

## Final Report on the Safety Assessment of Lauramine and Stearamine<sup>1</sup>

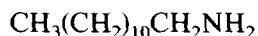
**Abstract:** Lauramine and Stearamine are aliphatic amines intended for use in cosmetic formulations as antistatic agents, but no current uses have been reported. In a subchronic feeding study in rats, 3,000 ppm of Stearamine in the diet caused weight loss and increased mortality, with an accumulation of histiocytes in the mucosa of the small intestine and mesenteric lymph nodes. A diet of 500 ppm did not produce these effects. Dogs fed Stearamine at 15 mg/kg/day showed the same histiocyte accumulation. In a 2-year chronic feeding study in rats, Stearamine at concentrations up to 500 ppm (maximum tested) showed no significant increase in the incidence of tumors. Stearamine at 0.01% in a high-fat diet promoted the carcinogenic effects of DMBA in female rats, whereas 0.1% significantly inhibited the production of tumors. Tests in animals showed Lauramine to cause severe dermal irritation and necrosis. Stearamine (in an ether vehicle) applied to the skin of albino mice caused severe hyperplasia at concentrations as low as 3 mg in a 0.2-ml application. These available data were insufficient to support the safety of Lauramine and Stearamine in cosmetic formulations. Additional data considered necessary to evaluate the safety of these ingredients include the following: impurities (especially data on nitrosamines); two different genotoxicity assays (one using a mammalian system and, if positive, a dermal carcinogenesis assay by National Toxicology Program standards may be required); and a human repeat-insult patch test. It cannot be concluded that these ingredients are safe for use in cosmetic products until the listed safety data have been obtained and evaluated. **Key Words:** Lauramine—Stearamine—Aliphatic amines—Antistatic agents.

Lauramine and Stearamine are aliphatic amines that function as antistatic agents. The following report is a review of the safety data on these ingredients.

### CHEMISTRY

#### Definition and Structure

Lauramine (CAS No. 124-22-1) is the aliphatic amine that conforms to the following formula (Estrin et al., 1982):

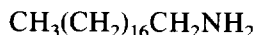


Other names for Lauramine include 1-Dodecanamine, Dodecylamine, and Lauryl Amine (Estrin et al., 1982).

<sup>1</sup> Reviewed by the Cosmetic Ingredient Review Expert Panel.

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Stearamine (CAS No. 124-30-1) is the aliphatic amine that conforms generally to the following formula (Estrin et al., 1982):



Other names for Stearamine are 1-Octadecanamine, Octadecylamine, and Stearyl Amine (Estrin et al., 1982).

### Properties

The physical properties of Lauramine and Stearamine are listed in Table 1.

Lauramine has the potential to form carcinogenic nitrosamines when ingested with nitrate (Lijinsky, 1982; Lijinsky et al., 1981).

### Method of Manufacture

In general, primary amines are produced by reacting fatty acids with ammonia, followed by dehydration to nitriles and subsequent catalytic hydrogenation to amines (Armak, 1978).

### Analytical Methods

Petrino and Russo (1980) developed a method of separating several aliphatic amines, including Lauramine, by thin-layer chromatography using silica gel plates. High-performance thin layer chromatography may be used to isolate Stearamine from water (Sherma et al., 1984).

### USE

#### Cosmetic Use

Lauramine and Stearamine are antistatic agents (Nikitakis, 1988). No formulation or frequency of use data on these ingredients were reported to the Food and Drug Administration (FDA) in 1993 (FDA, 1993).

TABLE 1. *Physical properties of Lauramine and Stearamine*

Property	Lauramine	Stearamine	References
Physical form	Liquid	Solid	Armak (1978)
Molecular weight	185.40	269.52	Sweet (1987)
Density	0.8015 (at 20°C)	0.8616 (at 20°C)	Weast (1982)
Solubility	Alcohol, ether, benzene, chloroform	Alcohol, ether, benzene, chloroform	Weast (1982)
Boiling Point (°C, atmosphere: 760 mm)	259	348.8	Weast (1982)
Melting point (°C)	28.3		Weast (1982)
Refractive index (20°C)	1.4421	1.4522	Weast (1982)

### Noncosmetic Use

Stearamine is used as a corrosion-inhibiting boiler-water additive (Sherma et al., 1984).

## BIOLOGY

### Absorption, Excretion, and Distribution

In a dermal absorption study, 100  $\mu$ l of 0.05, 0.5, 5, and 50% [ $^{14}$ C]-Lauramine was applied to the skin of groups of three hairless mice for 24 h. Three different solvents were used: squalene, castor oil, and triethyl citrate. Absorption differed according to the solvent used. When squalene was the solvent, 30% of 0.05 and 5% Lauramine, 57% of 0.5% Lauramine, and 5% of 50% Lauramine were absorbed. When castor oil was used, 6% of 0.05% Lauramine, 4% of 0.5% and 50% Lauramine, and 22% of 5% Lauramine were absorbed. With triethyl citrate as the solvent, approximately 5% of the applied dose of 0.05 and 50% Lauramine and 12% of 0.5 and 5% Lauramine was absorbed. Approximately 80% of the radioactivity recovered from the treated animals was found in the expired CO<sub>2</sub>. No details were given regarding the distribution of the remaining radioactivity in the urine, feces, or body homogenate (Iwata et al., 1987).

### Antimicrobial Activity

Lauramine has bacteriostatic, fungistatic, and algistatic activity (Hueck et al., 1966) as well as the ability to inhibit plaque formation in vitro (Turesky et al., 1972; Bass et al., 1975; Bapna et al., 1988). Stearamine also has antimicrobial properties (Kabara et al., 1972; Hueck et al., 1966).

## ANIMAL TOXICOLOGY

### Subchronic Oral Toxicity

Five male and five female Sprague-Dawley rats were fed 3,000 ppm Stearamine in their diet for 209 days. No untreated control animals were used in the experiment, but the results were compared with those for animals fed 3,000 ppm stearic acid. The two chemicals were equally toxic, causing anorexia, weight loss, and increased mortality. The animals fed the Stearamine diet had a lower daily feed intake than those fed the stearic acid diet. The average weight change was -31 g for the males and +30 g for the females fed the Stearamine diet and +12 g for the males and +58 g for the females fed the stearic acid diet. Four of the 10 rats from the Stearamine group survived to the end of the study. The average survival time was 87 days for the males and 199 days for the females. Only two female rats from the stearic acid group survived the study. The average survival time for the male and female rats from this group was 107 and 127 days, respectively. When microscopic examinations were performed on the tissues from five rats in the Stearamine group, accumulated histiocytes with pale or foamy cytoplasm were observed in the mucosa of the small intestine and mesenteric lymph nodes. Hepatic focal granulomas were also found in three rats. None of these lesions were

found in the four rats examined from the stearic acid group (University of Miami, Department of Pharmacology, 1957).

### Chronic Oral Toxicity

A 2-year toxicity study of Stearamine was conducted using Sprague-Dawley rats. Four groups of 24 rats each (12 of each sex) were fed diets containing 20, 100, 200, and 500 ppm Stearamine. A control group of animals was fed the base diet alone. The feed consumption, growth rate, death rate, and blood cell counts for the experimental animals were comparable to those of the control animals. The survival rate for this study was 17 to 33%, including the control group. At necropsy, no significant differences were found between the experimental and control groups in the incidence and types of lesions observed (University of Miami, Department of Pharmacology, 1957).

In a 1-year toxicity study using dogs, three groups of three dogs each were fed 0.6, 3.0, and 15.0 mg/kg/day Stearamine. A control group of dogs was given untreated feed. The high-dose group gained less weight than the control and lower-dose animals. The weight gain for the two lower-dose groups was similar to that of the controls. Blood cell counts were comparable in experimental and control animals. Only one dog died before study termination; this dog was from the group receiving 15.0 mg/kg/day Stearamine and suffered from anorexia and what appeared to be gastroenteric irritation. At necropsy, two animals from the high-dose group had lesions suggestive of accumulated Stearamine in the mucosa of the small intestine and the sinuses of the mesenteric lymph nodes, which were filled with pale histiocytes. However, no definite lesions were identified in the intestinal tracts of these animals or in any of the other experimental animals (University of Miami, Department of Pharmacology, 1957).

### Dermal Irritation

#### *In Vitro*

Lauramine and Stearamine were tested in a proposed *in vitro* model for identifying skin-irritating chemicals. The method was based on the correlation between irritation potential and the ability to reduce the skin's penetration barrier by lysis of the stratum corneum. The skin of male Wistar rats was clipped and removed as a single unit and subjected to tape stripping, abrasion, or immersion in water. Epidermal slices were taken from the skin and treated with 50% (wt/vol<sub>(ethanol)</sub>) Lauramine or Stearamine. Evaluation of the slices was made after 1, 4, and 24 h of exposure. The reduction in electrical resistance of the treated epidermal slices after contact with Lauramine and Stearamine was taken as a measure of irritating potential. The threshold resistance value for a positive effect was 4k $\Omega$ . skin disc. Lauramine and Stearamine were both skin corrosives. Lauramine caused resistance values ranging from 2.5 to 0.9 k $\Omega$ .skin disc over 24 h, and Stearamine caused a resistance value of 3.4 k $\Omega$ .skin disc after 24 h (Oliver et al., 1988).

*In Vivo*

Groups of three hairless mice had 0.1, 0.5, 1, 5, and 50% Lauramine applied under occlusive patches to their backs for 24 h. The skin was graded 1, 24, and 48 h after the patches were removed. Strong irritation and necrosis occurred at concentrations of 0.5% and greater, and slight irritation was observed with 0.1% Lauramine (Iwata et al., 1987).

Similar results were obtained in studies with rabbits. Using Food and Drug Administration methods, Iwata et al. (1987) reported that, at concentrations of 0.5% and greater, Lauramine was a strong irritant. A concentration of 0.1% Lauramine was slightly irritating. Lauramine also caused strong cutaneous irritation and necrosis during a percutaneous absorption study (described earlier in this report), in which concentrations ranging from 0.05 to 50% were applied to the skin of mice for 24 h (Iwata et al., 1987).

Rockland male albino mice had 0.2 ml of Stearamine (3 or 30 mg) in ether applied to their shaved backs on days 1, 3, and 5 of the experiment. On day 6, the treated skin was removed and the epidermis isolated. The tissues were analyzed for cholesterol and  $\Delta^7$ -cholestanol. Treatment with 30 mg of Stearamine caused very severe hyperplasia and a fivefold increase in epidermal weight. The sebaceous glands and hair follicles were absent, and  $\Delta^7$ -cholestanol and cholesterol concentrations had increased. Similar results were observed at the lower dose, except the appearance of hair follicles and sebaceous glands remained normal. The authors noted that these results did not correspond to responses characteristic of carcinogenic hydrocarbons (Brooks et al., 1957).

**CARCINOGENICITY**

In the 2-year chronic toxicity study (described earlier in report), no significant increase occurred in the incidence of lesions in Sprague-Dawley rats fed diets containing 20, 100, 200, and 500 ppm Stearamine (University of Miami, Department of Pharmacology, 1957).

**Tumor Promotion**

The effects of Stearamine on mammary carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) was investigated using female Sprague-Dawley rats on high-fat diets. Four groups of 21 rats each were given a single 5-mg dose of DMBA intragastrically at 47 to 51 days of age. One week later, the rats were fed diets containing 5% corn oil, 20% corn oil, 20% corn oil and 0.01% Stearamine, or 20% corn oil and 0.1% Stearamine. At 2-week intervals, the rats were weighed, examined, and palpated for neoplasms. All the rats were killed 16 to 17 weeks following DMBA administration; necropsies was performed.

As expected, a greater number of neoplasms with a shorter latency period was observed among rats fed the 20% corn oil diet than among those fed the 5% corn oil diet. The addition of 0.01% Stearamine to the 20% corn oil diet slightly reduced body weight gain and potentiated the effect of the high-fat diet, increasing the number of neoplasms that developed and shortening the latency period beyond

that observed with the high-fat diet alone. However, 0.1% Stearamine appeared to inhibit tumor growth as well as markedly reduce body weight gain. Significantly fewer neoplasms were found in the rats fed the 0.1% Stearamine and 20% corn oil diet compared with the other three groups. All the neoplasms were adenocarcinomas (Parenteau et al., 1991).

### SUMMARY

Lauramine and Stearamine are antistatic agents that are not presently used by the cosmetic industry but have been identified as being of interest for possible use in future formulations.

In a subchronic feeding study, 3000 ppm of Stearamine in the diet of rats caused weight loss, increased mortality, and accumulation of histiocytes in the mucosa of the small intestine and mesenteric lymph nodes. A diet of 500 ppm fed over 2 years did not produce these effects in rats. However, dogs fed 15.0 mg/kg/day for 1 year accumulated Stearamine in the mucosa of the small intestine, and their mesenteric lymph node sinuses were filled with histiocytes.

Stearamine was tested for its effects on mammary carcinogenesis induced by 7,12-dimethylbenz[a]anthracene in female rats on high-fat diets. At a concentration of 0.01%, Stearamine stimulated tumorigenesis and slightly inhibited body growth; however, at a concentration of 0.1%, Stearamine significantly inhibited both tumorigenesis and body growth.

Lauramine and Stearamine were classified as skin corrosives in both in vitro and in vivo tests. Lauramine caused severe dermal irritation and necrosis in mice treated with concentrations of 0.5% or greater, and 30 mg of Stearamine in ether caused severe hyperplasia.

### DISCUSSION

Section 1, paragraph (p), of the *Cosmetic Ingredient Review (CIR) Procedures* states that "A lack of information about an ingredient shall not be enough 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 Lauramine and Stearamine are insufficient to determine whether these ingredients, under each relevant condition of use, is safe or unsafe. The Expert Panel released a "Notice of Insufficient Data" announcement on August 23, 1993, outlining the data needed to assess the safety of Lauramine and Stearamine. The types of data required included the following:

1. Impurities on both Lauramine and Stearamine (especially data on nitrosamines)
2. Two different genotoxicity assays (one using a mammalian system); if positive, a dermal carcinogenesis assay by National Toxicology Program standards may be required
3. Human repeat-insult patch test

Although data on the individual ingredients are preferred for the second and third types of request listed above, the CIR Expert Panel considers these ingre-

dients sufficiently similar that data on Lauramine could suffice for both ingredients.

No offer to supply the data was received. In accordance with Section 45 of the *CIR Procedures*, the Expert Panel will issue a "Final Report—Insufficient Data." When the requested new data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the *CIR Procedures*, "Amendment of a Final Report."

### CONCLUSION

The safety of Lauramine and Stearamine has not been documented and substantiated. The CIR Expert Panel cannot conclude whether these ingredients are safe for use in cosmetic products until the appropriate safety data have been obtained and evaluated.

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