Final Amended Report

On the Safety Assessment of Ethanolamine and Ethanolamine Salts as Used in Cosmetics

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ABSTRACT: The CIR Expert Panel assessed the safety of ethanolamine and 12 salts of ethanolamine as used in cosmetics, finding that these ingredients are safe in the present practices of use and concentrations (rinse-off products only) when formulated to be non-irritating. These ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed. Ethanolamine functions as a pH adjuster. The majority of the salts are reported to function as surfactants; the others are reported to function as pH adjusters, hair fixatives, or preservatives. The Panel reviewed available animal and clinical data, as well as information from previous relevant CIR reports. Since data were not available for each individual ingredient, and since the salts dissociate freely in water, the Panel extrapolated from those previous reports to support safety.

INTRODUCTION

In 1983, the Cosmetic Ingredient Review (CIR) Expert Panel issued a safety assessment on triethanolamine (TEA), diethanolamine (DEA), and monoethanolamine (MEA). In that 1983 report, the Panel concluded that ethanolamine, an ingredient that functions in cosmetics as a pH adjuster, is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin, and ethanolamine should only be used in rinse-off products.[1]

In 2010, the Panel decided to reopen that 1983 safety assessment on TEA, DEA, and MEA as three separate reports (one for each ingredient), and to include additional related ingredients in each of the new reviews. Diethanolamine and its salts and triethanolamine and TEA-containing ingredients have been found safe in the present practices of use and concentration when formulated to be non-irritating, with the caveat that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.[2,3]

The International Nomenclature Cosmetic Ingredient (INCI) name for monoethanolamine is now ethanolamine. This assessment addresses ethanolamine and ethanolamine salts. The acid salt ingredients (listed below) would be expected to dissociate into ethanolamine and the corresponding acid, some of which have been reviewed separately. In most cases, this means that the composition of these salts is stoichiometrically half ethanolamine (i.e. as its conjugate acid).

The following 12 salts are included in the re-review of ethanolamine:

Inorganic Acid Salts
Ethanolamine HCl
MEA-Sulfite

Organic Acid Salts
MEA-Benzoate
MEA-Salicylate
MEA-Cocoate
MEA-Tallowate
MEA-Undecylenate
MEA-Laureth-6 Carboxylate
MEA PPG-6 Laureth-7 Carboxylate
MEA-PPG-8-Steareth-7 Carboxylate

Organic-Substituted Inorganic Acid Salts
MEA-Lauryl Sulfate
MEA-Laureth Sulfate

Ethanolamine HCl is reported to function as a pH adjuster and a buffering agent. MEA-sulfite is reported to function as a hair fixative. The majority of the ethanolamine salts are reported to function as surfactants. However, MEA-benzoate and MEA-salicylate are reported to function as preservatives and not as surfactants.

MEA-salicylate also has been reviewed previously by the CIR Expert Panel. In 2003, the Panel concluded that MEA-Salicylate is safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected; directions for use include the daily use of sun protection.[4]

The definitions and structures of ethanolamine and the ethanolamine-containing ingredients listed above are provided in Table 1. Since the ingredients included in this review consist of ethanolamine and one or more components, the conclusions of the components that have been reviewed previously by the CIR are provided in Table 2.

Information relevant to the safety of ethanolamine was included in the 1983 CIR safety assessment of TEA, DEA, and MEA. Information from that report is summarized in this review, and is identified by indented, italicized text.

CHEMISTRY

Ethanolamine is an amino alcohol. (Figure 1). Ethanolamine is produced commercially by aminating ethylene oxide with ammonia; the replacement of one hydrogen of ammonia with an ethanol group produces ethanolamine.

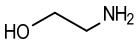


Figure 1. Ethanolamine

Ethanolamine is reactive and bifunctional, combining the properties of alcohols and amines. At temperatures of 140°-160°C, ethanolamine will react with fatty acids to form ethanolamides. Additionally, the reaction of ethanolamines and sulfuric acid produces sulfates, and, under anhydrous conditions, ethanolamine may react with carbon dioxide to form carbamates.

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

While many secondary amines are readily nitrosated to form isolatable nitrosamines, primary amines, such as ethanolamine, ultimately yield diazonium salts instead of nitrosamines.[5]

Acid Salts

The acid salts (inorganic acid salts, organic acid salts, and sulfate salts), named 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 ethanolamine. In other words, MEA-undecylenate, for example, is comprised of undecylenic acid and ethanolamine.

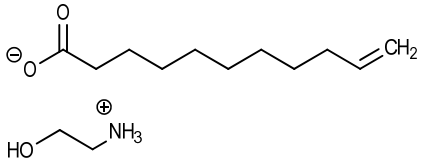


Figure 2. MEA-Undecylenate

Available physical and chemical properties are summarized in Table 3.

Method of Manufacture

Ethanolamine is produced by reacting 1 mole of ethylene oxide with 1 mole of ammonia. 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, which is then separated, achieving varying degrees of single component purity.[6] Ethanolamine combines with long-chain fatty acids to produce neutral carboxylates, also called alkanolamine soaps.[7]

Impurities

Ethanolamine contains a small amount of diethanolamine.

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

Residual ethylene oxide is not expected during the manufacture of ethanolamine.[6]

USE

Cosmetic

Ethanolamine and ethanolamine HCl are reported to function in cosmetics as pH adjusters; ethanolamine HCl is also reported to function as a buffering agent.[8] MEA-sulfite is reported to function as a hair fixative. The majority of the ethanolamine salts are reported to function as surfactants. However, MEA-benzoate and MEA-salicylate are reported to function as preservatives, not surfactants.

Amines, such as ethanolamine, can be useful in pH adjustment because they can both donate a proton in an alkaline environment and accept a proton in an acidic environment. For ethanolamine HCl, a proton has already been accepted from HCl, but ethanolamine HCl can certainly function as a proton donor.

The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained in 2011 report that ethanolamine is used in 788 formulations.[9] All of the uses are in rinse-off products (Don Havery, personal communication), and 772 uses are in hair coloring formulations.[10] A few of the other ethanolamine-containing ingredients are in use, but all of those are reported to be used in less than 15 rinse-off formulations.

According to data submitted by industry in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council), ethanolamine is used in rinse-off products (only) at up to 18%.[11] MEA-lauryl sulfate has the highest reported concentration of use, with a concentration of 35% reported in hair dye formula-

tions. Use data for ethanolamine and all other in-use ethanolamine-containing ingredients are provided in Table 4a. Ethanolamine ingredients not reported to be in use, according to VCRP data and the Council survey, are listed in Table 4b.

Ethanolamine is used in a hair color aerosol spray at a maximum concentration of 3%[11] and could possibly be inhaled In practice, 95% to 99% of the droplets/ particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[13-16] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[13,15]

Monoalkylamines, monoalkanolamines, and their salts are listed by the European Commission (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.[17] These restrictions for these ingredients include an allowed maximum secondary amine content of 0.5% in finished product; do not use with nitrosating agents; minimum purity of 99%; maximum secondary amine content of 0.5% for raw materials; maximum nitrosamine content of 50 μg/kg; and must be kept in nitrite-free containers. MEA-benzoate is listed by the EC in Annex V, a list of preservatives allowed in cosmetics; as a preservative, MEA-benzoate is allowed a maximum concentration in ready-for-use preparations of 0.5% as benzoic acid. MEA-salicylate is also listed in Annex V; as a preservative, MEA-salicylate is allowed a maximum concentration in ready-for-use preparations of 0.5% as salicylic acid, and it is not to be used in products for children under 3 years of age, except shampoos. The ingredients named in this report that have EC restrictions are listed in Table 4c.

Information provided by Health Canada indicates that ethanolamine is used primarily in hair coloring products, with concentrations of use of ≤30% (Health Canada, personal communication). Ethanolamine is also reported to be used in Canada at concentrations of ≤30% in non-coloring hair preparations and rinse-off formulations, and at ≤10% in leave-on formulations; this includes reported use at 0.3-3% in baby products and 3-10% in lipsticks.

Non-Cosmetic

Ethanolamine 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 also 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]

Ethanolamine has uses as an indirect food additive; according to 21 CFR 175.105 ethanolamine is allowed for use as a component of adhesives.[18] Ethanolamine is also used as a rust inhibitor in water-based metalworking fluids.[19]

TOXICOKINETICS

Ethanolamine is the only naturally occurring ethanolamine in mammals, and it is excreted in the urine. Ethanolamine was converted to phosphatidylethanolamine (PE) in the liver, blood, and brain of female rats that were dosed intraperitoneally (i.p.) with radiolabeled ethanolamine. The step-wise methylation of PE that converts it to phosphatidylcholine (PC) did not occur in the brain. Labeled respiratory carbon dioxide has been found in rats after i.p. administration of labeled ethanolamine.

A coenzyme-B_{12}-dependent ethanolamine deaminase-mediated conversion of ethanolamine to acetaldehyle and ammonia was demonstrated. Intraperitoneal administration of ethanolamine to rats increased blood urea and blood glutamine, and the researchers suggested that ethanolamine was an ammonia source. Additional researchers, upon detection of labeled acetate in the urine of rats fed labeled ethanolamine, suggested that ethanolamine is phosphorylated by ATP in vivo, converted to acetaldehyde, ammonia, and inorganic phosphate, and the acetaldehyde is oxidized to acetate. The researchers further hypothesized that the removal of phosphorylated ethanolamine by its conversion to acetate may exert a regulatory effect on PE biosynthesis.

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

Ethanolamine occurs naturally in phospholipids known as phosphatides.[7] Ethanolamine is a structural component of the phospholipids as part of the headgroups in phospholipid bilayers. In man and other animals, the alcohol group of ethanolamine is phosphorylated, and phosphorylated ethanolamine is transferred to cytidine monophosphate to form cytidine-5'-diphosphoethanolamine and phospholipids via diacylglycerol.

In Vitro

Ethanolamine

Three full thickness skin preparations from CD rats, CD-1 mice, and New Zealand White rabbits and 6 samples from female mammoplasty patients were used to compare the dermal penetration of ethanolamine through skin of different species.[20] [^{14}C]Ethanolamine (98.8% purity; specific activity [sp. act.] 15.0 mCi/mmol) was applied to the skin sample undiluted or as an aq. solution at a dose of 4 mg/cm^2. Dose volumes of 7 μl undiluted [^{14}C]ethanolamine or 32 μl of the aq. solution (22% w/w) were applied to the exposed surface of the skin (1.77 cm^2) for 6 h. With undiluted ethanolamine, the cumulative dose

absorbed (found in the effluent) was 5.98, 16.92, 8.66, and 0.61% through rat, mouse, rabbit, and human skin, respectively. With aq. ethanolamine, 1.32, 24.79, 1.87, and 1.11%, of the cumulative dose absorbed through rat, mouse, rabbit, and human skin, respectively. *In vitro* absorption of undiluted and aq. ethanolamine was much greater through mouse skin than human skin, and human skin was the least permeable of all the skin samples. With human skin samples, the cumulative dose absorbed was greater with aq. ethanolamine as compared to undiluted ethanolamine. The researchers hypothesized that enhanced penetration of aq. ethanolamine may be attributable to elevated skin hydration.

Ethanolamine HCl

The dermal penetration of [1,2-^{14}C]ethanolamine HCl was evaluated *in vitro* using split-thickness skin from weanling Yorkshire pigs.[21] An ethanolic solution was prepared so that a 5 µl application to 0.8 cm^2 of skin gave a chemical dose of 4 µg/cm^2 and a radioactive dose of approximately 0.05 µCi. After 50 h, 11% of the dose was lost to evaporation, 5% penetrated percutaneously, and 62% was recovered in the skin residue. Seven to nine times more radioactivity was recovered in the upper 100 µm layer compared to recovery from the remaining dermis.

Dermal

Non-Human

The distribution and metabolism of ethanolamine was determined using groups of 5 male athymic nude mice with human skin grafts and ungrafted athymic nude mice.[21] [1,2-^{14}C]Ethanolamine HCl in ethanol was applied at a dose of 4.0 µg (3.6 µCi) to a 1.45 cm^2 area of grafted or non-grafted skin. Penetration appeared similar for both groups. Radioactivity in expired carbon dioxide (CO_2) appeared 30 min after dosing, and the amount recovered at 30 min was 0.76% for grafted skin and 0.83% of the dose for ungrafted skin. After 24 h, 18.5-19% of the dose was recovered in expired CO_2. Distribution was also similar for both groups. At 24 h after dosing, 24.3-25.8% of the dose was recovered in the liver and 2.24-2.53% in the kidneys. At the application site, 18.4% of the radioactivity was recovered in the grafted skin, and 12.1% was recovered in the ungrafted skin. The amount of radioactivity recovered in the urine was 4.6 and 5.2% for grafted and ungrafted nude mice, respectively. Unchanged ethanolamine comprised 10.2% of the urinary radioactivity. The major urinary metabolites were urea and glycine, comprising 39.9 and 20.4% of the urinary radioactivity. Minor urinary metabolites were serine, uric acid, choline, and unidentified ninhydrin-positive compounds.

The radioactivity in proteins and amino acids isolated from the liver, human skin grafts, and mouse skin was determined as an evaluation of the metabolism of ethanolamine. The researchers stated that the appearance of ^{14}C in skin and hepatic amino acids and proteins, and the incorporation of ethanolamine into phospholipids, was evidence of extensive metabolism of the absorbed ethanolamine. The liver was the most active site of ethanolamine metabolism.

Oral

Non-Human

In a dietary two-generation reproductive toxicity study (described later in the 'Reproductive and Developmental Toxicity' section), blood samples were taken from groups of 10 male and 10 female F_0 and F_1 Wistar rats that were fed 0, 100, 300, or 1000 mg/kg ethanolamine HCl in feed for 10 wks.[22] Plasma levels of ethanolamine, calculated as ethanolamine HCl, increased in a dose-dependent manner. The plasma concentration of ethanolamine was <3 mg/kg for control male and female F_0 and F_1 animals. In the low dose group, the plasma concentration values of ethanolamine were <4 mg/kg, in the mid-dose animals, the levels were 8-11 mg/kg, and in the high dose animals, the plasma ethanolamine levels ranged from 60-81 mg/kg.

Other

Non-Human

Five male athymic nude mice were dosed intraperitoneally (i.p.) with 4.0 µg (3.6 µCi) of [1,2-14C]ethanolamine HCl in ethanol, and the distribution and metabolism were examined following dosing.[7] Radioactivity was detected in expired CO_2, increasing gradually over time. After 24 h, 18% of the radioactivity was detected in expired air.

TOXICOLOGICAL STUDIES

Acute (Single) Dose Toxicity

Dermal

Female C3H mice were used to determine the in vivo and in vitro morphological response of mouse skin exposed to a single application of 1, 5, or 10% ethanolamine in acetone.[23] In vivo, ethanolamine was applied to an area of skin 1 inch in diameter, the animals were killed the next day, and the treated skin was removed and processed. In vitro, ethanolamine was applied to a 1-inch diameter mouse skin disc for 1 min, and the skin discs were then cultured for 20 h. No lesions were observed in vivo or in vitro at any concentration tested. Lactate dehydrogenase activity in the in vitro samples was statistically significantly elevated with 5 and 10% ethanolamine, suggesting that ethanolamine was mildly toxic to the skin at these concentrations.

The dermal LD_{50} in rabbits is reported as 1.0-2.5 g/kg ethanolamine.[7] In a study determining the acute dermal toxicity of a mixture containing ethanolamine (as well as hydroxylamine, diglycolamine, propylene glycol, catechol, and water; percentages not specified), 2g/kg of the mixture were applied to the shaved backs of 5 male and 5 female rabbits.[24] The dermal LD_{50} of the mixture was greater than the 2 g/kg dose. In a similar study with a formulation containing ethanolamine (and hydrox-

ylamine, diglycolamine, gallic acid, and water; percentages not specified), the LD_{50} of the mixture in rabbits was 1.24 g/kg bw.[25]

Oral

The acute oral toxicity of ethanolamine, concentration not specified, ranged from 1.72-2.75 g/kg for rats. Using 90-120 rats, 20% aq. ethanolamine had an LD_{50} of 2.14-2.74 g/kg, based on results of studies performed over a 10 yr time period. With groups of 10 rats, a hair preparation containing 5.9% ethanolamine had an LD_{50} of 14.1 g/kg when diluted and 12.9 ml/kg when undiluted. In a study using guinea pigs, all in the group of 2 or 3 guinea pigs survived oral dosing with 0.6 g/kg ethanolamine, while none survived dosing with 7.0 g/kg.

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

In oral studies, the LD_{50} of ethanolamine is reported as 0.7-15.0 g/kg in mice and 1.0-2.9 g/kg in rabbits.[7] In a study determining the acute oral toxicity of a mixture containing ethanolamine (as well as hydroxylamine, diglycolamine, propylene glycol, catechol, glycolic acid and water; percentages not specified), groups of 5 male and 5 female rats were used.[26] The oral LD_{50} of the mixture was 0.95 g/kg. In a similar study with a formulation containing ethanolamine (and hydroxylamine, diglycolamine, gallic acid, and water; percent in formulation not specified), the oral LD_{50} of the mixture was 0.815 g/kg bw.

Inhalation

The acute inhalation toxicity of a mixture containing ethanolamine (as well as hydroxylamine, 1-amino-propano-2-ol, catechol, and water; percent of each not specified) was determined using groups of 5 male and 5 female rats. The animals were exposed to 1.11, 1.61, 2.13, or 2.84 mg/l for 4 h. All animals exposed to 2.84 mg/l died. All animals in the other test groups survived. The inhalation LC_{50} of the mixture was estimated to be 2.48 mg/l.[26]

Other

The intraperitoneal LD_{50} of ethanolamine was 1.05 g/kg for mice.

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

Repeated Dose Toxicity

Dermal

Percutaneous application of 4 mg/kg/day ethanolamine to rats resulted in nonspecific histological changes in the heart and lung, fatty degeneration of the liver parenchyma, and subsequent focal liver necrosis. The duration of dosing was not specified.

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

Oral

Groups of 10 rats were fed 0-2.67 g/kg/day ethanolamine for 90 days. Heavy livers and kidneys were observed at ≥0.64 g/kg/day, and deaths and "major pathology" occurred with ≥1.25 g/kg/day. In a 2-yr dietary study in which groups of 12 Beagle dogs were fed 0-0.0975 g/kg/day of a hair dye composite that contained 22% ethanolamine, no toxic effects were observed.

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

Inhalation

The dominant effects of "continuous exposure" of dogs, guinea pigs, and rats to 5-6 ppm ethanolamine vapor were skin irritation and lethargy. No dogs or rodents exposed to 12-26 ppm ethanolamine vapor for 90 days died, but mortality was reported in dogs exposed to 102 ppm ethanolamine vapor for 2 days and rodents exposed to 66-75 ppm ethanolamine vapor for 24-28 days. Dogs and rodents exposed to 66-102 ppm ethanolamine vapor had behavioral changes, pulmonary and hepatic inflammation, hepatic and renal damage, and hematological changes.

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Dermal

The developmental toxicity of dermally applied aq. ethanolamine was evaluated using groups of 30-45 gravid Sprague-Dawley rats and 15 gravid New Zealand White rabbits.[27] Ethanolamine was applied at doses of 0, 10, 25, 75, and 225 mg/kg bw/day to the backs of rats on days 6-15 of gestation, with a dose volume of 1 ml/kg. Significant skin irritation, consisting of erythema followed by necrosis, scabs, and scar formation, occurred with 225 mg/kg ethanolamine, but not at the other dose levels. No effects on kidney or liver weights were reported. Despite maternal effects in the 225 mg/kg dose group, no effects on reproductive parameters were observed at any dose, and there were no treatment-related increases in the visceral or skeletal malformations. In rats, the no-observed effect level (NOEL) was 75 mg/kg/day for maternal toxicity and 225 mg/kg/day for embryonal/fetal toxicity.

In rabbits, 0, 10, 25, and 75 mg/kg bw/day ethanolamine was applied to the back (2 ml/kg) on days 6-18 of gestation. Severe skin irritation at the application site, consisting of necrosis, exfoliation, and crusting, was observed in the 75 mg/kg group, and crusting, transient erythema, and edema were observed in a few rabbits of the 25 mg/kg dose group. No effects on kid-

ney or liver weights were reported. As with the rats, no effects on reproductive parameters were observed at any dose, and there were no treatment-related increases in the visceral or skeletal malformations. In rabbits, the NOEL was 10 mg/kg bw/day for maternal toxicity. No effect on embryonal/fetal toxicity was observed at the highest dose level of 75 mg/kg bw/day.

Oral

Ethanolamine

No reproductive or developmental effects were observed in groups of gravid rats given a hair dye and base containing 22% ethanolamine in the diet at concentrations ≤7800 ppm on days 6-15 of gestation. No differences in reproductive or developmental parameters were observed when male rats were fed treated diet for 8 wks prior to and during mating with undosed females or when female rats were fed treated feed for 8 wks prior to dosing until day 21 of lactation. These females were mated with undosed males. Additionally, no teratologic effects were induced by dosing rabbits with ≤19.5 mg/kg/day of the hair dye and base by gavage on days 6-18 of gestation.

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

The teratogenic potential of ethanolamine was evaluated in a Chernoff-Kavlock postnatal mouse screening assay.[28] Gravid CD-1 mice were dosed orally with 850 mg/kg/day ethanolamine on days 6-15 of gestation, resulting in 16% mortality of maternal mice and reduced numbers of viable litters. Litter size, percentage survival of pups, birth weight, and pup weight gains were not affected.

A preliminary study was performed in which gravid Wistar rats were dosed orally with 0-500 mg/kg/day aq. ethanolamine; details not provided.[29] Maternal effects were observed in the high dose animals, but no embryonal/fetal effects were observed at any dose. Based on these results, groups of 40 Wistar rats were dosed by gavage with 0, 40, 120, or 450 mg/kg bw/day aq. ethanolamine on days 6-15 of gestation. On day 20 of gestation, 25 dams/group were killed and necropsied, while the remaining 15 were allowed to litter and then killed on day 21 of lactation. Despite evidence of maternal toxicity in the 450 mg/kg group, as indicated by statistically significant decreases in maternal body weights and feed consumption, no effects on reproductive parameters, incidences of visceral or skeletal malformations, or postnatal growth were observed at any dose. The NOEL for maternal toxicity was 120 mg/kg/day. No effect on developmental toxicity was observed at the highest dose level of 450 mg/kg/day.

Groups of 10 gravid Long-Evans rats were dosed by gavage with 50, 300, or 500 mg/kg aq. ethanolamine on days 6-15 of gestation, and a negative control group of 34 gravid rats was dosed with water only.[30] The animals were killed and examined on day 20 of gestation. Significant maternal toxicity was not noted. Embryolethality was significantly increased in the 500 mg/kg group, and male pups were affected more than female pups. Male pups were also more severely affected than female pups at all dose levels in regards to intrauterine growth retardation and increased gross structural anomalies that were considered indicative of depressed fetal growth. However, pups of either sex who were contiguous to male siblings were more adversely affected that those contiguous to one or more female siblings. Male pups contiguous to male siblings (mMm) were, apparently, resorbed (mRm). The number of malformed pups per dam was significantly increased in animals dosed with 300 mg/kg ethanolamine. The number of malformed pups, when evaluated as a percent of the litter affected, was significantly increased for all 3 dose groups.

Ethanolamine HCl

Groups of 25 male and 25 female Wistar rats (F_0 parental generation) were fed 0, 100, 300, or 1000 mg/kg bw/d ethanolamine HCl for at least 75 days prior to mating.[22] Twenty-five male and 25 female F_1 pups/group were continued on the test diets of their parents, and then mated, becoming the F_1 parental generation. The study was terminated after the weaning of the F_2 pups. No test substance-related adverse reproductive, developmental, or toxic effects were observed in any of the pups or parental animals of the 100 or 300 mg/kg bw/d groups. In the 1000 mg/kg group, adverse effects on fertility and reproduction were evidenced by statistically significant decreases in absolute and relative weights of the epididymides and cauda epididymidis in male F_0 and F_1 parents and statistically significant decreased number of implantation sites, increased post-implantation loss, and smaller litters in female F_0 and F_1 parents. Sperm head count in the cauda epididymidis and absolute and relative liver weights were also statistically significantly decreased in male F_0 parents. Body weight gains of both the F_0 and F_1 parental animals were statistically significantly decreased during gestation when compared to controls, as was feed consumption during lactation. There were no test-related signs of developmental toxicity observed in F_1 and F_2 pups of this dose group. The NOAEL was 300 mg/kg bw/day for systemic toxicity and for reproductive effects. No effect on developmental toxicity was observed at the highest dose level of 1000 mg/kg/day.

GENOTOXICITY

In Vitro

Ethanolamine, with and without metabolic activation using liver preparations from rats induced with a polychlorinated biphenyl mixture, was not mutagenic to Salmonella typhimurium TA100 or TA1535.

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

Ethanolamine was negative in most Ames tests at concentrations ≤2000 µg/plate;[31,32] however "weak mutagenic effects" were reported in one study.[33] Ethanolamine, 25-500 µg/ml, was negative in a cell transformation assay using hamster embryo

cells.[34] Ethanolamine was clearly cytotoxic at 500 µg/ml. Ethanolamine did not produce chromosomal aberrations in rat liver cells,[31] but a "weak positive" response was reported in human lymphocytes.[33] (Concentrations tested were not provided.)

CARCINOGENICITY

Published carcinogenicity data were not found on ethanolamine or ethanolamine salts.

IRRITATION AND SENSITIZATION

Dermal Irritation

Non-Human

Ethanolamine was corrosive to rabbit skin with single semi-occlusive patches of 30, 85 and 100% on intact and abraded skin. When applied to rabbit ears using non-occlusive applications and to shaved skin of the abdomen under semi-occlusive patches, ≥10% was corrosive, >1% was extremely irritating, and 1% was irritating.

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

Human

In a study in which a formulation containing 5.9% ethanolamine was applied to the backs of 12 female subjects for 23 h/day for 21 days, the formulation was considered an experimental cumulative irritant. Results observed during the induction phase of a patch test of 165 subjects using a formulation containing 11.47% ethanolamine were interpreted by the Expert Panel as irritation.

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

Sensitization

Non-Human

A local lymph node assay was performed to evaluate the sensitization potential of ethanolamine (as the hydrochloride salt).[19,35] Groups of 6 female CBA/Ca mice were treated on the ear with 10, 40, or 70% w/w aq. ethanolamine HCl. Ethanolamine HCl did not have a skin sensitizing effect.

In a maximization study using 15 Dunkin-Hartley guinea pigs, intradermal and epicutaneous inductions with 0.6% and 10.3% aq. ethanolamine, respectively, were performed after 10% sodium lauryl sulfate pre-treatment.[19] (Ethanolamine contained less than 0.1% diethanolamine and triethanolamine.) At challenge with 0.41, 2.05, or 4.1% ethanolamine, 3, 2, and 3 animals, respectively, reacted positively after 3 days. Two of the 15 test animals reacted to the vehicle, but none of the control animals reacted to ethanolamine or the vehicle. Possible cross-reactions to 5% triethanolamine occurred in 3 animals, and to 7% diethanolamine in 2 animals. In a second test using the same protocol, no animals reacted to 0.41% ethanolamine, 2 reacted to 2.05% ethanolamine, and 1 reacted to 4.1% ethanolamine. Additionally, 1 animal reacted to 10% triethanolamine and 2 reacted to 7% diethanolamine. The control animals did not react to any of the ethanolamines.

Human

A formulation containing 5.9% ethanolamine, tested undiluted in a 48-h occlusive patch test with a 10-day non-treatment period prior to challenge, and one containing 11.47% ethanolamine, tested at 5% in 25% alcohol in a repeated insult patch test using semi-occlusive patches, were not sensitizing in clinical studies.

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

<u>Provocative Testing</u>

Metalworkers that were dermatitis patients were patch tested with 2% ethanolamine in petrolatum (pet.).[36] The patches were applied for 1-2 days. On day 3, 3 of 155 patients (1.9%) had positive reactions.

Patch testing was performed with 2% ethanolamine in pet. in 199 patients with suspected metalworking fluid contact dermatitis.[37] (All patients were metalworkers.) Patches were applied for 1 or 2 days. On day 3, 40 patients had positive reactions, i.e., 16 (?), 19 (+), 4 (++), and 1 (+++). The % positive reactions was 11.6%.

A patch test using 2% ethanolamine in pet. was performed on 370 patients with suspected dermatitis to ethanolamine-containing metal-working fluids and on 452 control subjects.[38] A 10-fold higher reaction was seen in the patient group, with 12.2% of the patients having positive reactions, as compared to 1.3% in the control group.

Over a 3-yr period, 11/595 hairdresser clients (1.9%) and 7/401 female hairdressers (1.8%) reacted positively to 2% ethanolamine in pet.[19] In 22 patients with suspected intolerance to oxidative hair dye components, 4 had a positive reaction to 2% ethanolamine in pet. Over a 15-yr period, provocative patch testing using ethanolamine was performed on 9602 subjects. There were 363 positive reactions (3.8%) to ethanolamine, and most of the reactions (277; 2.9%) were weak positives. There were 55 irritant reactions (0.6%) reported. Cosensitization was reported; 38% of the patients that reacted to ethanolamine also tested positive with diethanolamine. Occupational sensitization was reported; of 5884 male patients evaluated, 2.9% that did not work in the metal industry had positive reactions to ethanolamine, as opposed to 7.0% of those working in the metal industry and 15.2% of those exposed to water-based metalworking fluids.

Ocular Irritation

In Vitro

Ethanolamine

The ocular irritation potential of ethanolamine was evaluated in vitro in the rabbit corneal epithelium model.[39] At concentrations of 0.05, 0.5, and 1%; ethanolamine was classified as a moderate ocular irritant in this assay.

Non-Human

Using 6 rabbits, 30% aq. ethanolamine was moderately irritating to rabbit eyes. Undiluted ethanolamine, instilled as a volume of 0.005 ml, produced severe injury to rabbit eyes. A hair preparation containing 5.96% ethanolamine had a maximum avg. irritation score of 0.7/110 for rinsed and unrinsed eyes.

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

OCCUPATIONAL EXPOSURE

Ethanolamine inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma and clinical symptoms of acute liver damage and chronic hepatitis.

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

A case of occupational asthma in an industrial worker exposed to a detergent containing 8% ethanolamine was reported.[40] Since the detergent was used in hot water, release of ethanolamine vapor was greater than if the water temperature was lower. Exposure to vapors from ethanolamine in cleaning solutions can irritate the nose, throat, and lungs.[41]

Occupational Exposure Limits

The Occupational Safety and Health Administration permissible exposure level for ethanolamine is 3 ppm (6 mg/m^3) as an 8-hr time-weighted average concentration.[42] The National Institute for Occupational Health and Safety has a recommended exposure limit of 3 ppm (8 mg/m^3) for a 10 h workday and 40 h work week; the short-term exposure limit is 6 ppm (15 mg/m^3), for periods not to exceed 15 min.[43]

MISCELLANEOUS STUDIES

Effect on Hepatic Choline

The effects of ethanolamine HCl on hepatic choline was determined in the F_0 and F_1 parental rats from the two-generation feeding study described earlier in this report.[44] Liver weights were determined for all parental rats at necropsy, and the livers of control and high-dose animals (1000 mg/kg bw/day) were examined microscopically. Feeding ethanolamine HCl to rats did not affect liver weights of any of the animals. No adverse microscopic affects in the livers of high-dose rats were reported. Liver samples of F_1 female rats of the test and control groups were analyzed for choline, phosphocholine, glycerophosphocholine, and phosphatidylcholine. A statistically significant increase in phosphocholine and phosphatidylcholine was observed in the 100 and 300 mg/kg bw/day dose groups, but no other statistically significant difference in choline content were reported. In that there was no dose-response, these effects were not considered dose-related. The researchers concluded that "based on the combined hepatic observations, ethanolamine hydrochloride does not affect hepatic choline metabolism in the rat."

Effect on Bronchoconstriction

The effect of ethanolamine on bronchoconstriction was investigated using a group of 4 anesthetized male Hartley guinea pigs.[45] When an aerosol of 0.1 ml/kg of 3.3% ethanolamine solution was inhaled through a tracheal cannula, bronchoconstriction was observed. The results were compared to those obtained using an aerosol of potassium hydroxide. Bronchoconstriction induced by ethanolamine was greater than that induced by potassium hydroxide. Additional testing suggested that ethanolamine-induced bronchoconstriction may not result from induction of acetylcholine or histamine release, but that it may result partly from an agonistic effect of ethanolamine at the histamine-H_1 receptor and the muscarinic receptor.

SUMMARY

This report assesses the safety of ethanolamine and its salts as used in cosmetics. The ethanolamine salts are expected to dissociate into ethanolamine and the corresponding acid. Ethanolamine typically contains a small amount of diethanolamine as an impurity. (Diethanolamine has been found to be safe in the present practices of use and concentration when formulated to be non-irritating; it should not be used in cosmetic products in which N-nitroso compounds may be formed). Ethanolamine and ethanolamine HCl function in cosmetic formulations as pH adjusters. The organic salts and the organic-substituted inorganic salts mostly function as surfactants, with the exception of MEA-benzoate and MEA-salicylate, which are preservatives. MEA-sulfite is reported to function as a hair fixative.

In 2011, ethanolamine was reported to be used in 788 formulations, all of which were rinse-offs and 772 of which are hair coloring formulations. Of the ethanolamine-containing ingredients that are in use, none have more than 15 uses. Reported maximum use concentrations of ethanolamine are 0.0002-18%. MEA-lauryl sulfate has the highest reported maximum use concentration at 35% in rinse-off formulations. In Europe, monoalkylamines, monoalkanolamines, and their salts are on the list of substances which must not form part of the composition of cosmetic products, except subject to restrictions and conditions laid down. These restrictions include a maximum secondary amines contaminant content of 0.5% in finished

products, a maximum secondary amines content of 0.5% in raw materials, and a maximum nitrosamine content of 50 µg/kg. MEA-benzoate and MEA-salicylate are on the list of preservatives in Europe and both, as preservatives, are allowed a maximum concentration in ready-for-use preparations of 0.5% of the acid.

Ethanolamine is the only naturally occurring ethanolamine in mammals; it occurs in phospholipids known as phosphatides. In an in vitro study, absorption of undiluted and aq. ethanolamine was much greater through mouse skin than it was through human, rat, or rabbit skin; human skin was the least permeable. The cumulative dose absorbed through mouse and human skin (found in the effluent) was greater with aq. ethanolamine compared to undiluted ethanolamine; 16.92% of the undiluted and 24.79% of the aq. ethanolamine absorbed through mouse skin while 0.61% undiluted and 1.11% aq. ethanolamine absorbed through human skin. In split-thickness pig skin, 5% of the dose of ethanolamine HCl in ethanol penetrated percutaneously. In a metabolism and distribution study, ethanolamine HCl was applied dermally to human skin-grafted and ungrafted athymic nude mice. Radioactivity was recovered in the skin (18.4% recovered in grafted skin; 12.1% in ungrafted skin), liver (~24-26%), and kidneys (~2%). Approximately 5% of the radioactivity was recovered in the urine; 10% of the radioactivity recovered in the urine was unchanged ethanolamine, and the major urinary metabolites were urea and glycine. In an oral study in which Wistar rats were fed a diet containing 100-1000 mg/kg ethanolamine HCl for 10 wks, plasma ethanolamine concentrations increased in a dose-dependent manner from <3 mg/kg in control animals and <4 mg/kg in low dose animals to 60-81 mg/kg in high-dose animals.

Single applications of 5 and 10% ethanolamine were mildly toxic to mouse skin. The dermal LD_{50} in rabbits was 1.0-2.5 g/kg ethanolamine. Oral LD_{50} values were 0.7-15.0 g/kg in mice and 1.0-2.9 g/kg in rabbits. The 4 h inhalation LC_{50} of a mixture containing ethanolamine, hydroxylamine, 1-aminopropanolo-2-ol, catechol, and water was estimated as 2.48 mg/l. Percutaneous application of 4 mg/kg/day ethanolamine to rats for an unspecified length of time resulted in nonspecific histological changes in the heart and lung, fatty degeneration of the liver parenchyma, and subsequent focal liver necrosis. In a dietary study in which rats were fed 0-2.67 g/kg/day ethanolamine for 90 days, heavy livers and kidneys were observed at ≥0.64 g/kg/day, and deaths and "major pathology" occurred with ≥1.25 g/kg/day. In a 2-yr dietary study in which Beagle dogs were fed 0-0.0975 g/kg/day of a hair dye composite that contained 22% ethanolamine, no toxic effects were observed. In repeated-dose inhalation studies, the dominant effects of "continuous exposure" of dogs, guinea pigs, and rats to 5-6 ppm ethanolamine vapor were skin irritation and lethargy; mortality was observed in dogs exposed to 102 ppm ethanolamine vapor for 2 days and in some rodents exposed to 66-75 ppm ethanolamine vapor for 24-28 days. Dogs and rodents exposed to 66-102 ppm ethanolamine vapor had pulmonary and hepatic inflammation, hepatic and renal damage, and hematological changes.

Dermal developmental toxicity studies were performed using rats and rabbits. In a study in which gravid rats were dosed with 10-225 mg/kg bw/day ethanolamine on days 6-15 of gestation, the no-observed effect level (NOEL) was 75 mg/ kg/day for maternal toxicity and 225 mg/kg/day for embryonal/fetal toxicity. In rabbits that were dosed dermally with 10-75 mg/kg bw/day ethanolamine on days 6-18 of gestation, the NOEL was 10 mg/kg bw/day for maternal toxicity and 75 mg/kg bw/day for embryonal/fetal toxicity. Significant skin irritation was observed in the high dose groups for both rats and rabbits. In a Chernoff-Kavlock post-natal mouse screening assay, oral dosing with 850 mg/kg/day ethanolamine on days 6-15 of gestation resulted in 16% mortality of maternal mice and a reduced number of viable litters. In a study in which Wistar rats were dosed by gavage with 40-450 mg/kg bw/day aq. ethanolamine on days 6-15 of gestation, the NOEL was 120 mg/kg/day for maternal toxicity and 450 mg/kg/day for developmental toxicity. In an oral study in which Long-Evans rats were dosed with 50-500 mg/kg aq. ethanolamine on days 6-15 of gestation, there was no significant maternal toxicity, but embryolethality was increased in the 500 mg/kg group and more reproductive and developmental effects were observed involving male pups compared to female pups. There was an increase in malformed pups in all dose groups. In a dietary two-generation study in rats with 100-1000 mg/kg bw/day ethanolamine HCl, the NOAEL was 300 mg/kg bw/day for systemic toxicity and for reproductive effects, and the NOAEL was 1000 mg/kg bw/day for developmental toxicity. The effect of ethanolamine HCl on hepatic choline was investigated in the F_0 and F_1 parental rats, and it was concluded that ethanolamine HCl did not affect the hepatic choline metabolism in the rat.

Ethanolamine was mostly negative in Ames tests (≤2000 µg/plate). Ethanolamine (≤500 µg/ml) was negative in a cell transformation assay. Ethanolamine did not produce chromosomal aberrations in rat liver cells, but did produce a "weak positive" response in human lymphocytes. Carcinogenicity data were not found in the published literature.

Semi-occlusive application of 30-100% ethanolamine was corrosive to rabbit skin. Irritation responses ranging from irritating to corrosive were observed with 1-10% ethanolamine, respectively, applied non-occlusively to rabbit ears and under semi-occlusive patches to rabbit skin. The degree of irritation increased with the concentration applied. In human studies, a formulation containing 5.9% ethanolamine was a cumulative irritant in a 21-day study, and an irritant response was reported during the induction phase of a patch test of a formulation containing 11.47% ethanolamine. Ethanolamine HCl, ≤70%, did not have a sensitizing effect in a local lymph node assay. In a maximization study in guinea pigs with intradermal and epicutaneous inductions of 0.6 and 10.3% aq. ethanolamine, respectively, positive reactions were observed at challenge with 0.41, 2.05, and 4.1% ethanolamine. Possible cross-reactions to 5% triethanolamine and 7% diethanolamine were reported. In provocative testing of metalworkers with dermatitis, a higher reaction rate to ethanolamine was observed for the patients as compared to control subjects. In a study of hairdressers and clients, cosensitization to diethanolamine was reported for 38%

of the patients that reacted to ethanolamine. In ocular irritation studies in rabbits, 30% aq. ethanolamine was moderately irritating to rabbit eyes, and undiluted ethanolamine produced severe injury. A hair preparation containing 5.96% ethanolamine had a maximum average irritation score of 0.7/110 in rinsed and unrinsed eyes. Ethanolamine, tested at 0.05, 0.5, and 1%, was classified as a moderate irritant in the in vitro rabbit corneal epithelial model evaluating ocular irritation potential.

One-tenth ml/kg of a 3.3% ethanolamine aerosol solution induced bronchoconstriction in guinea pigs. Ethanolamine-induced bronchoconstriction may result partly from an agonistic effect of ethanolamine at the histamine-H_1 receptor and the muscarinic receptor.

DISCUSSION

This amended safety assessment originated as a re-review of ethanolamine, and was expanded to include 12 ethanolamine salts, the safety of which were supported by the data available in the original safety assessment and by other published and unpublished studies. These ingredients are reported to be used only in rinse-off products; therefore the CIR Expert Panel addressed the safety as used in rinse-off products only.

While the Panel noted gaps in the available safety data for the ethanolamine salts included in this group, the Panel relied on the information available for ethanolamine in conjunction with previous safety assessments of the components of these ingredients. Those data could be extrapolated to support the safety of these ingredients. For example, coconut acid has been found safe as used, and the Panel was able to extrapolate these data to support the safety of MEA-cocoate (i.e., the ethanolamine salt of coconut acid).

The Panel noted that small amounts of diethanolamine could be present in ethanolamine and was concerned with levels of free diethanolamine that could be present as an impurity. Therefore, ethanolamine and ethanolamine-containing ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

Also, because diethanolamine might be present as an impurity in ethanolamine, the Panel re-iterated its discussion regarding the positive findings reported in a dermal carcinogenicity study of diethanolamine. The hepatocarcinogenicity that was reported in mice was considered to have little relevance to the safety of diethanolamine in personal care products. Additionally, renal lesions reported in mice could have been the result of diethanolamine-induced choline deficiency, a mechanism that has little relevance in humans. If diethanolamine-induced choline deficiency was not the cause of the renal lesions, it was thought there was still no carcinogenic risk to humans because diethanolamine does not appear to penetrate human skin to any significant extent at concentrations relevant to human exposures from the use of personal care products.

Because ethanolamine can be used in products that may be aerosolized, i.e. a hair color spray, the Panel discussed the issue of incidental inhalation exposure. The limited inhalation data included a single dose study of a non-defined mixture that included ethanolamine and a repeated dose study of ethanolamine did not suggest potential respiratory effects at relevant doses. Since inhalation data were limited, the Panel considered other available data and noted that there was lack of relevant systemic toxicity in dermal and oral single and repeated dose toxicity and reproductive toxicity studies and mostly negative results in genotoxicity studies. Further, this ingredient is reportedly used at concentrations of $\leq$3% in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and bronchial regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. Nevertheless, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

Finally, the potential exists for dermal irritation with the use of products formulated using ethanolamine or ethanolamine salts. The Panel specified that products containing these ingredients must be formulated to be non-irritating.

CONCLUSION

The CIR Expert Panel concluded that ethanolamine and the 12 related ethanolamine salts, listed below, are safe in the present practices of use and concentration described in this safety assessment (rinse-off products only) when formulated to be non-irritating. The Panel cautioned that ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

Ethanolamine
Ethanolamine HCl*
MEA-Benzoate*
MEA Cocoate
MEA-Laureth-6 Carboxylate*
MEA-Laureth Sulfate
MEA-Lauryl Sulfate
MEA-PPG Laureth-6 Carboxylate*
MEA-PPG-8 Steareth-7 Carboxylate*
MEA-Salicylate*
MEA-Sulfite*
MEA-Tallowate
MEA-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. Definition and structures of ethanolamine and ethanolamine-containing ingredients

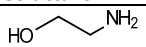
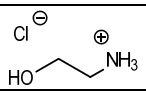
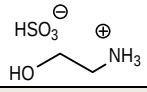
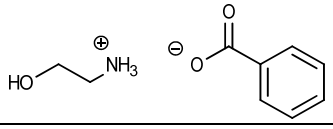
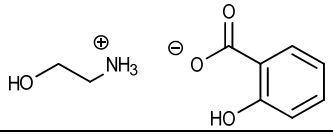
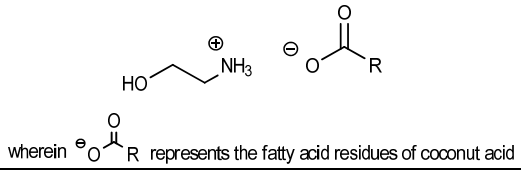
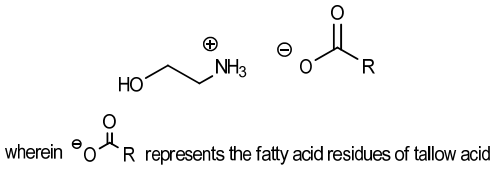
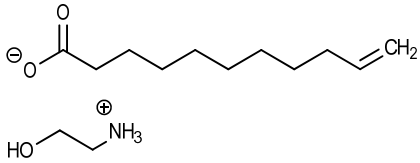
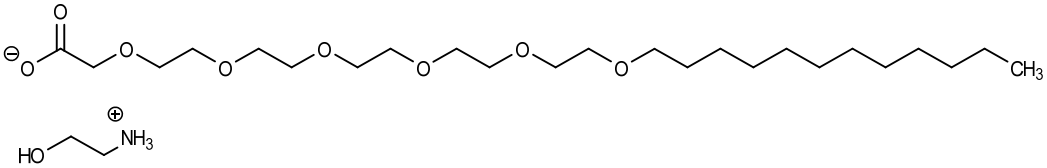
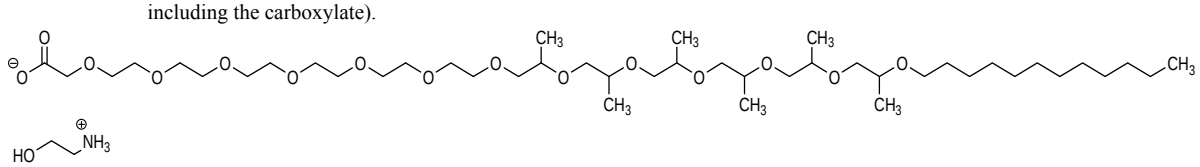
Ingredient/ CAS No.	Definition	Reported Function[8]	Structure
Ethanolamine 141-43-5	a primary amine with one ethanol functional group.	pH adjuster	
Ethanolamine HCl 2002-24-6	the ethanolamine salt of hydrochloric acid.	pH adjuster; buffering agent	
MEA-Sulfite 13427-63-9	the ethanolamine salt of hydrogen sulfite.	hair fixative	
Organic Acid Salts			
MEA-Benzoate 4337-66-0 33545-23-2	the ethanolamine salt of benzoic acid.	preservative	
MEA-Salicylate 59866-70-5	the ethanolamine salt of salicylic acid.	preservative	
MEA-Cocoate 66071-80-5	the ethanolamine salt of coconut acid.	surfactant – cleansing agent; surfactant – foam booster	 wherein represents the fatty acid residues of coconut acid
MEA-Tallowate	the ethanolamine salt of tallow acid.	In VCRP; not in INCI Dictionary	 wherein represents the fatty acid residues of tallow acid
MEA-Undecylenate 56532-40-2	ethanolamine salt of undecylenic acid	surfactant – cleansing agent	
MEA-Laureth-6 Carboxylate	the ethanolamine salt of laureth-6 carboxylic acid (wherein "-6" represents the number ethylene glycol units, including the carboxylate).	surfactant – cleansing agent	
MEA PPG-6 Laureth-7 Carboxylate	the ethanolamine salt of PPG-6 laureth-7 carboxylic acid (wherein "-7" represents the number ethylene glycol units, including the carboxylate).	surfactant – cleansing agent	

Table 1. Definition and structures of ethanolamine and ethanolamine-containing ingredients

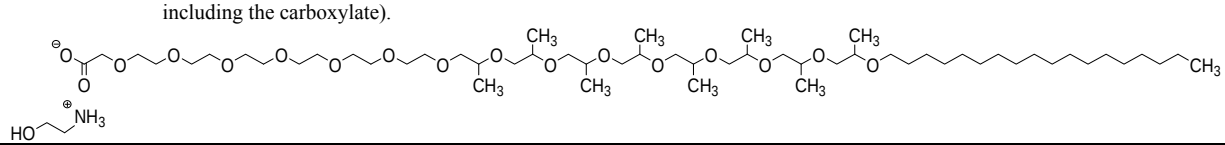
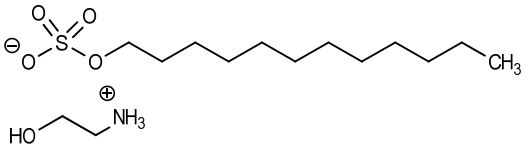
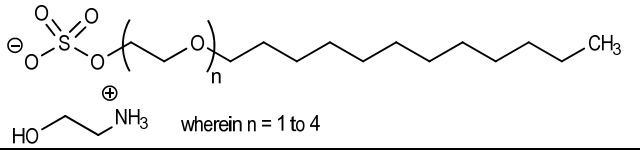
Ingredient/ CAS No.	Definition	Reported Function[8]	Structure
MEA-PPG-8-Steareth-7 Carboxylate	the ethanolamine salt of PPG-8 steareth-7 carboxylic acid (wherein "-7" represents the number ethylene glycol units, including the carboxylate).	surfactant – cleansing agent	
Organic-Substituted Inorganic Salts			
MEA-Lauryl Sulfate 4722-98-9	is the ethanolamine salt of sulfated lauryl alcohol.	surfactant – cleansing agent	
MEA-Laureth Sulfate 68184-04-3	the ethanolamine salt of sulfated, ethoxylated lauryl alcohol (wherein the number of ethylene glycol units ranges from 1 to 4).	surfactant – cleansing agent	

Table 2. Conclusions of previously reviewed ingredients and components

Ingredient	Conclusion
	PREVIOUSLY REVIEWED INGREDIENTS
Ethanolamine	is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin, and MEA should only be used in rinse-off products (1983)[1]
MEA-Salicylate	safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected; directions for use include the daily use of sun protection (2003)[4]
	COMPONENTS
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% (1983)[46]
Benzoic Acid	safe as used (2011)[47]
Coconut Acid	safe as used (2008)[48]
Laureths	safe as used when formulated to be non-irritating (2010)[49]
PPG	safe as used when formulated to be non-irritating (2010)[50]
Sodium Laureth Sulfate and related salts of ethoxylated alcohols	safe as used when formulated to be non-irritating (2010)[51]
Steareths	safe as used when formulated to be non-irritating (2010)[49]

Table 3. Physical and chemical properties

Property	Value	Reference
	Ethanolamine	
Physical Form	clear viscous liquid	[1]
Color	colorless	[1]
Odor	ammonia-like	[1]
Molecular Weight	61.08	[1]
Specific Gravity	1.0117 (25°C)	[1]
Viscosity	18.95 (25°C)	[1]
Refractive Index	1.4542 (20°C)	[7]
Vapor Pressure	0.48 mm Hg (20°C)	[1]
pK_a	9.5 (25°C0	[7]
Melting Point	10.3-10.5°C	[1]
Boiling Point	171°C	[1]
Water Solubility	miscible with water	[27]
Other Solubility	miscible with methanol and acetone	[27]
	soluble in alcohol, ethanol, chloroform, glycerol, logroin	[7]
log P_{ow} (estimated)	-1.31	[52]
	MEA Benzoate	
Molecular Weight	165.19 (calculated)	[53]
pKa	8.0 g/cm^3 ((most basic; 25°C) (calculated)	[53]
Density	1.119 g/cm^3 (20°C) (calculated)	[53]
Boiling Point	271.8°C (calculated)	[53]
log P	1.336 (25°C) (calculated)	[53]

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

	# of Uses[10]	*Max. Concs. of Use (%)*[11]	*# of Uses*[9]	*Max. Concs. of Use (%)*[11]	*# of Uses*[9]	*Max. Concs. of Use (%)*[11]
	Ethanolamine		**MEA Cocoate**		**MEA-Laureth Sulfate**	
Totals*	**788**	**0.0002-18**	**4**	**NR**	**13**	**NR**
Duration of Use						
Leave-On	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Rinse-Off	*788*	*0.0002-18*	*4*	*NR*	*13*	*NR*
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	3	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	3	0.0002-11	4	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	13	0.05-6	NR	NR	1	NR
Hair-Coloring	772	3-18	NR	NR	12	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.02-0.05	4	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

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

	# of Uses[9]	*Max. Concs. of Use (%)*[11]	*# of Uses*[9]	*Max. Concs of Use (%)*[11]	
	MEA-Lauryl Sulfate		**MEA-Tallowate**		
Totals*	**5**	**5-35**	**6**	**NR**	
Duration of Use					
Leave-On	*NR*	*NR*	*NR*	*NR*	
Rinse Off	*5*	*5-35*	*6*	*NR*	
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	
Exposure Type					
Eye Area	NR	NR	NR	NR	
Incidental Ingestion	NR	NR	NR	NR	
Incidental Inhalation-Spray	NR	NR	NR	NR	
Incidental Inhalation-Powder	NR	NR	NR	NR	
Dermal Contact	1	NR	6	NR	
Deodorant (underarm)	NR	NR	NR	NR	
Hair - Non-Coloring	4	5	NR	NR	
Hair-Coloring	NR	35	NR	NR	
Nail	NR	NR	NR	NR	
Mucous Membrane	NR	NR	6	NR	
Baby Products	1	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.
NR – no reported uses

Table 4b. Ingredients not reported to be in use

Ethanolamine HCl
MEA-Benzoate
MEA-Laureth-6 –Carboxylate
MEA-PPG-6 Laureth-7 Carboxylate
MEA-PPG-8 Steareth-7 Carboxylate
MEA-Salicylate
MEA-Sulfite
MEA Undecylenate

Table 4c. Status for use in Europe according to the EC CosIng Database for ethanolamine ingredients

Fatty Acid Monoalkylamines, monoalkanolamines, and their salts – listed in Annex III – restrictions[17]
(maximum secondary amine content of 0.5% in the finished product; do not use with nitrosating systems; minimum purity – 99%; maximum secondary amine content of 0.5% for raw materials; maximum nitrosamine content of 50 µg/kg; keep in nitrite free containers)

Ethanolamine
Ethanolamine HCl
MEA PPG-6 Laureth-7 Carboxylate
MEA-Benzoate
MEA-Cocoate
MEA -Laureth Sulfate
MEA -Laureth-6 Carboxylate
MEA -Lauryl Sulfate
MEA -PPG-8-Steareth-7 Carboxylate
MEA -Salicylate
MEA -Sulfite
MEA –Undecylenate

List of Preservatives Allowed in Cosmetics – Annex V
MEA-Benzoate (maximum concentration in ready-for-use preparations of 0.5% benzoic acid)
MEA-Salicylate (maximum concentration in ready-for-use preparations of 0.5% salicylic acid; not to be used in products for children under 3 years of age, except shampoos)

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