Isostearamidopropyl Morpholine Lactate) in water was instilled into the conjunctival sac of three New Zealand white rabbits in a Draize ocular irritation assay. The cornea and iris were not affected, but the conjunctiva scores were (out of 20) 4, 2, and 6 for Rabbits 1 to 3, respectively, at 24 hours. At 48 hours, all three rabbits had scores of 2. At 72 hours, one rabbit still had a score of 2/10. The maximum mean irritation score was 4/110. In a second assay, a maximum mean irritation score of 3.3/110 was produced by instillation of 16% Isostearamidopropyl Morpholine Lactate in water. In both studies, Isostearamidopropyl Morpholine Lactate was considered minimally irritating (Tox Monitor Laboratories, Inc. 1989b).

Dermal Irritation

Isostearamidopropyl Morpholine Lactate, at a concentration of 10% in water, was applied as a 0.5-ml dose to the intact and abraded skin of six New Zealand white rabbits. The test solution had a primary skin irritation score of 1.83/8.0 and was mildly irritating to the skin (Tox Monitor Laboratories, Inc. 1989b).

TABLE 1
Cosmetic product formulation data on Isostearamidopropyl Morpholine Lactate (FDA 1996)

Product category	Total no. formulations in category	Total no. of formulations containing Isostearamidopropyl Morpholine Lactate
Baby shampoos	23	1
Hair sprays (aerosol fixatives)	334	3
Shampoos (noncoloring)	972	10
Tonics, dressings, and other hair grooming aids	604	2
Other personal cleanliness products	339	1
Cleansing preparations	820	3
1996 Total		**20**

MUTAGENICITY

The mutagenicity of Isostearamidopropyl Morpholine Lactate was assayed in a *Salmonella typhimurium/Escherichia coli* plate incorporation test, both with and without S9 metabolic activation. Strains of bacteria used were *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2 *uvr*A (pKM101). After toxicity was observed during a preliminary concentration range-finding test, in which plates were tested with 10 log dilutions of Isostearamidopropyl Morpholine Lactate (up to 100 μl/plate), 5 half-log dilutions were tested. A range of five half-log dilutions of the test material was tested to a maximum concentration of 1.0 μl/plate (without activation) or 10.0 μl/plate (with activation). No evidence of mutagenicity was observed. In the absence of metabolic activation, toxicity was observed at 0.01 μl/plate (TA1537), 0.10 μl/plate (TA98 and TA100), 0.316 μl/plate (TA1535), and 1.0 μl/plate (WP2). Precipitated test material was noted at 0.316 μl/plate (TA98), 1.0 μl/plate (TA1537), and 0.10 μl/plate (TA100). In the presence of activation, toxicity was observed at 0.316 μl/plate (TA1537), 1.0 μl/plate (TA1535, TA98, and TA100), and 10.0 μl/plate (WP2). Precipitated test material was observed at 3.16 μl/plate (TA1537 and TA98), 1.0 μl/plate (TA1535 and TA100), and 10.0 μl/plate (WP2). The test was repeated at concentrations up to 0.05 μl/plate or 0.5 μl/plate, respectively. No mutagenic response was observed, either with or without S9 activation. Toxicity was observed at 0.5 μl/plate in strains TA1537 and WP2 in the absence of metabolic activation; in the presence of activation, 0.158 μl/plate and 0.05 μl/plate were toxic to strains TA1537 and TA100, respectively. No precipitated test material was observed in any plate (Genesys Research, Inc. 1996).

CLINICAL ASSESSMENT OF SAFETY

Repeated-Insult Patch Test

An antidandruff conditioning rinse containing an effective concentration of 4.0% Isostearamidopropyl Morpholine Lactate and a two-in-one shampoo (shampoo/conditioner) containing an effective concentration of 3.0% Isostearamidopropyl Morpholine Lactate were evaluated in a 6-week repeated-insult patch test using 99 panelists (male and female) between the ages of 19 and 78. During induction, nine consecutive applications of the test material and subsequent evaluations of the test site (the infrascapular area of the back; to the right or left of the midline) were made. The effective concentration of the antidandruff rinse was 4.0%. For the shampoo/conditioner, a volume of 0.2 ml, diluted to a 5.0% *v/v* solution with distilled water, was administered for the first two patch applications. Beginning with the third patch application of the shampoo formulation, the test concentration was decreased to 1.0% *v/v* in distilled water due to a significant number of erythematous reactions. The effective concentrations of Isostearamidopropyl Morpholine Lactate were 0.15 and 0.03%, respectively. The occlusive patches were removed by the subjects 24 hours after application; test sites were evaluated and new patches applied at 48 hours. Patches applied on Friday were evaluated at 72 hours, on the following Monday. A 14-day rest period followed the ninth evaluation. During the 6th week of the study, the challenge phase was initiated. Identical patches were applied to previously unexposed sites. The patches were again removed 24 hours after application, and graded at 48 and 72 hours. If there was evidence of sensitization, a rechallenge test was performed on unexposed skin under both occlusive and semiocclusive conditions, 1 or 2 weeks after the completion of the challenge phase. Patches were applied for 24 hours, and evaluated at 48, 72, and 98 hours after application. Detailed results were not available. It was reported, however, that two subjects underwent rechallenge under both occlusive and semiocclusive conditions to the antidandruff rinse. Low-level irritant responses were observed to varying degrees, but no evidence of sensitization was detected upon rechallenge. Irritation was also seen with the shampoo formulation to varying degrees, with no sensitization reactions in any of the subjects tested. The researchers attributed the irritation observed to the detergent nature of the products (TKL Research, Inc. 1991).

Dermal Irritation

A 2% *v/v* concentration of a two-in-one shampoo (shampoo/conditioner) was evaluated for its irritancy potential using 19 panelists, aged 25–75 years, and an occlusive soap chamber test. In order to qualify for this study, each subject had first demonstrated a positive reaction characterized by definite erythema with or without edema/vesiculation to a 24-hour occlusive patch test with 0.75% aqueous sodium lauryl sulfate. Five other formulations, not containing Isostearamidopropyl Morpholine Lactate, were also tested using the same volunteers. The patch used was a 25-mm diameter molded plastic chamber lined with a nonwoven cotton pad attached with hypoallergenic tape. On day 1, 0.3 ml of the product (effective concentration of 0.06% Isostearamidopropyl Morpholine Lactate) was applied to the cotton padding of the patch, which was then affixed to the volar aspect of the forearm for 24 hours. On days 2–4, the product was applied for 18-hour per day. Test sites were evaluated on days 2–4 prior to application, 6 hours after patch removal on day 5 and on day 8. If grade 4 erythema and/or grade 3 fissuring or grade 4 scaling were observed, patches were not reapplied. Total irritancy scores for each product were obtained on days 5 and 8 by summing the scores for erythema, dryness/scaling, and fissuring on each of the two days. An average irritancy score was obtained by dividing the total irritancy score by the number of subjects (19) and the number of scoring days (two). The total irritancy score for the shampoo/conditioner was 174.0; the average irritancy score was 4.58. Detailed responses were not provided. Erythema, scaling, and fissuring were observed following application of the formulation (TKL Research, Inc. 1991).

SAFETY ASSESSMENT OF MORPHOLINE

The CIR Expert Panel issued a Final Report on the safety of Morpholine in 1987. The following is a summary of the

data reviewed by the Panel and the conclusion it reached (Elder 1989).

Morpholine is a heterocyclic secondary amine that is readily nitrosated, so the potential exists for the formation of *N*-nitrosomorpholine when Morpholine is used in formulations. *N*-Nitrosomorpholine, in turn, is carcinogenic in laboratory animals.

Morpholine is largely unmetabolized by rats and rabbits, whereas in guinea pigs it is extensively metabolized by *N*-methylation and *N*-oxidation. Most of the Morpholine administered to rats and hamsters was excreted unchanged in the urine.

The oral LD_{50} of Morpholine was between 1.05 and 1.63 g/kg for rats and 0.9 g/kg for guinea pigs. Unneutralized solutions of Morpholine caused severe corneal necrosis, but upon neutralization Morpholine was not injurious to rabbit eyes. Undiluted Morpholine was corrosive to the skin of rabbits, but a mascara formulation containing 1% Morpholine was nonirritating.

In studies of acute and short-term dermal toxicity, deaths of guinea pigs and rabbits were caused by undiluted/unneutralized Morpholine and diluted/unneutralized Morpholine, respectively. In both cases, the skin was necrotic.

Short-term oral administration of Morpholine at various doses caused swelling, congestion, and necrosis of various organs in rats and guinea pigs. At higher dosages, deaths occurred in both species.

The most severe toxic effects observed in acute inhalation studies of Morpholine were irritation to the eyes and nose and increased respiratory rate. In short-term inhalation studies with rats, irritation of the mucous membranes and an increased respiratory rate were observed. Nasal lesions, as well as red, white, and dark foci in the lungs, were noted. In another study, the weight, residual volume, and total capacity of the lungs were decreased. Chronic inhalation studies in rats and guinea pigs produced the observations that the exposure to Morpholine caused changes in nervous system activity, arterial blood pressure, and peripheral blood indices at both high and low concentrations. No changes were observed in the functions of the liver, kidneys, and testes, with the exception of liver function in guinea pigs at the higher dosage. At the higher concentration of Morpholine, the lesions included swelling of the alveolar cells and atrophy of lymphoid elements in the spleen; these effects were still obvious 1 month after the Morpholine exposure ended. At lower concentrations of Morpholine, a decrease in the size of lymph nodules in the spleen was noted, but this effect was not observed 1 month after exposure had ended. Chromosomal aberrations were noted at both dosages, but those of the low dosage were not significantly greater than the control rate.

Nitrosation of Morpholine produces *N*-nitrosomorpholine, which has been mutagenic in a variety of test systems. Simultaneous exposure of laboratory animals to Morpholine and nitrites has caused a number of different cancers. Exposure to Morpholine combined with the inhalation of NO_2 increased the incidence of pulmonary adenomas in mice; *N*-nitrosomorpholine was present in the lungs of mice exposed to both Morpholine and atmospheric NO_2. Endogenous formation of *N*-nitrosomorpholine in humans has not been demonstrated; but the presence of *N*-nitrosoproline in human urine suggests that nitrosation does occur in humans. Morpholine can be nitrosated in human gastric juice in the presence of nitrities.

Morpholine was a weak positive mutagen in the L5178 mouse lymphoma assay, in BALB/3T3 malignant cell transformation and fibroblast transformation, and in sister chromatid exchange assays. Morpholine was negative for mutagenicity in the Ames test with and without activation by S9 rat liver fraction; a modification of this same test also produced negative results. At nontoxic doses, Morpholine did not increase the rate of DNA repair in rat hepatocytes. In the intrahepatic host-mediated assay with mice, Morpholine alone was negative for the production of revertants, but when Morpholine and sodium nitrite were administered in combination, reversions were significantly increased. Results from other host-mediated assays were the same. In a transplacental mutagenesis study in hamsters, the combination of Morpholine and sodium nitrite caused an increase in micronucleation and chromosome aberrations in embryonic fibroblasts; morphologic or malignant transformations of fetal cells were also noted. Pyrolysates of Morpholine at 500 and 600°C were mutagenic in the Ames test.

A carcinogenic response was produced in rats in a long-term feeding study of Morpholine in which nitrites were present in the diet. It was suggested that Morpholine was nitrosated in the stomachs of the test animals. Morpholine and nitrites were also carcinogenic to hamsters, although hamsters appeared to be more resistant than rats to the carcinogenic effects. The most common neoplasms reported in rats were sarcomas, adenomas, and carcinomas of the liver. Other neoplasms of the liver were also noted. In mice treated with Morpholine and nitrites, pulmonary adenoma was the most common neoplasm.

Addition of sodium ascorbate had an inhibitory effect on the carcinogenicity of the Morpholine-nitrite combination. An increase was observed in the incidence of gastric neoplasms in test animals fed diets with added sodium ascorbate (with Morpholine and nitrites present); this was attributed to increased longevity or a consequence of the reduced incidence of hepatic neoplasms. The increase in gastric neoplasms after the administration of sodium ascorbate was observed in both rats and mice.

In humans, Morpholine was a cutaneous, ocular, and mucous membrane irritant, and a skin sensitizer. Morpholine was absorbed through the skin, by which route it was highly toxic; the toxicity diminished when Morpholine vapor was diluted to less than 25%. Ocular irritation from Morpholine vapor could lead to corneal edema, a lesion resulting in "hazy" or "halo" vision.

Results of a patch test using a panel of human subjects with a mascara formulation containing 1% Morpholine indicated that the mascara was not an irritant or sensitizer. In its Discussion, the CIR Expert Panel indicated that it is aware of reports that Morpholine is an occupational irritant and sensitizer; however, cosmetic formulations containing Morpholine have produced neither irritation nor sensitization.

Morpholine is not considered to be an animal carcinogen. It reacts easily with nitrosating agents resulting in the formation of *N*-nitrosomorpholine. Under conditions of use, it is highly unlikely that Morpholine is totally free of carcinogenic nitrosamines. Therefore, the Expert Panel could not conclude that Morpholine is safe without additional data regarding the formation of *N*-nitrosomorpholine under conditions of use. The Expert Panel issued a formal conclusion of insufficient data. The type of information required was either analytical in-use data regarding the formation of *N*-nitrosmorpholine or an appropriate risk assessment.

SUMMARY

Isostearamidopropyl Morpholine Lactate is the lactic acid salt of Isostearamidopropyl Morpholine that is used as an antistatic agent in cosmetic products. In 1996, the cosmetic industry reported to the FDA that Isostearamidopropyl Morpholine Lactate was used in 20 formulations. The typical concentrations of use for hair preparations were 1–5%; the most common use concentration was reportedly 0.5% of the active material (25%), or 2% of the "as sold" material (concentration not specified).

Isostearamidopropyl Morpholine Lactate is produced by the condensation of isostearic acid and aminopropylmorpholine to form isostearamidopropyl morpholine. This product is neutralized in an aqueous medium with lactic acid, resulting in a 25% solution of Isostearamidopropyl Morpholine Lactate. Isostearamidopropyl Morpholine Lactate typically contains 0.15% unreacted aminopropylmorpholine and 0.2% unreacted isostearic acid. *N*-nitroso impurities were not detected.

The acute oral LD_{50}s of Isostearamidopropyl Morpholine Lactate in rats were >5.0 g/kg and >5.0 ml/kg. Isostearamidopropyl Morpholine Lactate at a concentration of 16% caused minimal irritation to the eyes of rabbits. At a concentration of 10%, Isostearamidopropyl Morpholine Lactate was mildly irritating to the intact and abraded skin of rabbits.

Isostearamidopropyl Morpholine Lactate was nonmutagenic in the Ames Test using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2 *uvr*A (pKM101), with or without metabolic activation. The compound was toxic at most test concentrations.

Shampoos containing effective concentrations of 3–4% Isostearamidopropyl Morpholine Lactate did not cause sensitization in repeated-insult patch tests using 99 subjects, although skin irritation attributed to the shampoo's detergent was observed. A shampoo containing 2% Isostearamidopropyl Morpholine Lactate was evaluated for skin irritancy using 19 volunteers; the average irritancy score was 4.58, and erythema, scaling, and fissuring were observed following application of the test formulation.

This review included a summary of data on Morpholine from an earlier safety assessment. Although Morpholine is an occupational irritant and sensitizer, cosmetic formulations containing Morpholine have produced neither irritation nor sensitization, Morpholine is not considered to be an animal carcinogen, although it reacts easily with nitrosating agents resulting in the formation of *N*-nitrosomorpholine. These data raised concerns regarding the presence of *N*-nitrosomorpholine in cosmetic products. Without quantitative data regarding the formation of *N*-nitrosomorpholine under conditions of use, it was concluded that the safety of Morpholine had not been documented and substantiated (Elder 1989).

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel noted that mild to moderate skin irritation was to be expected in leave-on products containing Isostearamidopropyl Morpholine Lactate, but believed that irritation would not be of concern in rinse-off products. Although ultraviolet (UV) absorption maxima and minima were not available, the Expert Panel concluded that Isostearamidopropyl Morpholine Lactate was not likely to absorb UVA or UVB light.

The Panel noted that Isostearamidopropyl Morpholine Lactate was toxic at many of the concentrations used to test for mutagenicity, but that there was no evidence of genotoxicity at the lowest concentrations assayed in bacterial systems. Data were available showing an absence of *N*-nitroso compounds.

Isostearamidopropyl Morpholine Lactate exhibits none of the human irritation and sensitization reactions observed with occupational exposure to Morpholine. Based on the animal and clinical toxicity data in this report, the Expert Panel concluded that Isostearamidopropyl Morpholine Lactate was safe for use in rinse-off products.

Additional data, however, are needed to support safety in leave-on formulations. Section 1, paragraph (p) of the CIR Procedures states that "a lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Isostearamidopropyl Morpholine Lactate were not sufficient for determining whether this ingredient, under relevant conditions of use, was either safe or unsafe. The Panel released an Insufficient Data Announcement on March 5, 1996, outlining the data needed to assess the safety of Isostearamidopropyl Morpholine Lactate in rinse-off and leave-on formulations. Data and comments were received relating to rinse-off use and incorporated into the safety assessment, but no data were received to address leave-on use issues. The additional data needed to support safety in leave-on products are: (1) skin penetration; if there is significant skin penetration, then both a 28-day dermal toxicity study to assess general skin and systemic toxicity, and a reproductive and developmental toxicity study are needed; (2) one genotoxicity study in a mammalian system; if positive, then a 2-year dermal carcinogenesis study using National Toxicology Program (NTP) methods may be needed; and (3) inhalation toxicity data.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that Isostearamidopropyl Morpholine Lactate is safe for use as a cosmetic ingredient in rinse-off formulations in the present concentrations and practices of use. The Panel also concludes that the available data are insufficient to support safety in leave-on formulations.

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