Amended Final Safety Assessment

Triethanolamine and Triethanolamine-Containing Ingredients as Used in Cosmetics

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ABSTRACT

The CIR Expert Panel assessed the safety of triethanolamine and 31 related triethanolamine-containing ingredients as used in cosmetics. Triethanolamine is reported to function as a surfactant or pH adjuster; the related triethanolamine-containing ingredients included in this safety assessment are reported to function as surfactants and hair or skin conditioning agents. The exception is TEA-sorbate, which is reported to function as a preservative. The Panel reviewed available animal and clinical data. While data were not available for all ingredients, the Panel relied on the information available for triethanolamine in conjunction with previous safety assessments of components of triethanolamine-containing ingredients. Those data could be extrapolated to support the safety of all included ingredients. The Panel concluded that triethanolamine and related triethanolamine-containing ingredients named in this report are safe as used when formulated to be non-irritating. These ingredients should not be used in cosmetic products in which N-nitroso compounds can be formed.

INTRODUCTION

In 1983, the Cosmetic Ingredient Review (CIR) Expert Panel issued a report on the safety of Triethanolamine, Diethanolamine, and Monoethanolamine. In 2010, the Panel decided to reopen that safety assessment as three separate reports and to include related ingredients in each of the new reviews. This assessment addresses triethanolamine and 31 related triethanolamine-containing ingredients.

Triethanolamine, an ingredient reported to function as a surfactant or pH adjuster in cosmetic products, previously had been reviewed by the CIR Expert Panel. In 1983, the Expert Panel concluded that triethanolamine is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin.[1] In products intended for prolonged contact with the skin, the concentration of triethanolamine should not exceed 5%. Triethanolamine should not be used in products containing N-nitrosating agents. In the 1983 assessment, data demonstrated that triethanolamine was a mild skin and eye irritant, and that irritation increased with increasing ingredient concentration.

The following 31 ingredients are also included in this safety assessment of triethanolamine. These ingredients are reported to function in cosmetics as surfactants, skin conditioning agents, or hair conditioning agents. TEA-sorbate is reported to function only as a preservative.

Inorganic salts
TEA-Hydrochloride
TEA-Sulfate

Organic acid salts
TEA-Laurate
TEA-Laurate/Myristate
TEA-Myristate
TEA-Palmitate
TEA-Stearate*
TEA-Isostearate
TEA-Undecylenate
TEA-Sorbate
TEA-Oleate
TEA-Canolate
TEA-Cocoate
TEA-Hydrogenated Cocoate
TEA-Tallate
TEA-Glyceryl Dimaleate

Hydroxy Acid Salts
TEA-Lactate*

Organo-Substituted Sulfates
Magnesium/TEA-Coco-Sulfate
Sodium/TEA C12-13 Pareth-3 Sulfate
TEA-Lauryl Sulfate*
TEA-Laureth Sulfate
TEA-Oleyl Sulfate
TEA-C10-15 Alkyl Sulfate
TEA-C11-15 Alkyl Sulfate
TEA-C12-13 Alkyl Sulfate
TEA-C12-14 Alkyl Sulfate
TEA-C12-15 Alkyl Sulfate
TEA-Coco-Sulfate
TEA-C11-15 Pareth Sulfate
TEA-C12-13 Pareth-3 Sulfate
TEA-PEG-3 Cocamide Sulfate

The ingredients marked with an asterisk have been previously reviewed by the CIR, and the conclusions of safety on these ingredients are provided in Table 1. The safety of many of the "components" of these ingredients has been reviewed by CIR, and these conclusions are also provided in Table 1.

CHEMISTRY

Triethanolamine is an amino alcohol. Triethanolamine is produced commercially by aminating ethylene oxide with ammonia. The replacement of three hydrogens of ammonia with ethanol groups produces triethanolamine. (Figure 1). Triethanolamine contains small amounts of diethanolamine and ethanolamine. Triethanolamine is reactive and bifunctional, combining the properties of alcohols and amines. The reaction of ethanolamines and sulfuric acid produces sulfates. Triethanolamine can act as an antioxidant against the autoxidation of fats of both animal and vegetable origin.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine[1]

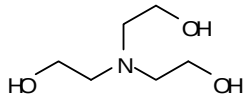


Figure 1. Triethanolamine

Of concern in cosmetics is the conversion (*N*-nitrosation) of secondary amines (R^1-NH-R^2), such as diethanolamine (wherein R^1 and R^2 are each ethanol), into *N*-nitrosamines that may be carcinogenic. Tertiary alkyl amines ($NR^1R^2R^3$), such as triethanolamine (wherein R^1, R^2, and R^3 are each ethanol), however, do not tend to react with *N*-nitrosating agents to directly form nitrosamines. However, tertiary amines can act as precursors in nitrosamine formation by undergoing nitrosative cleavage (e.g., one ethanol functional group can be cleaved off of triethanolamine to generate diethanolamine).[2] The resultant secondary amine (i.e. diethanolamine) can then be *N*-nitrosated (i.e. to *N*-nitrosodiethanolamine [NDELA]). Accordingly, triethanolamine can react, in a formulation or in vivo, with nitrites or oxides of nitrogen to form a nitrosamine. Nitrous anhydride is the oxide of nitrogen that most commonly initiates nitrosation in vivo.[3-6]

Acid Salts

The acid salts (inorganic salts, organic acid salts, and hydroxy acid salts), mentioned above, are ion pairs which freely dissociate in water (e.g., Figure 2). Therefore, these salts are closely related to the corresponding free acids and triethanolamine. In other words, TEA stearate is closely related to stearic acid and triethanolamine.

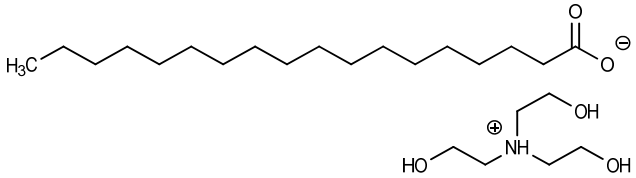


Figure 2. TEA Stearate

Organo-Substituted Sulfates

The sulfates consist of organic acid salts which have the additional functional group of sulfate. For example, TEA lauryl sulfate is a twelve carbon alkyl chain (i.e. lauryl) bonded to a sulfate anion, balanced with a triethanolammonium cation (Figure 3).

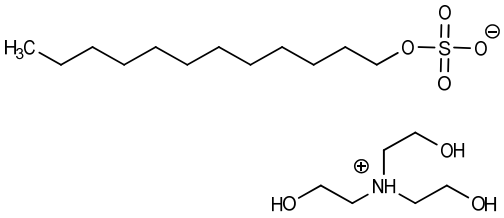


Figure 3. TEA-Lauryl Sulfate

Definition and Structure

The definitions and structures of triethanolamine and triethanolamine-containing ingredients are provided in Table 2. Chemical and physical properties are described in Table 3.

Method of Manufacture

Triethanolamine

Triethanolamine is produced by reacting 3 moles of ethylene oxide with 1 mole of ammonia; additional ethylene oxide will continue to react to produce higher ethylene oxide adducts of triethanolamine.[7] Typically, ethylene oxide is reacted with ammonia in a batch process to produce a crude mixture of approximately one-third each ethanolamine, diethanolamine, and triethanolamine. The crude mixture is later separated by distillation.

TEA-Stearate

TEA stearate was produced by mixing partially neutralized stearic acid and triethanolamine at temperatures above 80°C, and then cooling.[8] It was determined that the acid-soap complex at a 2:1 fixed stoichiometric ratio was formed between TEA stearate and stearic acid.

TEA-Lauryl Sulfate

> TEA-lauryl sulfate is manufactured by neutralizing lauryl sulfuric acid with aqueous (aq.) triethanolamine.
> From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

Commercial alkyl sulfates are produced by the sulfation of primary alcohols using sulfur trioxide or chlorosulfonic acid followed by neutralization with a base to produce the corresponding salt.[10]

Stability

TEA-Stearate

TEA stearate was produced as described previously. On cooling, a lamellar gel phase formed.[11] Solid crystals were observed after 5 h. Upon storage, the sample gradually separated into two phases; after a few weeks, a separate liquid phase and a solid-pearly crystalline phase were observed.

Impurities

Triethanolamine

Based on unpublished survey data collected by the Food and Drug Administration (FDA), a diethanolamine impurity level of 0.3% was found in triethanolamine samples.[12] (Additional details were not provided).

TEA Lauryl Sulfate

> Impurities in TEA-lauryl sulfate may include triethanolamine, TEA-sulfate, unsulfated alcohol, TEA chloride, and formaldehyde (some grades).
> From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

Sodium sulfate and residual alcohols may be present as impurities in commercial alkyl sulfate products.[10] Typically, industrial alkyl sulfates contain 1-4% sodium sulfate and 0.5-18% residual alcohol.

N-Nitrosodiethanolamine Formation

Nitrosamines are compounds containing the R^1R^2N-NO functional group.[2] *N*-Nitrosation is the process of converting organic compounds (e.g., alkyl amines) into *N*-nitroso derivatives (e.g., nitrosamines) by reaction with nitrosating agents. These agents include nitrous acid (HNO_2), oxides of nitrogen (e.g., nitrous anhydride or nitrite), and other compounds capable of generating a nitrosonium ion, NO^{+2}.

The formation of a specific nitrosamine, NDELA, from reaction of triethanolamine with nitrite was examined in vitro and in vivo.[13] The triethanolamine used in these studies had an impurity content of 0.4% diethanolamine. In an aq. matrix, approximately 3% triethanolamine converted to NDELA at a pH of 4.0 in the presence of acetic acid. At the same pH, in the presence of sulfuric or hydrochloric acid, only about 1% of the triethanolamine was nitrosated. At pH 7, the greatest nitrosation to NDELA, 0.5%, occurred in the presence of sulfuric acid. No conversion of triethanolamine to NDELA was detected at pH 2 or 10. In nutrient broth cultures (neutral pH), 0.08% and 0.68% of the triethanolamine was nitrosated to NDELA in a diluted (high cecal inoculum) and full-strength (low cecal inoculum) media. (The percent nitrosation was determined using values that were corrected for diethanolamine impurity-related NDELA formation).

In vivo, female $B6C3F_1$ mice were dosed dermally or orally with 1000 mg/kg triethanolamine, in conjunction with oral exposure to sodium nitrite.[13] Following 7 days of dermal dosing, no NDELA was detected in the blood, ingesta, or urine of test, vehicle control, or sodium nitrite control mice. (The limits of detection for the blood, ingesta, and urine were 0.001, 0.006, and 0.47 µg/ml, respectively). With a single oral dose, the concentrations of NDELA found in the blood and ingesta of mice 2 h post-dosing were 0.001 ± 0.0005 µg/g and 0.044 ± 0.059 µg/g, respectively.

USE

Cosmetic

Triethanolamine is reported to function in cosmetics as a surfactant or pH adjuster, and it can be used in fragrances.[14] Most of the other triethanolamine ingredients are reported to function in cosmetics as surfactants, skin conditioning agents, or hair conditioning agents. TEA-sorbate is reported to function only as a preservative.

Voluntary Cosmetic Registration Program (VCRP) data obtained from the FDA in 2011 indicate that triethanolamine is used in 3756 formulations; 3034 of those products are leave-on formulations, and 3106 formulations involve dermal exposure.[15] According to data submitted by industry in response to a survey conducted by the Personal Care Products Council (Council), triethanolamine is used at concentrations of 0.0002-19%.[16] In leave-on products, the reported use concentrations range from 0.0002-6%. With the exception of TEA-lauryl sulfate (302 uses) and TEA-stearate (130 uses), all other in-use triethanolamine-containing ingredients had less than 20 reported uses.[15] TEA-lauryl sulfate had the highest concentrations of use, with ≤40% being reported for rinse-off and ≤8% for leave-on formulations.[17] The available use data on all in-use ingredients are provided in Table 4a. Ingredients not reported to be in use, according to VCRP data and the Council survey, are listed in Table 4b.

The dermal exposure of consumers to triethanolamine was estimated assuming 2.5% triethanolamine in cosmetic products (based on the limit set by the European Commission [EC]) and that all triethanolamine is unreacted.[18] Using an EC algorithm method, the dermal exposure of consumers to triethanolamine in an eye make-up powder is 0.0125 mg/kg bw/day and to triethanolamine in a body lotion is 6.25 mg/kg bw/day. Using a DERMAL program method, the dermal potential dose rate for a bar soap containing 2.5% triethanolamine is 5.182 mg/day.

Some of the ingredients reviewed in this assessment may be applied to baby skin, used near the eye area or mucous membranes, or could possibly be ingested. Triethanolamine, TEA-lauryl sulfate, and TEA-stearate are reported to be in products that could be inhaled. In practice, 95% to 99% of the aerosols released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 μm range.[19,20] Therefore, most aerosols incidentally inhaled from these sprays are deposited in the nasopharyngeal region and are not respirable.[21,22] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic diameters in the range considered to be respirable.[22] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

All of the ingredients named in this report are listed by the EC in Annex III Part 1, the list of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down.[23] The ingredients reviewed in this safety assessment, as trialkylamines, trialkanolamines, and their salts, are allowed at concentrations of up to 2.5% in non-rinse-off products; "other" product types do not have a concentration limit for triethanolamine. In leave-on and rinse-off, the following limitations apply: do not use with nitrosating systems; minimum allowable purity is 99%; maximum allowable secondary amine content is 0.5% in raw material; maximum allowable nitrosamine content is 50 μg/kg; must be kept in nitrite-free containers. Sorbic acid and its salts and undec-10-enoic acid and its salts, including their ethanolamine salts, are listed by the EC for use as preservatives, with maximum concentrations of use of 0.6 and 0.2%, respectively, based on the free acid.[24]

According to data obtained from Health Canada, some leave-on type products reportedly use triethanolamine as high as 10 and 30%, with some reporting concentration ranges of 30-100% (Health Canada, personal communication).

Non-Cosmetic

Triethanolamine

> Triethanolamine is used in the manufacture of emulsifiers and dispersing agents for textile specialties, agricultural chemicals, waxes, mineral and vegetable oils, paraffin, polishes, cutting oils, petroleum demulsifiers, and cement additives. It is an intermediate for resins, plasticizers, and rubber chemicals. It is used as a lubricant in the textile industry, as a humectant and softening agent for hides, as an alkalizing agent and surfactant in pharmaceuticals, as an absorbent for acid gases, and in organic syntheses.
>
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

Triethanolamine, TEA-myristate, TEA-palmitate, TEA-oleate, TEA-cocoate, and TEA-tallate have uses as an indirect food additive.[25] Triethanolamine is used as a rust inhibitor in water-based metalworking fluids.[26]

TOXICOKINETICS

Dermal

In Vitro

Triethanolamine and TEA-Stearate

The penetration of oil-in-water (o/w) emulsions containing triethanolamine was determined in vitro using human skin samples.[27] Emulsions were prepared using 1% triethanolamine and 5% stearic acid and using 5% triethanolamine and 10.5% stearic acid; the pH values of these emulsions were 8.0 and 8.2, respectively. Because the pH values of commercial lotions containing triethanolamine were reported to be ~7.0, emulsions were also prepared with the pH adjusted to 7.0. The

test samples were applied to the skin for 24 h at a concentration of 3 mg/cm^2, and the area of exposed skin was 0.64 cm^2. Penetration and absorption was measured at 24 h using the emulsions with a pH of ~8, and at 24 and 72 h using the emulsions with a pH of 7.0. The 24-h skin sample was tape-stripped, while the 72 h sample was not.

Using the emulsions with a pH of ~8, there was no statistically significant difference in penetration between a 1 or 5% triethanolamine emulsion; the total triethanolamine recovered in the skin was 20.9 and 15.4% of the applied dose for the 1 and 5% triethanolamine emulsions, respectively, and the amount recovered in the receptor fluid was 1.1 and 1.2% of the applied dose, respectively. Using the emulsion with a pH of 7 and concentration of 1% triethanolamine, there was no statistically significant difference in penetration observed when comparing the 24 and 72 h values; 9.4 and 8.9% of the applied dose was found in the skin and 0.43 and 0.68% of the applied dose was found in the receptor fluid at 24 and 72 h, respectively. There was a statistically significant difference in the total recovery of triethanolamine using the 5% emulsion, pH 7, at 24 h compared to that recovered at 72 h. At this concentration, the amounts found at 24 and 72 h were 5.5 and 6.3% of the total dose, respectively, in the skin and 0.28 and 0.60% of the applied dose, respectively, in the receptor fluid.

The researcher stated that all of the triethanolamine in a triethanolamine/stearic acid emulsion presumably existed as the TEA stearate salt, since an excess of stearic acid was used. Radiolabeled TEA stearate was prepared by mixing stearic acid with a radiotracer dose of 0.64 µCi [^{14}C]triethanolamine (5 µg triethanolamine) in an o/w emulsion; the ratio of triethanolamine to stearic acid was 1:4. Using this emulsion, at pH 8.2, 50.1% of the applied dose of TEA-stearate was found in the skin and 0.51% in the receptor fluid after 24 h. With pH 7.0, 29.1% of the applied dose was found in the skin and 0.46% in the receptor fluid after 24 h. The researchers stated that the "data suggest that the penetration rate of the triethanolamine molecule determines the penetration of its salts."

Non-Human

Triethanolamine

The blood kinetics and absorption, distribution, metabolism, and excretion (ADME) of [^{14}C]triethanolamine were determined following dermal application of 2000 mg/kg neat [^{14}C]triethanolamine without occlusion to 24 male C3H/HeJ mice and with occlusion to 3 male mice.[28] (Non-radiolabeled triethanolamine was 99.6% pure; radiochemical purity was 98.6%). Triethanolamine was extensively and rapidly absorbed following a single open application of 2000 mg/kg neat [^{14}C]triethanolamine. The majority of the radioactivity, 49-62% of the total dose (~58-72% of the absorbed dose), was excreted in the urine, primarily as unmetabolized triethanolamine. Diethanolamine and ethanolamine were not detected in the urine. Approximately 18-28% of the total dose (~20-32% of the absorbed dose) was excreted in the feces. The amount of radioactivity remaining in the body after 48 h ranged from 3.3-6.1%, and the amount recovered at the application site ranged from 1.2-2.1% for the open application and 6-11% for the occluded application.

The National Toxicology Program (NTP) examined the ADME of triethanolamine following dermal administration to B6C3F$_1$ mice and F344 rats.[29] With mice, groups of 4 females were given a single dose of 79 or 1120 mg/kg [^{14}C]triethanolamine in acetone; the dose contained 12-15 µCi, with the appropriate amount of non-labeled triethanolamine in a volume of 190 µl/dose. (Radiochemical purity of [^{14}C]triethanolamine was 97%; the purity of non-labeled triethanolamine was confirmed, but the purity was not stated). The dose was applied to a 1.44 cm^2 area of clipped skin, and a non-occlusive cover was used. Approximately 60-80% of the dose was absorbed, and absorption increased with increasing dose. In the urine, 22.5-27.5% and 48-56% of the dose was recovered after 24 and 72 h, respectively, and triethanolamine was excreted mostly unchanged. Approximately 5-9 and 8-13% of the dose was recovered in the feces at the same time periods.

With rats, groups of 4 females were given a single dermal dose of 68 or 276 mg/kg [^{14}C]triethanolamine in acetone; the dose contained 65 µCi, with the appropriate amount of non-labeled triethanolamine in a volume of 190 µl/dose. The dose was applied to a 12 cm^2 area of clipped skin, and a non-occlusive cover was used. Only 19-28% of the dose was absorbed over 72 h; absorption increased with increasing dose, but not significantly. In the urine, 13-24% of the dose was recovered in 72 h as mostly unchanged triethanolamine. The amount recovered in the feces after 72 h was <0.25%. Very little radioactivity, <1%, was present in the tissues; a number of tissues had elevated concentrations of radiolabel relative to blood.

Oral

Non-Human

Triethanolamine

Triethanolamine (purity not specified) was administered orally to male and female rats as a single dose, or as a repeated dose for 5-6 days.[30] (Dosing details were not described). At 24 h after administration of the single dose, the excretion ratio of unchanged triethanolamine in the urine and feces was 53 and 20% of the dose, respectively. With repeated administration, the excretion ratio per day remained constant. Gender did not affect the ratios. TEA glucuronide was detected, but

in a very small amount. (Actual concentration not specified). Triethanolamine was rapidly absorbed in the gastrointestinal tract, and excreted mostly in the urine in unchanged form.

Other

Non-Human

Triethanolamine

A group of 27 male C3H/HeJ mice was given an intravenous (i.v.) injection of 1 mg/kg [^{14}C]triethanolamine as an aq. solution (0.5 mg/ml), and the dose volume was 2 ml/kg.[28] (Non-radiolabeled triethanolamine was 99.6% pure; radiochemical purity was 98.6%). Radioactivity in the blood declined in a biphasic exponential manner for 24 h, with a relatively rapid initial phase of [^{14}C] elimination followed by a slower terminal phase. The majority of the radioactivity, approximately 69%, was excreted in the urine, primarily as unmetabolized triethanolamine. Diethanolamine and ethanolamine were not detected in the urine. Some of the radioactivity, ~17%, was excreted in the feces. The average amount of radioactivity recovered in the tissues after 24 h was 3.1%.

The NTP examined the ADME of triethanolamine following i.v. administration to B6C3F$_1$ mice and F344 rats.[29] Groups of 4 female mice and 4 female rats were given a single i.v. dose of 3 mg/kg [^{14}C]triethanolamine in isotonic saline. For mice, the dose contained 6 μCi, with the appropriate amount of non-labeled triethanolamine, for a dosing volume of 2 ml/kg. (Radiochemical purity of [^{14}C]triethanolamine was 97%; the purity of non-labeled triethanolamine was confirmed, but the purity was not stated). At 24 h, 26 and 14% of the dose was excreted in the urine and feces, respectively, while at 72 h, these values were 62 and 28%, respectively. Triethanolamine was excreted mostly unchanged. Little, <0.5%, was detected in expired carbon dioxide. For rats, the dose contained 47 μCi, with the appropriate amount of non-labeled triethanolamine, for a dosing volume of 1 ml/kg. Much more of the radioactivity was excreted in the urine for rats compared to mice, and excretion was more rapid. Approximately 90% of the dose was recovered in the urine in 24 h, and 98% in 72 h, mostly as unchanged triethanolamine. Like mice, <0.5%, was detected in expired carbon dioxide. Only 0.9% of the radioactivity was detected in the tissues after 72 h.

TOXICOLOGICAL STUDIES

Acute (Single) Dose Toxicity

Dermal

Triethanolamine

The acute dermal toxicity of triethanolamine was examined using groups of 6 rabbits. Undiluted triethanolamine, 91.8 and 88.1% active, was applied to the intact and abraded skin of 3 rabbits under a 24 h occlusive patch. The exposure to actual triethanolamine was 2 g/kg. None of the animals died. Mild erythema and edema were reported at 24 h.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

Oral

Triethanolamine

The acute oral toxicity of triethanolamine was determined using guinea pigs and rats. In guinea pigs, undiluted triethanolamine has an LD_{50} of 8 g/kg, and the LD_{50} of triethanolamine in a gum arabic solution was between 1.4 and 7.0 g/kg. Using rats, the oral LD_{50} of undiluted triethanolamine ranged from 4.19 g/kg- 11.26 g/kg. The purity ranged from 78.6% triethanolamine (with 8.6% diethanolamine and 1.7% ethanolamine) to unspecified high purity.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine[1]

TEA-Lauryl Sulfate

TEA-lauryl sulfate was moderately to slightly toxic in acute oral studies with rats, LD_{50} values ranged from 0.27 > 1.95 g/kg.
From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

The oral LD_{50} of TEA-lauryl sulfate in male and female Wistar rats was >2 g/kg.[31]

Other

Triethanolamine

The intraperitoneal LD_{50} of triethanolamine was 1.45 g/kg for mice.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.1

Repeated Dose Toxicity

Dermal

Triethanolamine

> A closed-patch continuous exposure test was performed using 10 guinea pigs in which commercial and high purity triethanolamine, 8 g/kg, was applied daily 5 days/wk. All guinea pigs died by the 17th application; adrenal, pulmonary, hepatic, and renal damage were observed. In a 13-wk study, 1 mg/kg of a hair dye formulation containing 0.1-0.15% or 1.5% triethanolamine was applied to the backs of 12 rabbits for 1 h, twice weekly. The test site skin was abraded for half of the animals. No systemic toxicity was observed, and there was no histomorphologic evidence of toxicity. In a 6-mos study in which triethanolamine was applied caudally to rats for 1 h/day, 5 days/wk, no toxic effects were observed with a 6.5% solution. However, using a 13% solution, changes (not specified) were seen in liver and central nervous system function. The addition of 1.4 mg/l triethanolamine to the drinking water of the rats dosed dermally with 13% triethanolamine did not increase the toxic effects.
>
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

In a 2-wk study, undiluted triethanolamine (purity not specified) was applied dermally to B6C3F$_1$ mice and F344 rats, 5 days/wk.[32] Dose levels of triethanolamine were 0.21, 0.43, 0.84, 1.69, and 3.37 g/kg for the mice and 0.14, 0.28, 0.56, 1.13, and 2.25 g/kg for rats. Chronic active necrotizing inflammation of the skin at the application site occurred at a greater frequency and severity in rats than in mice. No renal or hepatic lesions were detected with either species.

In a preliminary study, 50 µl of 1-100% triethanolamine was applied to the backs of male C3H mice, 5 days/wk for 2wks, and mild epidermal hyperplasia was observed in mice treated with 25, 50, or 100% triethanolamine.[33] Based on these results, a 13-wk study was completed in which 50 µl of 0, 10, 33, or 100% triethanolamine (99.3% pure) in acetone was applied 3x/wk to a clipped site on the backs of 15 male and female C3H/HeJ mice. (The approximate daily doses were 0, 0.14, 0.46 or 2.0 g/kg for males, respectively, and 0, 0.16, 0.54, or 2.3 g/kg for females, respectively.) No treatment-related clinical signs of toxicity, skin irritation, or mortality were observed during the study. A mild epidermal hyperplasia was observed in treated male and female mice at all three concentrations tested, and this reaction was considered to be evidence of mild irritation associated with repeated application of triethanolamine.

In a 13-wk NTP dermal study using male and female B6C3F$_1$ mice, application of 250, 500, 1000, or 2000 mg/kg bw triethanolamine in acetone or 4000 mg/kg neat resulted in decreased mean body weights and body weight gains for some male mice.[34] (Purity of triethanolamine was 99%. Functional group titration indicated <0.4% ethanolamine or diethanolamine). Irritation was observed for the highest dose group. Microscopically, inflammation was observed for this dose group and acanthosis was noted for all dose groups, with severity increasing with dose. Absolute kidney and liver weights of males and females of the 4000 mg/kg group and relative kidney to body weights of males dosed with ≥1000 mg/kg were increased compared to controls. Absolute and relative spleen weights were also significantly increased in high dose female mice compared to controls.

In a 13-wk dermal study using male and female F344/N rats, application of 125, 250, 200, or 1000 mg/kg bw triethanolamine (99% pure) in acetone or 2000 mg/kg neat, resulted in significant decreases of mean body weights and body weight gains in the high dose animals.[34] (Functional group titration indicated <0.4% ethanolamine or diethanolamine present). Irritation was observed at the application site. Microscopic lesions included acanthosis and inflammation. Kidney weights of males and females dosed with ≥500 mg/kg were increased compared to controls, and dosed females, but not males, had greater incidences of nephropathy, as compared to controls.

TEA-Lauryl Sulfate

> In a 28-day dermal study, application of a diluted shampoo containing 1% TEA-lauryl sulfate to rabbit skin caused erythema, edema, wrinkling, eschar formation, and severe desquamation. In a 13-wk dermal study in rabbits with a diluted shampoo containing 2.4% TEA-lauryl sulfate, mild erythema and dryness were observed.
>
> From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

Oral

Triethanolamine

> Oral studies were conducted in which groups of 8-20 rats were dosed with 0.2-2.61 g/kg/day triethanolamine for 60 days to 6 mos, and groups of 8 guinea pigs were dosed with 0.2-1.6 g/kg/day triethanolamine for 60 or 120 doses. Repeated oral ingestion of triethanolamine produced evidence of hepatic and renal damage in both species. Some deaths occurred in groups of rats fed ≥0.3 g/kg/day triethanolamine.
>
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

Male and female B6C3F$_1$ mice and F344 rats were given drinking water containing 2 -8% triethanolamine (purity not specified) for 14 days.[35,36] Male and female high dose mice, and male and female rats given ≥4% triethanolamine, had

decreased body weights. All but one of the high dose rats were euthanized early due to severe dehydration. No treatment-related changes were observed in mice given 4% triethanolamine or rats given 2% triethanolamine in the drinking water.

Inhalation

Triethanolamine

> In inhalation studies with triethanolamine in rats and mice, no observations were reported that were indicative of a toxic pulmonary effect.
>
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

In a dose-range finding inhalation study, 5 male and 5 female Wistar rats were exposed, nose only, for 5 consecutive days to 100, 200, or 400 mg/m^3 triethanolamine (target concentrations; 98.9% pure) for 6 h.[37] Concentration-dependent laryngeal inflammation and edema were observed at microscopic examination, and the no observed adverse effect concentration (NOAEC) was 100 mg/m^3. The full, 28 day/20 exposure study used target concentrations of 0, 20, 100, and 500 mg/m^3, and the mass median aerodynamic diameter (MMAD) was 0.7-1.1 μm. A functional observational battery was conducted using 7 rats/sex/group. Minimal to moderate focal inflammation in the submucosa of the larynx was observed; effects were concentration-dependent. No systemic toxicity was observed, and there were no effects on organ weights. There were no indications of neurotoxicological effects. Based on the results of this study, the 90-day NOAEC for local irritation was calculated to be 4.7 mg/m^3. (The extrapolation of the 28-day laryngeal irritation used the calculation of benchmark concentrations for a 5% incidence of mucosal inflammation, without consideration of severity, using a multistage model).

In 14-day inhalation studies, B6C3F$_1$ mice and F344 rats were exposed to 125, 250, 500, 1000, or 2000 mg/m^3 triethanolamine (purity not specified) 6h/day, 5 days/wk, for 2 wks.[38,39] Female mice and male and female rats of the high dose group had decreased body weights, and male mice of the high dose group had increased kidney weights. Increased kidney weights in rats dosed with ≥500 mg/m^3, and decreased thymus and heart weights in mice at all doses, were not clearly associated with triethanolamine. The only histopathologic observation was a minimal acute inflammation of the laryngeal submucosa in both mice and rats; however, this occurred sporadically and there was no dose-response associated with this lesion.

REPRODUCTIVE AND DEVELOPMENTAL STUDIES

Dermal

Triethanolamine

> Hair dyes containing 0.1-0.15% or 1.5% triethanolamine were applied topically to the shaved skin of groups of 20 gravid rats on days, 1, 4, 7, 10, 13, 16, and 19 of gestation, and the rats were killed on day 20 of gestation. No developmental effects were observed.
>
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

Triethanolamine, 0.5 g/kg in acetone (purity not stated), was applied dermally to clipped skin on the back of male and female F344 rats.[40] A volume of 1.8 ml/kg was applied daily for 10 wks prior to mating, during mating, and through gestation and lactation. No effect on mating or fertility or offspring growth or survival was observed. A similar study was performed in which Swiss CD-1 mice were given daily applications of 2 g/kg triethanolamine at a volume of 3.6 ml/kg.[41] No adverse developmental effects were observed.

Oral

Triethanolamine

A Chernoff-Kavlock teratogenicity screening test was performed using mated female CD-1 mice, in which the animals were dosed by gavage with 1125 mg/kg/day triethanolamine on days 6-15 of gestation.[42] (It was stated that the triethanolamine was the "purest grade commercially available"). No adverse developmental effects were observed.

In Vitro

Triethanolamine

> Triethanolamine, at concentrations of ≤100 mg/plate, was not mutagenic in *Salmonella typhimurium* with or without metabolic activation. Triethanolamine with sodium nitrite, but not triethanolamine alone, was mutagenic in *Bacillus subtilis* without metabolic activation. NDELA, which is not mutagenic in *B. subtilis* without metabolic activation, was found in the mixture. In an unscheduled DNA synthesis test in which primary rat hepatocyte cultures were exposed to 10^{-8} to 10^{-1} M triethanolamine and [^{3}H]thymidine, simultaneously, triethanolamine did not appear to cause DNA-damage-inducible repair.
>
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

Triethanolamine, in distilled water or dimethylsulfoxide, was not mutagenic to *Escherichia coli*[43] or *S. typhimurium*, with or without metabolic activation, at doses of 0-20,000 μg/plate.[43-45] Triethanolamine (88.2% purity) did not cause gene conversion in *Saccharomyces cerevisiae*.[44] Triethanolamine was negative in a *rec* assay at doses of 0-4000 μg/disk. No

induction of sister chromatid exchanges occurred in Chinese hamster ovary cells at 0-1010 µg/ml without metabolic activation or 0-10,100 µg/ml with metabolic activation,[46] and chromosomal aberrations were not induced in cultured rat liver cells[44] or at doses of 5-100 µg/ml in cultured Chinese hamster cells.[43,46] Triethanolamine, 25-500 µg/ml, was negative in a cell transformation assay using hamster embryo cells.[43]

In Vivo

Triethanolamine

A mouse peripheral blood micronucleus test was performed using samples collected from mice that were dosed dermally for 90-days with 0-4 g/kg triethanolamine in an NTP study.[47] Results were negative in both male and female mice.

CARCINOGENICITY

Dermal

Triethanolamine

> In a series of 3 experiments using a total of 560 CBA x $C_{57}Bl_6$ male mice, the carcinogenic effects of 99%+ pure triethanolamine and 80%+ industrial grade triethanolamine and the cocarcinogenic effect of triethanolamine and syntanol DC-10 (alcohols C10-18 ethoxylated) were examined over a 14-18 mo timeframe. Triethanolamine was not carcinogenic or cocarcinogenic.
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

An initial carcinogenicity study of triethanolamine using $B6C3F_1$ mice performed by the NTP was deemed inadequate due to a *Helicobacter hepaticus* infection.[34] Therefore, a second 2-yr study was performed in which triethanolamine in acetone was applied dermally at doses of 200, 630, or 2000 mg/kg/day to male $B6C3F_1$ mice and at doses of 100, 300, or 1000 mg/kg/day to female $B6C3F_1$ mice.[48] (Purity of triethanolamine was 99+%. Using high-performance liquid chromatography/mass spectrometry, 0.491% diethanolamine was detected as an impurity. A slight increase in diethanolamine was seen in acetone and ethanol solutions after 11 days of storage; the dose formulations were prepared approximately every 2 wks). The body weights of high dose males were decreased compared to controls during wks 17-37 and at the end of the study. Dermal irritation increased with increasing dose, and was more severe in males than in females. At necropsy, treatment-related epidermal hyperplasia, suppurative inflammation, and ulceration and dermal chronic inflammation occurred at the application site in most test groups, and the incidence and severity increased with increasing dose. Lesions were found, and it was concluded that there was *equivocal evidence of carcinogenic activity* of triethanolamine in male mice, based on the occurrence of liver hemangiosarcoma, and *some evidence of carcinogenic activity* in female mice, based on increased incidences of hepatocellular adenoma.

In a 2-yr NTP dermal carcinogenicity study using F344/N rats, triethanolamine in acetone was applied at doses of 32, 63, or 125 mg/kg/day in acetone to males and at doses of 63, 125, or 250 mg/kg/day to females.[34] (Purity of triethanolamine was 99%. Functional group titration indicated <0.4% ethanolamine or diethanolamine). Irritation was observed at the application site, and frequency increased with increasing dose. At the interim necropsy, the absolute and relative kidney weights of high dose females were significantly greater than the controls. Microscopically, at the site of application, dermal lesions, including acanthosis, inflammation, and/or ulceration, were observed. It was concluded that there was *equivocal evidence of carcinogenic activity* in male rats, based on a marginal increase in the incidences of renal tubule cell adenoma, and there was *no evidence of carcinogenic activity* in female rats.

The carcinogenic potential of triethanolamine was evaluated using a Tg·AC transgenic mouse model.[49] Groups of 10-15 female homozygous mice were dosed dermally with 3-30 mg triethanolamine/mouse in acetone, 5x/wk for 20 wks. Triethanolamine was inactive in Tg·AC mice.

Oral

Triethanolamine

> Groups of 40 male and 40 female ICR-JCL mice were fed a diet containing 0.01, 0.03, or 0.3% triethanolamine throughout their lifetime. The malignant tumor incidence was 2.8, 27, and 36% for females, respectively, and 2.9, 9.1, and 3.6% for males, respectively. Treated females had a much higher incidence of thymic and non-thymic tumors in lymphoid tissues than treated males. Survival was similar for treated and control animals.
> From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

The oral carcinogenic potential of triethanolamine was examined by administering 1 or 2% triethanolamine in drinking water to groups of male and female $B6C3F_1$ mice for 82 wks.[50] (Diethanolamine was present as an impurity at 1.9%). Body weights of male mice of the 2% group were decreased during wks 1-20 when compared to controls. No significant changes in organ weights were observed. No dose-related increase of the incidence of any tumors was observed in the treated groups, and there was no evidence of carcinogenic potential of triethanolamine upon oral administration.

Drinking water containing 1 or 2% triethanolamine was given to groups of male and female F344 rats for 2 yrs.[51] (Diethanolamine was present as an impurity at 1.9%). From wk 69 on, the dose concentrations for females were reduced by half because of associated nephrotoxicity. A dose-related decrease in body weight gain was reported for male and female test group rats, and a dose-dependent increase in mortality, starting at wk 60, was observed. Absolute and relative kidney-to-body weights were significantly increased in males and females, and the increase was dose-related. Severe chronic nephropathy was statistically significantly increased in males of the high dose group and females of both dose groups. No treatment-related effects were found in the liver. There was no increase in the incidence of any tumors in the treated groups compared to controls when using the Chi-square test. Since increased nephrotoxicity appeared to affect the lifespan of the treated animals, especially the females, an age-adjusted statistical analysis was performed on the incidences of main tumors or tumor groups for males and females, and a positive trend was noted in the occurrence of hepatic tumors (neoplastic nodule/hepatocellular carcinoma) in males and of uterine endometrial sarcomas and renal-cell adenomas in females. The researchers stated that, because these tumors have been observed spontaneously in F344 rats, and since their incidences in the control group was lower than that of historical controls, the occurrence of the tumors may not be attributable to triethanolamine. Instead, increased incidence of renal tumors in the high-dose group may have been associated with renal damage. The researchers concluded that triethanolamine was toxic to the kidneys, especially in females, but it was not carcinogenic to F344 rats.

Possible Mode of Action for Carcinogenic Effects of Triethanolamine

It has been reported that choline deficiency induces liver cancer in rodents;[52,53] therefore, the potential of triethanolamine to cause choline deficiency in the liver of female $B6C3F_1$ mice was investigated as a mode of tumorigenesis.[54] Female mice were dosed dermally with unoccluded applications of 10, 100, 300, or 1000 mg/kg/day triethanolamine in acetone, 5 days/wk for 3 wks, and female CDF rats were dosed in a similar manner with 250 mg/kg/day triethanolamine. (Purity of triethanolamine was 99+%; diethanolamine impurity levels were 0.04 and 0.45%). No clinical signs of toxicity were noted for mice or rats. Phosphocholine and betaine levels were statistically significantly decreased in the high dose mice, and choline levels were decreased in these mice. The decrease in phosphocholine levels was variable, but dose-related. (More pronounced effects were observed when the triethanolamine having 0.45% diethanolamine impurity was used). In rats, no changes in choline or its metabolites were noted. The potential of triethanolamine to inhibit the uptake of [^{3}H]choline by CHO cells was also investigated, and a dose-related decrease was observed. The researchers concluded that triethanolamine may cause liver tumors in mice via a choline-depletion mode of action, and this effect is likely caused by the inhibition of choline uptake by the cells. The researchers stated that, while diethanolamine impurity may contribute to choline depletion, a choline-deficiency mode of tumorigenesis appears to be a property of triethanolamine, exclusive of any diethanolamine impurity.

Carcinogenic Potential in Humans

Triethanolamine

According to an evaluation of triethanolamine by the International Agency for Research on Cancer (IARC) Working Group, there is *inadequate evidence* in humans, as well as in animals, for the carcinogenicity of triethanolamine.[55] The overall evaluation of the IARC is that triethanolamine is *not classifiable as to its carcinogenicity to humans (Group 3).*

IRRITATION AND SENSITIZATION

Dermal Irritation

In Vitro

Triethanolamine

The dermal irritation potential of triethanolamine was determined in two in vitro assays, and these results were compared to results obtained in the in vivo Draize test and human patch test.[56] The tissues used in the in vitro tests were fully-differentiated three-dimensional reconstituted human epidermal cultures. Each in vitro test was performed in triplicate. In the first test, the in vitro patch test, triethanolamine was applied to the skin samples for 4 h using a 0.95 cm^2 polypropylene chamber. In the second in vitro test, the direct topical application test, 100 µl triethanolamine was applied directly to a 0.63 cm^2 area of the epidermal surface for 4 h. Histology, cell viability determined via 3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) reduction, and interleukin (IL)-1α release endpoints were measured in both tests, and a combination of the outcomes of these endpoints was used to determine the potential for irritation. Triethanolamine, which was described as "non-classified" in the Draize and human patch tests, was classified as a non-irritant in the in vitro patch test and an irritant in the direct topical application test. The irritant classification was based on tissue necrosis and a higher amount of released IL-1α compared to the negative control (water). The concentration of triethanolamine tested for each of the studies was not specified.

Non-Human

Triethanolamine

The primary skin irritation potential of undiluted triethanolamine was determined using rabbits. After 10 open applications of 0.1 ml to rabbit ears and 10 unoccluded applications to the intact skin of the abdomen, and 3 semi-occluded 24-h applications to abraded skin, it was concluded that triethanolamine was slightly to moderately irritating, and prolonged or repeated exposure may be irritating. Twenty-four h occluded patch tests using groups of 8 male rabbits were performed in 22 laboratories; the primary irritation score ranged from 0-5.5/24, and the total score for all 22 laboratories was 27.3/400. In a preliminary study, occlusive dermal applications of 50-100% aq. triethanolamine to pairs of guinea pigs resulted in one erythematic reaction to undiluted triethanolamine, and in another preliminary study, no irritation was observed when 5, 10, or 25% triethanolamine was applied to the backs of guinea pigs.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

The irritancy potential of triethanolamine (purity not specified) was evaluated in an ear swelling test using female BALB/c mice.[57] A significant increase in irritancy was observed with 25 and 50% triethanolamine compared to the vehicle (4:1 acetone/olive oil).

TEA-Lauryl Sulfate

The dermal irritation of TEA-lauryl sulfate ranged from not-irritating to moderately irritating to rabbit skin at concentrations up to 46%. Concentrations of up to 10% produced slight to mild irritation, while concentrations of 25 and 39% produced moderate irritation. Mild irritation was reported with 40% TEA lauryl sulfate, while testing with 46% TEA-lauryl sulfate produced non-irritant results in some laboratories and irritant results in others.

From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

Human

Triethanolamine

Clinical studies were performed with formulations containing triethanolamine. In a few studies on formulations containing 0.45-2.4% triethanolamine, the researchers concluded that no irritation was observed, while short-lived acute irritation was reported for formulations containing 1.9-2.6% triethanolamine. However, according to the Expert Panel's interpretation of the results of a number of other studies, formulations containing 0.83-20.04% triethanolamine were irritating. In clinical provocative testing using 5-10 "hyper reactors," 100% triethanolamine produced an irritant reaction on non-scarified skin, 10% triethanolamine in ethanol was a marked irritant on scarified skin, while 5% in ethanol was a slight irritant on scarified skin.

From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

A patch test with triethanolamine (purity not specified) was performed on 20 subjects, and erythema and transepidermal water loss (TEWL) were measured, and the contents of suction blister fluids (SBF) were evaluated for primary proinflammatory mediators.[58] Aq. triethanolamine, 50-100%, was applied occlusively for 24 h; 100-200 µl, concentrated to 20 µl with drying, were applied. The percent of non-responders to 100% triethanolamine was 80%; those that did respond had weak and non-uniform erythema. The incidence was below or about that found with the solvent controls. For the challenge phase, 765 µmol/cm^2 triethanolamine was applied occlusively to 12 subjects for 6-24 h. No increase in TEWL or change in eicosanoid profile of the SBF was observed. Triethanolamine was a non-irritant.

TEA-Lauryl Sulfate

In clinical studies, shampoos containing 10.5% TEA-lauryl sulfate caused no irritation with semi-occlusive patches or "use" testing, while diluted shampoos containing 0.15-7.5% produced no to moderate irritation. In an occlusive patch test, a diluted shampoo containing 4.4% TEA-lauryl sulfate was highly irritating in a 21-day cumulative irritation test.

From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

The dermal irritation potential of a 10% solution of TEA-lauryl sulfate (vehicle not identified) at neutral pH was determined using 10 subjects.[59] Duhring chambers were applied to the forearm of each subject for 5 days. A 10% solution of TEA-lauryl sulfate caused intense erythema in nearly all subjects by day 4. Testing was terminated. (Additional details were not provided).

Sensitization

Non-Human

Triethanolamine

Triethanolamine was not a sensitizer to guinea pigs when 20 guinea pigs were given dermal applications of undiluted triethanolamine 1x/wk for 3 wks, followed by challenge applications 14 and 21 days after dosing. No sensitization was seen when four lots of triethanolamine were evaluated using groups of 20 guinea pigs; induction applications were applied for up to 6 h, 1x/wk, for 3 wks, and the challenge was performed after 14 days. One of the studies used undiluted triethanolamine during in-

duction, while the other 3 studies used 50% triethanolamine at induction. All four studies used challenge patches with 90% triethanolamine. No sensitization was observed in a similar study in which induction patches contained a 25% active triethanolamine solution, and a challenge patch with the 25% solution was applied after 1 wk of non-treatment.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

The sensitization potential of triethanolamine was evaluated in a local lymph node assay (LLNA) performed with groups of 5 BALB/c mice.[57] This study was performed in conjunction with the ear-swelling test described previously. Lymphocyte proliferation increased with dose, but the increases were not statistically significant. Triethanolamine was not identified as a sensitizer in the LLNA.

The hypersensitivity of mice to triethanolamine (99+% pure) was determined.[60] Triethanolamine, in an acetone: olive oil mixture (4:1) at concentrations of 3%, 10%, or 30%, was applied daily for 5 consecutive days to groups of 8 female $B6C3F_1$ mice, and the animals were challenged 7 days later with a 30% solution. For some animals, dermabrasion, as well as intradermal injections of Freund's complete adjuvant (FCA), was used. There were no treatment-related effects on survival or body weights. There were no statistically significant or dose-related hypersensitivity responses to triethanolamine observed with a radioisotopic method or in an ear swelling test, with or without FCA.

Results were negative in three maximization studies examining the sensitization potential of triethanolamine.[26] In the first test, performed using Pirbright-White guinea pigs, induction consisted of intradermal injections of 2% triethanolamine (98.9% pure) in isotonic saline and epicutaneous application of undiluted triethanolamine, and challenge used 10% triethanolamine in isotonic saline. In the second test using 20 Dunkin-Hartley guinea pigs, intradermal and epicutaneous inductions used 1.5% technical grade triethanolamine and 25% technical grade triethanolamine with 10% sodium lauryl sulfate pre-treatment, respectively, and challenge doses consisted of 1, 5, and 10% technical and analytical grade triethanolamine. In the third study, with 15 animals and the same induction protocol just described (grade of triethanolamine not specified); 2/15 reacted to 10% triethanolamine after 1, but not 3, days.

Human

Triethanolamine

In cumulative reports on patch tests conducted over a number of years, triethanolamine, tested at 2% aq., 5% (vehicle not specified), or 5% in petrolatum, had positive reactions for contact dermatitis in 23/500, 9/479, and 2/100 subjects. The Expert Panel interpreted these findings as sensitizing. In a patch test with 64 subjects in which 0.5 ml of 1% triethanolamine (containing 88.6% triethanolamine and 6% diethanolamine) was used, the test solution was not sensitizing.

The majority of formulations containing 0.83-4.2% triethanolamine were not sensitizing, and a formulation containing 20.04% triethanolamine, tested on 26 subjects, was not considered sensitizing when it produced 2 slight reactions upon challenge. However, according to the interpretation of the Expert Panel, there were a few cosmetic formulations containing 2.1 and 2.4% Triethanolamine that the Panel determined to be sensitizing. In other studies with cosmetic formulations containing 2.1% triethanolamine, the researchers concluded that reactions observed at challenge were probably due to skin fatigue.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

TEA-Lauryl Sulfate

Undiluted shampoo formulations containing 10.5% TEA-lauryl sulfate and dilutions of formulations containing 0.15-7.5% TEA-lauryl sulfate were not sensitizers in clinical studies.
From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

Provocative Testing

A group of 737 patients was patch tested with 6 different emulsifiers, including 2.5% triethanolamine (purity not specified) in petrolatum.[61] The patch tests were performed according to International Contact Dermatitis Research Group (ICDRG) recommendations. A total of 39 patients had positive reactions to the emulsifiers, and 20 of those patients, 5 males and 15 females, had positive reactions to triethanolamine. There were 106 irritant reactions reported. The results were clinically relevant in 7 patients. Many of the patients allergic to triethanolamine were also allergic to other ingredients.

Over a 4-yr period, the incidences of positive patch test reactions to the same triethanolamine-containing cream were 69/171 patients in one clinic and 49/191 in another.[62] It was hypothesized that the difference between the clinics was due to differences in sampling methods; the first clinic tested only those patients that had recently used the triethanolamine-containing cream or who had suspected reactions. In follow-up patch testing with a total of 54 subjects from the 2 clinics, 15 of which were controls, 19 subjects had a positive allergic response to the triethanolamine-containing cream, 40 had a positive irritant response, and 13 had negative responses. With 1.45-5% triethanolamine, 6 subjects had a positive response. However, with 5-20% TEA stearate, 8/8 patients and 15/15 controls had a positive irritant response. (TEA stearate was tested because it was demonstrated that TEA stearate was formed from the combination of triethanolamine and stearic acid in for-

mulation). The researchers postulated the reactions were irritant reactions to TEA stearate. (The amount of TEA stearate present in formulation was estimated to be 4.8%, and 6/23 subjects patch tested with 5% TEA stearate had irritant reactions).

Over a 15-yr period, provocative patch testing using triethanolamine was performed on 85,098 dermatological patients.[26] There were 323 positive reactions to triethanolamine, and most of the reactions (289) were weak positives. The researchers stated that occupational exposure was not a risk factor for triethanolamine contact allergy.

Metalworkers that were dermatitis patients were patch tested with 2.5% triethanolamine in pet [63] The patches were applied for 1-2 days. On day 3, one of 216 patients (0.5%) had a positive reaction.

Patch testing was performed with 2.5% triethanolamine in pet. in 184 patients with suspected metalworking fluid contact dermatitis.[64] (All patients were metalworkers.) Patches were applied for 1 or 2 days. On day 3, 4 patients had any type of positive reactions, 2 (?) and 2 (+). The % positive reactions was 1.1%.

Phototoxicity/Photoallergenicity

Non-Human

Triethanolamine

A formulation containing 1% triethanolamine was applied to the stripped skin of 6 guinea pigs, and each animal was then exposed to ultraviolet A (UVA) light for 2 h. No erythema or edema was observed.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

Human

Triethanolamine

There were no phototoxicity or photosensitization reactions in clinical studies with a number of formulations containing 0.45-4.2% triethanolamine, nor were there any reactions with a formulation containing 20.04% triethanolamine. However, in one study with a formulation containing 4.2% triethanolamine, the Expert Panel felt that the formulation was either mildly phototoxic or there was UV enhancement of an irritant response.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

TEA-Lauryl Sulfate

Aq. shampoo formulations containing 0.3-0.42% TEA-lauryl sulfate were not photosensitizers in clinical studies.
From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

Ocular Irritation

In Vitro

Triethanolamine

The ocular irritation potential of triethanolamine was evaluated in several in vitro studies. The ocular irritation potential of triethanolamine was evaluated in the rabbit corneal epithelium model at concentrations of 0.05, 0.5,and 1%; triethanolamine was classified as non/mildly irritating at these concentrations. In the luminescent bacterial toxicity test (i.e. the Microtox® test), triethanolamine had an EC_{50} of 110 mg/l, corresponding to non/moderate irritant potential.[65] In the EYTEX assay, undiluted triethanolamine had an EYTEX/Draize equivalent of 42.1, corresponding to a prediction of severe ocular irritant.[66]

Non-Human

Triethanolamine

The ocular irritation potential of 0.005-0.1 ml undiluted triethanolamine was evaluated in a number of studies using rabbits. With high concentrations and long contact time, triethanolamine may be irritating to rabbit eyes. Using rabbits, 10% aq. triethanolamine produced essentially no irritation with or without rinsing. A formulation containing 12.6% triethanolamine, 0.1 ml, was evaluated in a study using 6 rhesus monkeys. Slit lamp examination revealed some corneal effects in 2 monkeys at 24 h and slight positive fluorescein staining in one monkey at 72 h.
From the Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine.[1]

TEA-Lauryl Sulfate

The ocular irritation potential of TEA-lauryl sulfate was evaluated in rabbit eyes; irritation ranged from not-irritating to severely irritating at concentrations up to 40%. The severity of irritation observed with each concentration varied among the studies, as illustrated by 5% TEA lauryl sulfate causing no ocular irritation in one study, but significant irritation in another.
From the Final Report on the Safety Assessment of TEA-Lauryl Sulfate.[9]

CLINICAL ASSESSMENT

Case Reports

Triethanolamine

Eczema of the face of 2 female patients was exacerbated by a cream that contained triethanolamine.[67] Patch testing was performed using the ICDRG standard series, a cosmetic battery, the triethanolamine-containing cream, and triethanolamine at 1%, 2%, and 5% in petrolatum (pet.). Both patients reacted to the triethanolamine-containing cream (+ reaction) and to 5% triethanolamine pet. (++ reaction). One patient reacted to 2% triethanolamine (+ reaction), and neither reacted to 1% triethanolamine pet. Patch tests were negative for all other compounds. In a control group of 50 subjects, patch testing with 5% triethanolamine pet. was negative.

Two cases of occupational asthma in metal workers exposed to cutting fluid containing triethanolamine were reported.[68] Exposure to triethanolamine at temperatures higher than that of ambient air was a common feature.

TEA-PEG-3 Cocamide Sulfate

Two patients with a reaction to a shampoo were patch tested with the ICDRG standard series and a 1% aq. solution of the shampoo.[69] Both patients had positive patch results to the shampoo only. Subsequent patch test with 1% aq. TEA-PEG-3 cocamide sulfate (as well as 1% cocamidopropyl betaine) produced positive results in both patients. Twenty eczema patients patch used as controls had negative patch test results to 10% aq. TEA-PEG-3 cocamide sulfate.

SUMMARY

This report is a safety assessment of triethanolamine and triethanolamine-containing ingredients as used in cosmetics. Triethanolamine is reported to function as a surfactant or pH adjuster, and the other triethanolamine-containing ingredients as surfactants, skin conditioning agents, or hair conditioning agents. TEA-sorbate is reported to function only as a preservative. Triethanolamine is reported to be used in 3756 cosmetic ingredients at concentrations of up to 6% in leave-on formulations, 19% in rinse-off formulations, and 0.7% in products that are diluted for (bath) use. All the other ingredients named in this safety assessment that are in use, with the exception of TEA-lauryl sulfate (302 uses) and TEA-stearate (130 uses), are reported to have less than 20 uses. Triethanolamine may contain diethanolamine as an impurity.

The ingredients reviewed in this report, as trialkylamines, trialkanolamines, and their salts, are allowed for use by the EU at concentrations of up to 2.5% in leave-on products; "other" product types do not have a concentration limit for triethanolamine. There are additional restrictions regarding conditions for use in leave-on and rinse-off products, including a maximum allowable secondary amine content of 0.5% in raw material and a maximum allowable nitrosamine content of 50 μg/kg.

Dermal absorption studies of triethanolamine were performed in vitro using human skin samples and in vivo using mice and rats. In vitro, the absorption of triethanolamine through human skin was low under conditions simulating perceived cosmetic use, i.e., 1-5% at pH 7.0; approximately 5.5-9.5% of the dose was recovered in the skin after 24 or 72 h, however, only ~0.5% was recovered in the receptor fluid. In mice, [^{14}C]triethanolamine in acetone was rapidly absorbed, and absorption increased with increasing dose. The majority of the radioactivity was excreted in the urine, 48-56% in 72 h, primarily as unchanged triethanolamine. Triethanolamine was absorbed more slowly and less extensively in rats than mice. In rats, 19-28% of the dose was absorbed over a 72-h period, and 13-24% of the dose was recovered in the urine, mostly as unchanged triethanolamine. In an oral dosing study with rats, triethanolamine was rapidly absorbed in the gastrointestinal tract and excreted mostly in the form of unchanged triethanolamine.

In 2 and 13-wk repeated dose dermal toxicity studies in mice with 250-2000 mg/kg bw triethanolamine in acetone or 4000 mg/kg bw neat, dermal irritation was observed in the highest dose group, and kidney and liver weights were increased with the higher doses. In rats, 125-1000 mg/kg bw triethanolamine in acetone or 2000 mg/kg bw neat was applied to rats for 13 wks, and irritation was observed at the dosing site. Kidney weights were increased in male and female rats dosed with ≥500 mg/kg triethanolamine, and dosed females had higher incidences of nephropathy. In a 14-day drinking water study, animals given 8% triethanolamine were all killed due to severe dehydration before study termination. Treatment-related changes were not observed for animals given 2 or 4% triethanolamine in their water. In inhalation studies with triethanolamine in rats (≤400 mg/m^3) and mice (≤2000 mg/m^3), no observations were reported that were indicative of a toxic pulmonary effect.

No adverse developmental effects were seen in dermal studies in which rats and mice were dosed with 0.5 and 2 g/kg triethanolamine, respectively, in acetone from before mating through lactation or in an oral teratogenicity screening test in mice with 1125 mg/kg/day triethanolamine on days 6-15 of gestation.

Triethanolamine was negative for genotoxic effects in an Ames test with or without metabolic activation, gene conversion assay, rec assay, sister chromatid exchange assay with or without metabolic activation, chromosomal aberration assay, and cell transformation assay.

In 2-yr dermal carcinogenicity studies with doses of up to 1000 and 2000 mg/kg/day triethanolamine for male and female mice, respectively, and up to 125 and 250 mg/kg/day triethanolamine for male and female rats, respectively, it was concluded that triethanolamine produced equivocal evidence of carcinogenic activity in male mice based on the occurrence of liver hemangiosarcoma, some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular adenoma, equivocal evidence of carcinogenic activity in male rats based on a marginal increase in the incidence of renal tubule cell adenoma, and no evidence of carcinogenic activity in female rats. In oral carcinogenicity studies in rats and mice, triethanolamine was not carcinogenic to rats or mice, but it was toxic to the kidneys of rats, especially females. Based on preliminary data, it has been hypothesized that triethanolamine may cause liver tumors in mice via a choline-depletion mode of action.

Triethanolamine can be a dermal irritant in both animals and human, but it has not been shown to be a sensitizer. Many of the ingredients in this report are surfactants, which can be irritating to skin and eyes.

DISCUSSION

While the CIR Expert Panel noted gaps in the available safety data for the 31 triethanolamine-containing ingredients included in this group, the Panel relied on the information available for triethanolamine in conjunction with previous safety assessments of the components of triethanolamine-containing ingredients. Those data could be extrapolated to support the safety of these ingredients. For example, myristic acid has been found safe as used, and the Panel was able to extrapolate these data to support the safety of TEA-myristate (i.e., the triethanolamine salt of myristic acid). Additionally, some of the ingredients reviewed in this assessment, such as TEA-lauryl sulfate, have previously been reviewed by the CIR and found to be safe for use in cosmetics.

The Panel was concerned with levels of free diethanolamine that could be present as an impurity in triethanolamine or triethanolamine-containing ingredients. The Panel stated that the amount of free diethanolamine available must be limited to the present practices of use and concentration of diethanolamine itself.

Dermal carcinogenicity studies performed by the NTP on triethanolamine reported equivocal evidence of carcinogenic activity in male mice based on the occurrence of liver hemangiosarcoma, some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular adenoma, and equivocal evidence of carcinogenic activity in male rats based on a marginal increase in the incidence of renal tubule cell adenoma. It has been hypothesized that triethanolamine may cause liver tumors in mice via a choline-depletion mode of action. Humans are much less sensitive to this deficiency, and these hepatic findings are considered to have little relevance to humans regarding the safety of use of triethanolamine in personal care products.

The Panel was concerned that the potential exists for dermal irritation with the use of products formulated using triethanolamine or triethanolamine-related ingredients. The Panel specified that products containing these ingredients must be formulated to be non-irritating.

Tertiary alkyl amines such as triethanolamine do not react with *N*-nitrosating agents to directly form nitrosamines. However, tertiary amines can act as precursors in nitrosamine formation by undergoing nitrosative cleavage. The resultant secondary amine (i.e. diethanolamine) can then be *N*-nitrosated to products that may be carcinogenic. Because of the potential for this process to occur, triethanolamine and triethanolamine-containing ingredients should not be used in cosmetic products in which N-nitroso compounds can be formed.

Triethanolamine, TEA-lauryl sulfate, and TEA-stearate can be used in products that may be sprayed, and so the Panel discussed the issue of potential inhalation toxicity. In the absence of sufficient safety test data to evaluate this endpoint directly, the Panel considered other data that were available to characterize the potential for these ingredients to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95 – 99% of particles produced in cosmetic aerosols are not respirable. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

CONCLUSION

The CIR Expert Panel concluded that triethanolamine and the 31 related triethanolamine-containing ingredients, listed below, are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and when the levels of free diethanolamine do not exceed the present practices of use and concentration of diethanolamine itself. These ingredients should not be used in cosmetic products in which N-nitroso compounds can be formed.

Triethanolamine
Magnesium/TEA-Coco-Sulfate*
Sodium/TEA C12-13 Pareth-3 Sulfate*
TEA-C10-15 Alkyl Sulfate*
TEA-C11-15 Alkyl Sulfate*
TEA-C12-13 Alkyl Sulfate*
TEA-C12-14 Alkyl Sulfate*
TEA-C12-15 Alkyl Sulfate*
TEA-C11-15 Pareth Sulfate*
TEA-C12-13 Pareth-3 Sulfate*
TEA-Canolate*
TEA-Cocoate
TEA-Coco-Sulfate*
TEA-Glyceryl Dimaleate*
TEA-Hydrochloride
TEA-Hydrogenated Cocoate*
TEA-Isostearate
TEA-Lactate
TEA-Laurate
TEA-Laurate/Myristate*
TEA-Laureth Sulfate
TEA-Lauryl Sulfate
TEA-Myristate
TEA-Oleate*
TEA-Oleyl Sulfate*
TEA-Palmitate
TEA-PEG-3 Cocamide Sulfate*
TEA-Sorbate*
TEA-Stearate
TEA-Sulfate
TEA-Tallate*
TEA-Undecylenate*

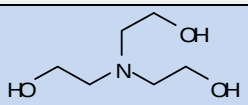
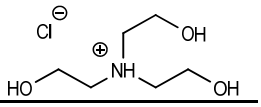
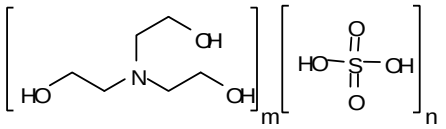
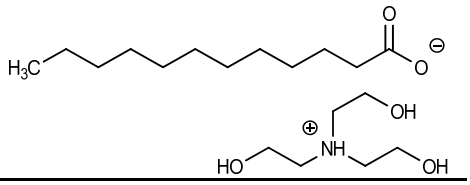
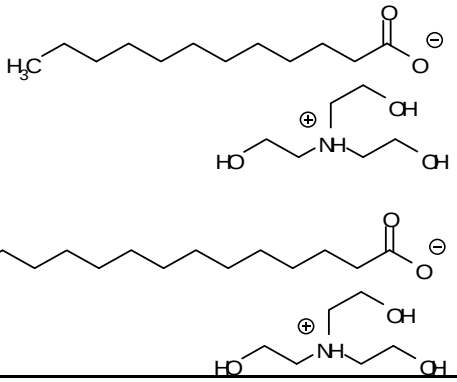
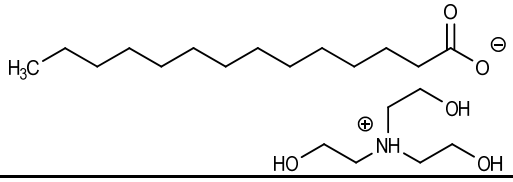
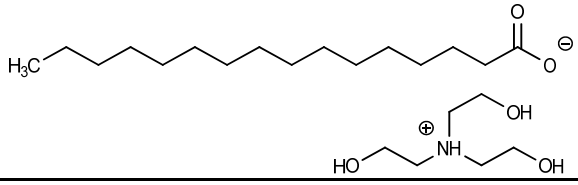
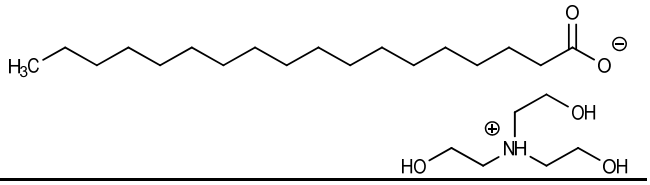
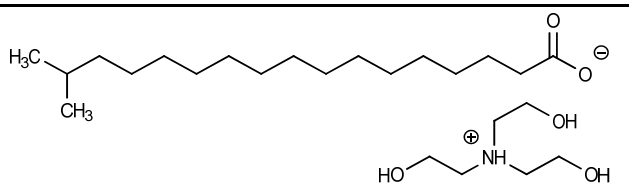
*Were the ingredients not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

TABLES

Table 1. Conclusions of previously reviewed ingredients and components

Ingredient	Conclusion	Reference
	PREVIOUSLY REVIEWED INGREDIENTS	
Triethanolamine	safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin; in products intended for prolonged contact with the skin, the concentration of diethanolamine should not exceed 5%; should not be used with products containing N-nitrosating agents.	1
TEA-Lactate	safe for use in cosmetic products at concentrations ≤10%, at final formulation pH≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations ≤30%, at final formulation pH≥3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection	70
TEA-Lauryl Sulfate	can be used without significant irritation at a final concentration thereof not exceeding 10.5%; greater concentrations may cause irritation, especially if allowed to remain in contact with the skin for significant periods of time	9
TEA Stearate	safe as used in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing; in products intended for prolonged contact with the skin, the concentration should not exceed 15% in formulation; should not be in products under conditions resulting in N-nitrosation reactions	71
	PREVIOUSLY REVIEWED COMPONENTS	
Alkyl PEG Ethers	safe as used when formulated to be non –irritating	72
Ammonium Lauryl Sulfate Sodium Lauryl Sulfate	safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin; in products intended for prolonged contact with skin, concentrations should not exceed 1%	73
Coconut Ingredients	safe as used	74
Isostearic Acid	safe as used	75
Lauric Acid Myristic Acid Oleic Acid Palmitic Acid Stearic Acid	safe as used	76 77
Plant-Derived Fatty Acid Oils	safe as used	78
Sodium Cetearyl Sulfate and Related Alkyl Sulfates	safe as used	79
Sodium Laureth Sulfate and Sulfated Ethoxylated Alcohols	safe as used when formulated to be non-irritating	80,81
Sorbic Acid	safe as used	82
Tall Oil Acid	safe as used	83

Table 2. Definitions and structures

Ingredient CAS No.	Definition	Formula/structure
Triethanolamine and inorganic salts		
Triethanolamine 102-71-6	Triethanolamine is a tertiary amine with three ethanol functional groups.	
TEA-Hydrochloride 637-39-8	TEA-Hydrochloride is the triethanolamine salt of hydrochloric acid.	
TEA-Sulfate 7376-31-0	TEA-Sulfate is the triethanolamine salt of sulfuric acid.	
Organic acid salts		
TEA-Laurate 2224-49-9	TEA-Laurate is the triethanolamine salt of a twelve carbon fatty acid, lauric acid.	
TEA-Laurate/ Myristate	TEA-Laurate/Myristate is the triethanolamine salt of a mixture of a twelve carbon fatty acid, lauric acid, and a fourteen carbon fatty acid, myristic acid.	
TEA-Myristate 41669-40-3	TEA-Myristate is the triethanolamine salt of a fourteen carbon fatty acid, myristic acid.	
TEA-Palmitate 49719-60-0	TEA-Palmitate is the triethanolamine salt of a sixteen carbon fatty acid, palmitic acid.	
TEA-Stearate 4568-28-9	TEA-Stearate is the triethanolamine salt of an eighteen carbon fatty acid, stearic acid.	
TEA-Isostearate 88120-12-1	TEA-Isostearate is the triethanolamine salt of a branched, eighteen carbon fatty acid, isostearic acid.	

one example of an "iso"

Table 2. Definitions and structures

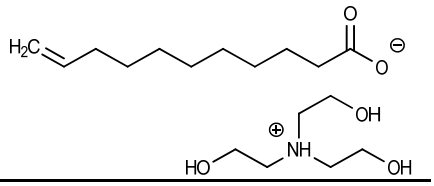
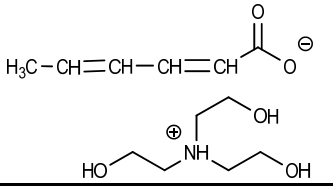
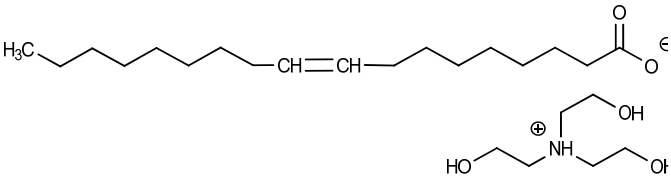
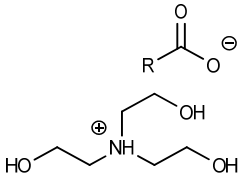
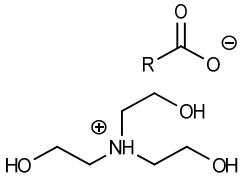
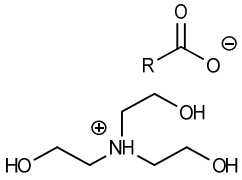
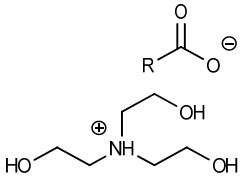
Ingredient CAS No.	Definition	Formula/structure
TEA-Undecylenate	TEA-Undecylenate is the triethanol-amine salt of a terminally unsaturated, eleven carbon fatty acid, undecylenic acid.	
TEA-Sorbate	TEA-Sorbate is the triethanolamine salt of an α, β, γ, δ-unsaturated six carbon acid, sorbic acid.	
TEA-Oleate 2717-15-9	TEA-Oleate is the triethanolamine salt of an eighteen carbon, Ω-9 fatty acid, oleic acid.	
TEA-Canolate	TEA-Canolate is the triethanolamine salt of the fatty acids derived from canola oil.	 wherein $RC(O)O^-$ = the fatty acid anions derived from Canola Oil
TEA-Cocoate 61790-64-5	TEA-Cocoate is the triethanolamine salt derived from coconut fatty acids.	 wherein $RC(O)O^-$ = the fatty acid anions derived from coconut
TEA-Hydrogenated Cocoate	TEA-Hydrogenated Cocoate is the triethanolamine salt of hydrogenated coconut fatty acids	 wherein $RC(O)O^-$ = the fatty acid anions derived from hydrogenated coconut
TEA-Tallate 8043-27-4 67784-78-5	TEA-Tallate is the triethanolamine salt of tall oil acid.	 wherein $RC(O)O^-$ = the fatty acid anions derived from Tall Oil Acid
TEA-Glyceryl Dimaleate [63358-71-4] per CAS	TEA-Glyceryl Dimaleate is the tretha-nolamine salt of the diester of glycerin and maleic acid.	*Not enough information for a structure*

Table 2. Definitions and structures

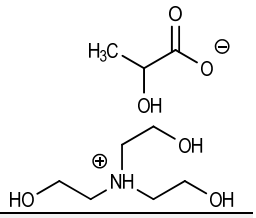
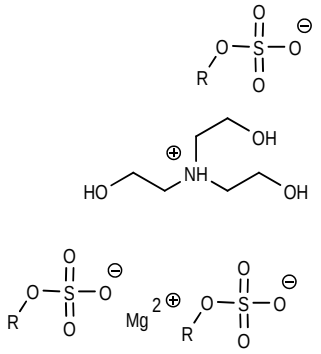
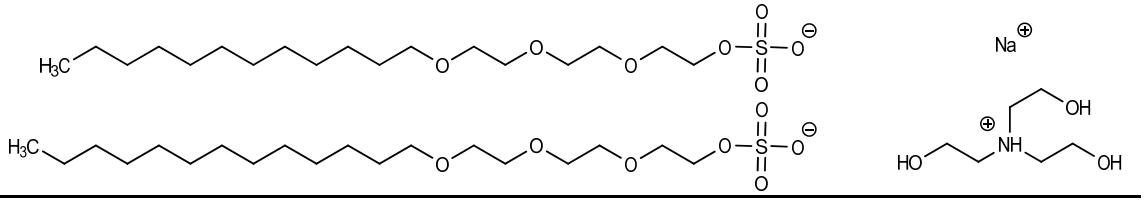
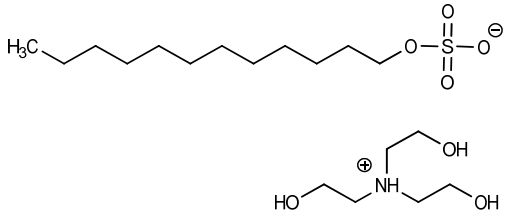
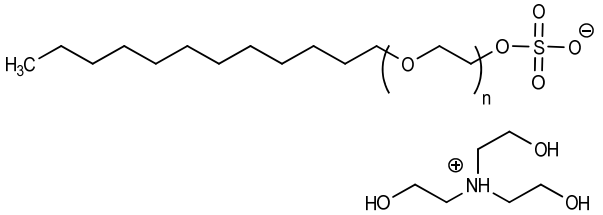
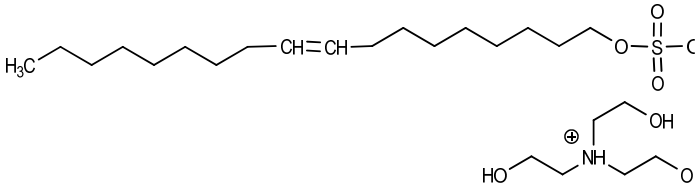
Ingredient CAS No.	Definition	Formula/structure
Hydroxy Acid Salt		
TEA-Lactate 20475-12-1	TEA-Lactate is the triethanolamine salt of the three carbon, α-hydroxy acid, lactic acid	
Organo-Substituted Sulfates		
Magnesium/TEA-Coco-Sulfate	Magnesium/TEA-Coco-Sulfate is the mixed magnesium and triethanolamine salt of coco-sulfate.	 where R represents the alkyl groups derived from coconut oil
Sodium/TEA C12-13 Pareth-3 Sulfate	Sodium/TEA C12-13 Pareth-3 Sulfate is the mixed sodium and triethanolamine salt of the sulfate ester of C12-13 pareth-3.	
TEA-Lauryl Sulfate 139-96-8	TEA-Lauryl Sulfate is the triethanol-amine salt of lauryl sulfuric acid.	
TEA-Laureth Sulfate 27028-82-6	TEA-Laureth Sulfate is the triethanol-amine salt of polyethoxylated lauryl sulfate.	 where n = 1-4
TEA-Oleyl Sulfate	TEA-Oleyl Sulfate is the triethanol-amine salt of Ω-9 unsaturated eighteen carbon alkyl sulfate, oleyl sulfate.	

Table 2. Definitions and structures

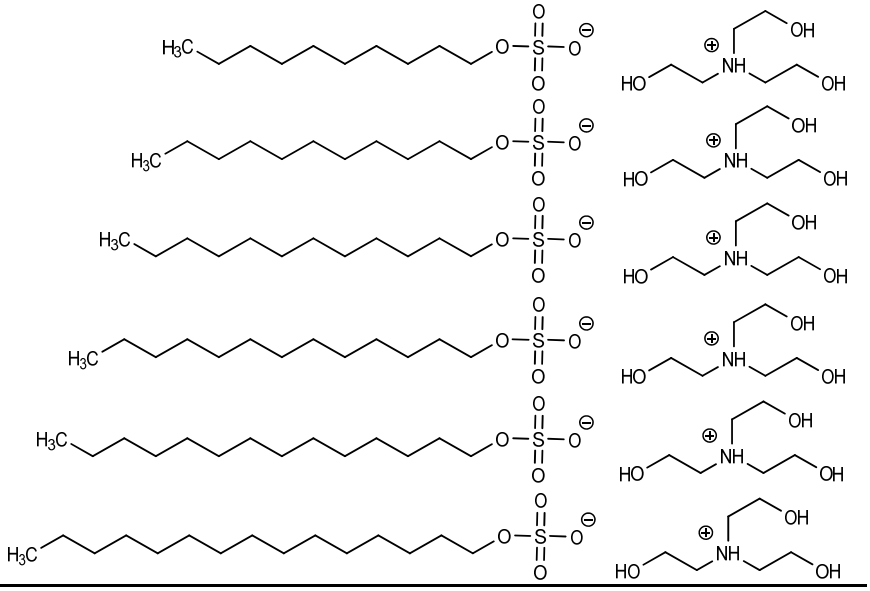
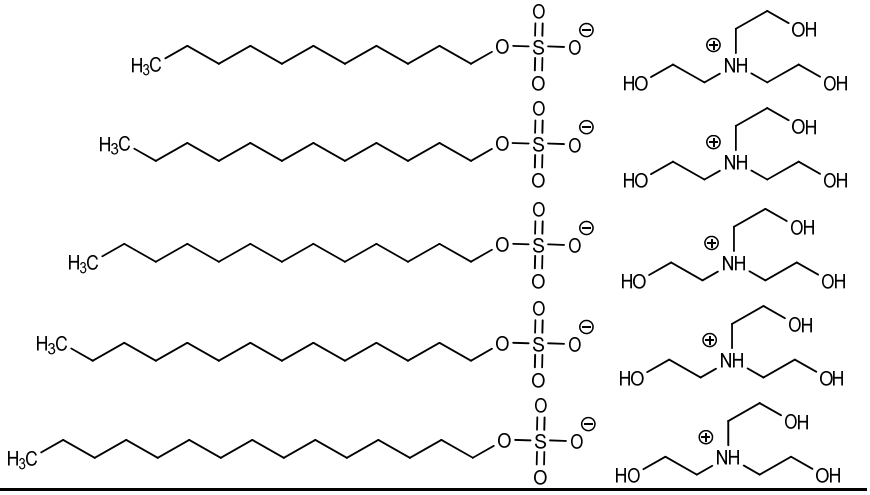
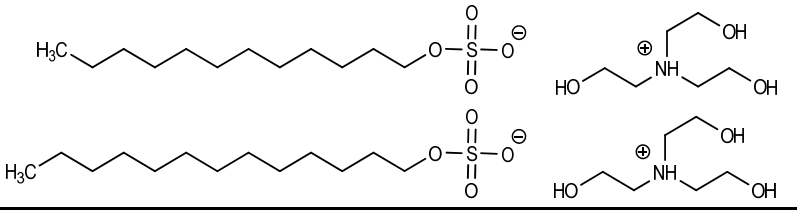
Ingredient CAS No.	Definition	Formula/structure
TEA-C10-15 Alkyl Sulfate	TEA-C10-15 Alkyl Sulfate is the mixture of 10 to 15 carbon alkyl sulfate triethanolamine salts.	
TEA-C11-15 Alkyl Sulfate	TEA-C11-15 Alkyl Sulfate is the mixture of 11 to 15 carbon alkyl sulfate triethanolamine salts.	
TEA-C12-13 Alkyl Sulfate	TEA-C12-13 Alkyl Sulfate is the mixture of 12 to 13 carbon alkyl sulfate triethanolamine salts.	

Table 2. Definitions and structures

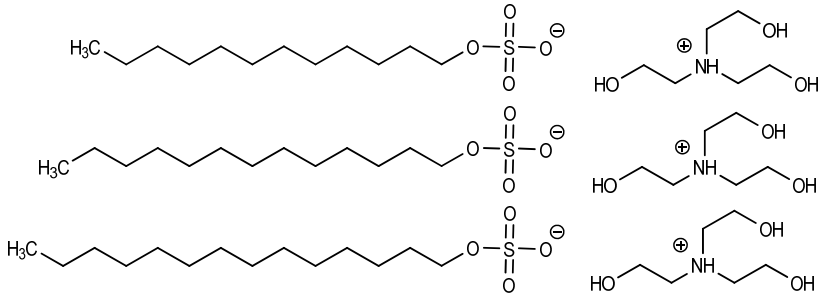
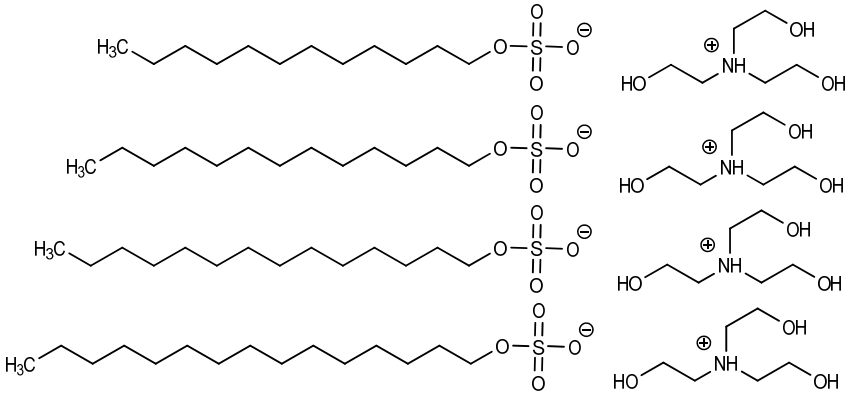
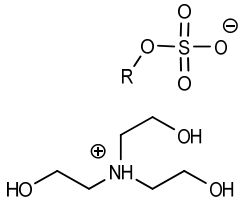
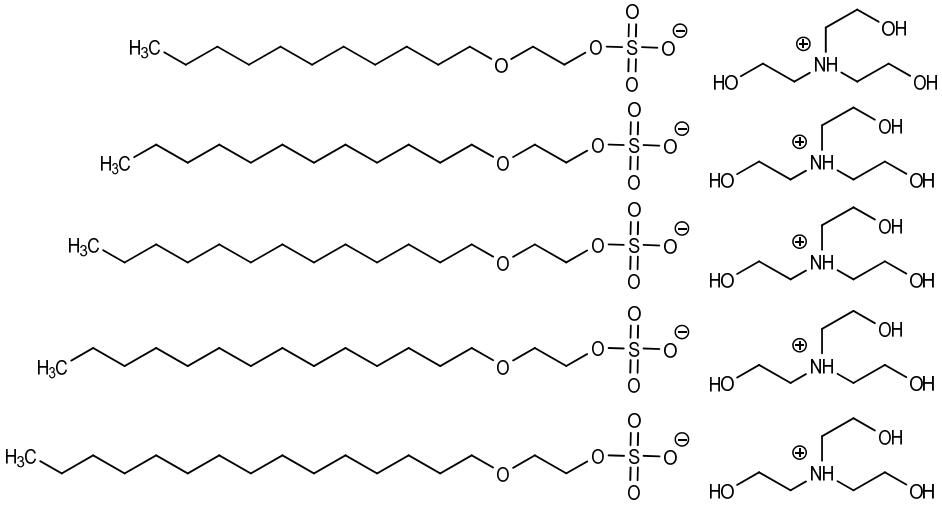
Ingredient CAS No.	Definition	Formula/structure
TEA-C12-14 Alkyl Sulfate	TEA-C12-14 Alkyl Sulfate is the mixture of 12 to 14 carbon alkyl sulfate triethanolamine salts.	
TEA-C12-15 Alkyl Sulfate	TEA-C12-15 Alkyl Sulfate is the mixture of 12 to 15 carbon alkyl sulfate triethanolamine salts.	
TEA-Coco-Sulfate	TEA-Coco-Sulfate is the triethanolamine salt of sulfated Coconut Alcohol.	 where R represents the alkyl groups derived from coconut oil
TEA-C11-15 Pareth Sulfate	TEA-C11-15 Pareth Sulfate is the triethanolamine salt of the sulfate ester of a mixture of monoethoxylated, 11 to 15 carbon fatty alcohols.	

Table 2. Definitions and structures

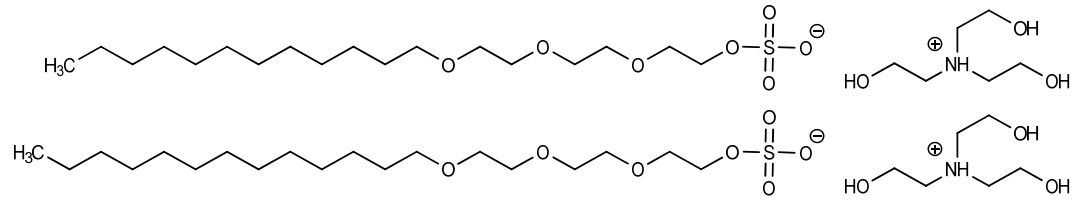
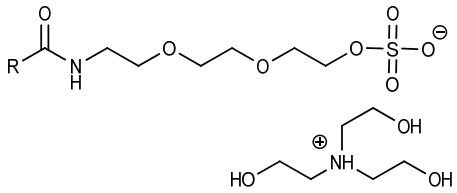
Ingredient CAS No.	Definition	Formula/structure
TEA-C12-13 Pareth-3 Sulfate	TEA-C12-13 Pareth-3 Sulfate is the tri-ethanolamine salt of the sulfate ester of a mixture of triethoxylated, 12 to 13 carbon fatty alcohols.	
TEA-PEG-3 Cocamide Sulfate	TEA-PEG-3 Cocamide Sulfate is the tri-ethanolamine salt of the sulfate ester of triethoxylated cocamide.	 where RCO- represents the fatty acids derived from coconut oil

Table 3. Physical and Chemical Properties

Property	Value	Reference
	Triethanolamine	
Physical Form	clear viscous liquid	[1]
Color	colorless to pale yellow	[29]
Odor	ammonia-like	[1]
Molecular Weight	149.19	[1]
Melting Point	21.6°C	[29]
Boiling Point	335.4°C @ 760 mm Hg	[29]
Water Solubility	miscible in water	[29]
Other Solubility	insoluble in benzene, ether, and petroleum distillates	[1]
	miscible with methanol or acetone; sparingly soluble in hydrocarbon solvents; readily forms salts with organic and inorganic acids	[84]
log K_{ow}	-1.59 @ 20°C	[18]
pKa	7.76 @ 25°C	[37]
Viscosity	590.5 cP @25°C	[84]
	TEA-Hydrochloride	
Melting Point	177°C	[85]
	TEA-Lactate	
Melting Point	-54.9°C	[86]
Density	1.222 g/cm^3	[86]
	TEA Lauryl Sulfate	
Density	approx. 1 g/cm^3 (20°C)	[10]

Table 4a. Frequency and concentration of use according to duration and type of exposure

	# of Uses[15,87]	*Conc of Use (%)*[16]	*# of Uses*[15,87]	*Conc of Use (%)*[16]	*# of Uses*[15,87]	*Conc of Use (%)*[16]
	Triethanolamine		**TEA-Cocoate**		**TEA-Hydrochloride**	
Totals*	**3756**	**0.0002-19**	**2**	**NR**	**NR**	**0.5**
Duration of Use						
Leave-On	*3034*	*0.0002-6*	*1*	*NR*	*NR*	*NR*
Rinse-Off	*697*	*0.0003-19*	*1*	*NR*	*NR*	*0.5*
Diluted for (Bath) Use	*25*	*0.4-0.7*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	413	0.2-4	NR	NR	NR	NR
Incidental Ingestion	18	0.2-1	NR	NR	NR	NR
Incidental Inhalation-Spray	120[a]	0.001-2	NR	NR	NR	NR
Incidental Inhalation-Powder	14	0.06-2	NR	NR	NR	NR
Dermal Contact	3106	0.0002-19	2	NR	NR	NR
Deodorant (underarm)	11[b]	0.1-0.4	NR	NR	NR	NR
Hair - Non-Coloring	373	0.0003-6	NR	NR	NR	0.5
Hair-Coloring	5	1-13	NR	NR	NR	NR
Nail	14	0.2-3	NR	NR	NR	NR
Mucous Membrane	203	0.2-19	1	NR	NR	NR
Baby Products	16	0.2-2	NR	NR	NR	NR

	TEA-Isostearate		**TEA Lactate**		**TEA Laurate**	
Totals*	**1**	**NR**	**13**	**0.06**	**NR**	**8**
Duration of Use						
Leave-On	*1*	*NR*	*13*	*0.06*	*NR*	*NR*
Rinse Off	*NR*	*NR*	*NR*	*NR*	*NR*	*8*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	13	0.06	NR	8
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	TEA-Laureth Sulfate		**TEA-Lauryl Sulfate**		**TEA-Myristate**	
Totals*	**17**	**3-14**	**302**	**0.0009-40**	**2**	**NR**
Duration of Use						
Leave-On	*NR*	*NR*	*29*	*0.0009-8*	*NR*	*NR*
Rinse-Off	*1517*	*3-14*	*241*	*0.0009-40*	*2*	*NR*
Diluted for (Bath) Use	*NR*	*3*	*32*	*12-15*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1[b]	4-8	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	3	3-9	236	0.2-40	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	14	14	65	0.0009-40	NR	NR
Hair-Coloring	NR	6	NR	2	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	3-9	179	5-30	NR	NR
Baby Products	NR	NR	2	NR	NR	NR

Table 4a. Frequency and concentration of use according to duration and type of exposure

	# of Uses[15,87]	*Conc of Use (%)*[16]	*# of Uses*[15,87]	*Conc of Use (%)*[16]	*# of Uses*[15,87]	*Conc of Use (%)*[16]
	TEA-Palmitate		**TEA-Stearate**		**TEA-Sulfate**	
Totals	**5**	**14**	130	**9**	**6**	**0.2**
Duration of Use						
Leave-On	*3*	*NR*	*108*	*NR*	*NR*	*NR*
Rinse Off	*2*	*14*	*22*	*9*	*6*	*0.2*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	9	NR	NR	NR
Incidental Ingestion	NR	NR	1	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	2[b]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	2	NR	NR	NR
Dermal Contact	4	14	109	9	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	16	NR	6	0.2
Hair-Coloring	NR	NR	1	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	4	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

***** Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.

[a]Includes suntan products, in that it is not known whether or not the product is a spray.

[b]It is not known whether or not the product is a spray.

NR – no reported uses

Table 4b. Ingredients not reported to be used

Magnesium/TEA-Coco-Sulfate
Sodium/TEA C12-13 Pareth-3 Sulfate
TEA-C10-15 Alkyl Sulfate
TEA-C11-15 Alkyl Sulfate
TEA-C12-13 Alkyl Sulfate
TEA-C12-14 Alkyl Sulfate
TEA-C12-15 Alkyl Sulfate
TEA-C11-15 Pareth Sulfate
TEA-C12-13 Pareth-3 Sulfate
TEA-Canolate
TEA-Coco-Sulfate
TEA-Glyceryl Dimaleate
TEA-Hydrogenated Cocoate
TEA-Laurate/Myristate
TEA-Oleate
TEA-Oleyl Sulfate
TEA-PEG-3 Cocamide Sulfate
TEA-Sorbate
TEA-Tallate
TEA-Undecylenate

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