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Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine

Triethanolamine (TEA), Diethanolamine (DEA), and Monoethanolamine (MEA) are amino alcohols used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. The nitrosation of the ethanolamines may result in the formation of N-nitrosodiethanolamine (NDELA) which is carcinogenic in laboratory animals.

In single-dose oral toxicity for rats, TEA was practically nontoxic to slightly toxic, and DEA and MEA were slightly toxic. Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney. Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage. TEA and DEA showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semioccluded patch application and at a >10% concentration in 10 open applications over a period of 14 days.

The ethanolamines were nonmutagenic in the Ames test and TEA is also nonmutagenic to *Bacillus subtilis*. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test. TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months.

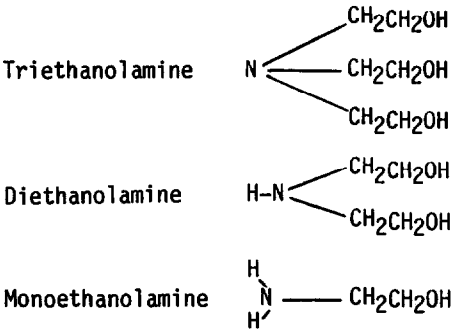
Clinical skin testing of TEA and cosmetic products containing TEA and DEA showed mild skin irritation in concentrations above 5%. There was very little skin sensitization. There was no phototoxicity or photosensitization reactions with products containing up to 20.04% TEA. A formulation containing 11.47% MEA and a formulation containing 1.6% DEA and 5.9% MEA were irritating to human skin in patch tests.

The Panel concludes that TEA, DEA, and MEA are 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 ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used in products containing N-nitrosating agents.

CHEMICAL AND PHYSICAL PROPERTIES

Structure

Triethanolamine (CAS No. 102-71-6) (TEA), Diethanolamine (CAS No. 111-42-2) (DEA), and Monoethanolamine (CAS No. 141-43-5) (MEA) are amino alcohols. They are produced by aminating ethylene oxide with ammonia. The replacement with ethanol groups of three, two, or one hydrogen of ammonia results in TEA, DEA, or MEA, respectively. The chemical formulas of the ethanolamines are as follows:



Properties

TEA, DEA, and MEA are clear, colorless, viscous liquids with ammoniacal odors. They are hygroscopic and are strong bases. The ethanolamines are soluble in water, alcohol, and chloroform, and are insoluble in benzene, ether, and petroleum distillates.[1-6] Chemical and physical properties of TEA, DEA, and MEA are presented in Table 1. A sampling of the variety of values available in the literature is given for several chemical and physical properties. This variation may reflect the use of different grades of chemicals.

Reactivity

TEA, DEA, and MEA are reactive and are bifunctional, combining the properties of alcohols and amines. The ethanolamines will react at room temperature with fatty acids to form ethanolamine soaps, and DEA and MEA will react at temperatures between 140° and 160°C with fatty acids to form ethanolamides. The reaction of ethanolamine and sulfuric acid produces sulfates, and DEA and MEA may react, under anhydrous conditions, with carbon dioxide to form carbamates.[1-3]

The ethanolamines can act as antioxidants in the autoxidation of fats of both animal and vegetable origin. TEA and DEA have stronger antioxidant effects than MEA.[7] TEA is an antioxidant as measured by the *Tetrahymena* photodynamic assay.[8]

TEA and DEA can react with nitrite or oxides of nitrogen to form N-nitrosodiethanolamine (NDELA). As yet, MEA has not been found to form a stable nitrosamine.[9,10] MEA can react with an aldehyde to form DEA, and then can be

TABLE 1. Chemical and Physical Properties.

Property	*TEA*	*DEA*	*MEA*	*Ref.*
Molecular weight	149.19	105.14	61.08	6
Specific gravity				
20/4 °C	1.1242			
20/20 °C			1.0179	3,5
25/4 °C			1.0117	6
30/4 °C		1.0881		6
30/20 °C		1.0919		2
30/20 °C		1.092		5
40/4 °C			0.9998	6
60/4 °C	1.0985	1.0693	0.9844	6
not specified	1.1255			1
not specified	1.124			4
not specified	1.126			5
Viscosity (cps)				
20 °C	1013			1
25 °C	590.5		18.95	6
30 °C		380		2
30 °C		351.9		6
60 °C	65.7	53.85	5.03	6
not specified			24	3
Boiling Point (°C)				
760 mm Hg	360	decomposes	171	1–3
760 mm Hg	335.4	268.8	170.8	6
not specified	277–279	268.0	172.2	4
not specified	335, decomposes		170.5	5
Melting Point (°C)	17.9	28.0	10.3	1–3
	20–21.2	28.0	10.5	4
	21.2	28.0	10.5	5
	21.57	28.0	10.3	6
Heat of Vaporization (joules/g)				
760 mm Hg	534	660	825	1–3
Vapor Pressure (mm Hg)				
20 °C	<0.01		0.48	5
not specified	0.01	0.01	0.4	1–3
Refractive Index				
20 °C			1.4544	3
20 °C	1.4852		1.4539	6
30 °C		1.4747		2
30 °C		1.4753		6
pH of a 0.1 N aqueous solution	10.5	11.0	12.05	6

nitrosated to form NDELA.[9] The optimum pH for nitrosamine formation is variously reported to be between 1 and 6, and the reaction rate decreases as the pH increases.[9-12] Neutral solutions require 100,000 times as much nitrite as strong acid solutions in order to form the same amount of nitrosamine.[10,12] However, in the presence of catalysts such as chloral or an aldehyde, nitrosation reactions may occur up to a pH of 11.[9] The rate of NDELA formation in the pH range 4–9 is four to six times greater in the presence of formaldehyde than in its absence.[13] Higher temperatures and longer reactions times increase the yield of

nitrosamine.[11] Nitrosation reactions and salt formation reactions compete in aqueous solutions.[10] The nitrosation by nitrites of DEA in an oil-in-water emulsion to NDELA can be inhibited by ascorbic acid or sodium bisulfite or much less effectively inhibited by potassium sorbate incorporated into the aqueous phase or can be inhibited by ascorbyl palmitate incorporated into the oil phase.[14]

Methods of Manufacture and Impurities

The ethanolamines are commercially produced by aminating ethylene oxide with ammonia. The reaction temperature can be adjusted to produce mostly TEA or MEA.[1-3,15] The product is purified by distillation. A "low freeze grade" product can be prepared by adding up to 15% water.[1-3]

TEA contains small amounts of DEA and MEA, and DEA contains small amounts of TEA and MEA. MEA contains a small amount of DEA.[1-3,16] TEA used in cosmetics may contain a maximum of 0.5% water, 0.05% sulfated ash, and 15 ppm iron.[17]

Analytical Methods

Qualitative and quantitative determinations of the ethanolamines are made by colorimetric procedures,[16,18-21] titrimetric methods,[16,20,22-28] thin-layer chromatography,[29-32] gas chromatography,[23-25,33-39] gravimetric analysis,[39] thermogravimetric analysis,[40] the Kjeldahl method,[18] and the Van Slyke procedure.[41] Positive identification of the ethanolamines can be made by comparison with published infrared spectra.[39,42,43] UV absorbance spectra are available for TEA and MEA.[44]

Jones et al.[33] used gas chromatography to determine the amount of TEA in a simulated vanishing cream and shampoo. They did a preliminary separation into classes of compounds and were then able to recover between 96% and 101% of the TEA added to the cosmetic formulations.

USE

Purpose in Cosmetics

Ethanolamine soaps, formed from the reaction at room temperature of TEA, DEA, or MEA and fatty acids, and ethanolamides, formed from the reaction at elevated temperatures of DEA and MEA and fatty acids, are used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents.[1-3,45]

Scope and Extent of Use in Cosmetics

Product types and the number of product formulations containing TEA, DEA, or MEA reported voluntarily to the Food and Drug Administration (FDA) in 1981 are presented in Table 2. Table 2 does not include products containing TEA-lauryl sulfate or TEA-coco-hydrolyzed animal protein. These two ingredients have been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in

TABLE 2. Product Formulation Data.

Product category	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)							
			Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Triethanolamine										
Baby shampoos	35	1	–	–	–	–	–	–	1	–
Baby lotions, oils, powders, and creams	56	4	–	–	–	–	–	2	2	–
Other baby products	15	1	–	–	1	–	–	–	–	–
Bath oils, tablets, and salts	237	1	–	–	–	–	1	–	–	–
Bubble baths	475	5	–	–	–	–	–	–	2	3
Other bath preparations	132	5	–	–	–	–	–	–	5	–
Eyebrow pencil	145	6	–	–	–	–	–	1	5	–
Eyeliner	396	60	–	–	–	4	2	17	34	3
Eye shadow	2582	157	–	–	–	–	–	73	81	3
Eye lotion	13	1	–	–	–	–	–	–	–	1
Eye makeup remover	81	3	–	–	–	–	–	2	–	1
Mascara	397	141	–	–	–	5	10	94	32	–
Other eye makeup preparations	230	36	–	–	–	–	–	14	22	–
Colognes and toilet waters	1120	12	–	–	–	–	–	–	5	7
Perfumes	657	5	–	–	–	–	–	1	4	–
Sachets	119	40	–	–	–	–	–	17	23	–
Other fragrance preparations	191	40	–	–	–	–	–	14	26	–
Hair conditioners	478	10	–	–	–	1	–	2	6	1
Hair sprays (aerosol fixatives)	265	3	–	–	–	–	–	1	2	–
Permanent waves	474	3	–	–	–	–	–	3	–	–
Hair rinses (noncoloring)	158	1	–	–	–	–	–	–	–	1
Hair shampoos (noncoloring)	909	36	–	–	1	1	5	16	13	–
Tonics, dressings, and other hair grooming aids	290	24	–	–	–	–	1	9	10	4
Wave sets	180	44	–	–	–	–	–	3	41	–
Other hair preparations (noncoloring)	177	8	–	–	–	–	–	2	6	–

TABLE 2. (Continued.)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)							
			Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Triethanolamine (Cont'd.)										
Hair dyes and colors (all types requiring caution statement and patch test)	811	40	–	–	–	–	–	–	40	–
Hair rinses (coloring)	76	1	–	–	–	–	–	–	1	–
Other hair coloring preparations	49	8	–	–	–	8	–	–	–	–
Blushers (all types)	819	65	–	–	–	–	–	32	28	5
Face powders	555	14	–	–	–	–	–	–	3	11
Makeup foundations	740	211	–	–	–	–	–	71	139	1
Lipstick	3319	17	–	–	–	–	–	–	14	3
Makeup bases	831	273	–	1	–	–	–	90	181	1
Rouges	211	11	–	–	–	–	–	4	6	1
Makeup fixatives	22	2	–	–	–	–	–	–	2	–
Other makeup preparations (not eye)	530	20	–	–	–	–	–	4	15	1
Cuticle softeners	32	9	–	–	–	–	2	–	6	1
Nail creams and lotions	25	6	–	–	–	–	–	3	3	–
Nail polish and enamel remover	41	1	–	–	–	–	–	–	1	–
Other manicuring preparations	50	2	–	–	–	–	1	–	1	–
Bath soaps and detergents	148	8	–	–	4	–	4	–	–	–
Deodorants (underarm)	239	2	–	–	–	–	–	–	2	–
Other personal cleanliness products	227	7	–	–	1	1	1	2	2	–

Aftershave lotions	282	22	–	–	–	–	–	1	18	3
Beard softeners	4	2	–	–	–	–	2	–	–	–
Shaving cream (aerosol, brushless, and lather)	114	64	–	–	–	–	3	56	5	–
Other shaving preparation products	29	11	–	–	–	–	–	3	6	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	214	–	–	–	–	1	69	131	13
Depilatories	32	1	–	–	–	–	–	1	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	403	2	–	–	–	4	105	276	16
Foot powders and sprays	17	1	–	–	–	–	–	–	1	–
Hormone skin care preparations	10	3	–	–	–	–	–	1	2	–
Moisturizing skin-care preparations	747	388	–	1	–	–	–	115	248	24
Night skin care preparations	219	88	–	–	–	–	–	34	48	6
Paste masks (mud packs)	171	19	–	–	–	–	–	1	16	2
Skin lighteners	44	5	–	–	–	–	–	2	3	–
Skin fresheners	260	19	–	–	–	–	1	–	11	7
Wrinkle smoothers (removers)	38	7	–	–	–	–	–	1	6	–
Other skin care preparations	349	69	–	–	1	–	1	21	40	6
Suntan gels, creams, and liquids	164	47	–	–	–	–	1	15	31	–
Indoor tanning preparations	15	3	–	–	–	–	–	–	3	–
Other suntan preparations	28	10	–	–	–	–	–	6	41	–
1981 TOTALS		2757	2	2	8	20	40	908	1650	127

TABLE 2. (Continued.)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)							
			Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Diethanolamine										
Bubble baths	475	4	–	–	–	–	–	–	–	4
Permanent waves	474	1	–	–	–	–	–	1	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	12	–	–	–	–	–	12	–	–
Nail basecoats and undercoats	44	1	–	–	–	–	–	1	–	–
1981 TOTALS		18	–	–	–	–	–	14	–	4
Monoethanolamine										
Mascara	397	1	–	–	–	–	–	–	1	–
Hair conditioners	478	2	–	–	–	–	–	–	2	–
Hair straighteners	64	2	–	–	–	–	–	2	–	–
Permanent waves	474	13	–	–	–	–	2	9	2	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	25	–	–	–	–	9	7	9	–
Hair shampoos (coloring)	16	1	–	–	–	–	–	–	1	–
Hair bleaches	111	2	–	–	–	–	–	2	–	–
Other personal cleanliness products	227	3	–	–	–	–	–	2	–	1
Shaving cream (aerosol, brushless, and lather)	114	1	–	–	–	–	–	–	1	–
Moisturizing skin care preparations	747	1	–	–	–	–	–	–	1	–
1981 TOTALS		51	–	–	–	–	11	22	17	1

Data from Ref. 48.

other documents.[46,47] Voluntary filing of product formulation data by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations (21 CFR, Part 720.4). Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the actual concentration of the finished product; the concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

In 1981, TEA, DEA, and MEA were reported to be ingredients of 2757, 18, and 51 cosmetic products, respectively. The majority of these products contained TEA, DEA, or MEA in a concentration of less than or equal to 5%.[48]

Surfaces to Which Commonly Applied

Cosmetic products containing ethanolamines may be applied to or come in contact with skin, eyes, hair, nails, mucous membranes, and respiratory epithelium. Small amounts may be ingested from lipstick (Table 2).[48]

Frequency and Duration of Application

Product formulations containing ethanolamines may be applied as many as several times a day and may remain in contact with the skin for variable periods of time following each application. Daily or occasional use may extend over many years (Table 2).[48]

Potential Interactions with Other Cosmetic Ingredients

N-nitrosating agents, present as intentional ingredients or as contaminants of cosmetics, may react with the ethanolamines to form N-nitrosodiethanolamine (NDELA). NDELA has been found in cosmetic raw materials. Ninety-nine samples of 17 materials were evaluated and NDELA was detected in concentrations of greater than 1000 ppb, 501–1000 ppb, 101–500 ppb, and 50–100 ppb in 6, 3, 6, and 6 samples, respectively. NDELA was found in trace levels in nine samples and was not detected in 69 samples.[13,49] NDELA has also been detected in a variety of cosmetic products.[50-60] An on-going study by the FDA has provided NDELA analysis for 335 off-the-shelf cosmetic formulations. The FDA data are presented in Table 3. NDELA was detected in 110 of a total of 252 products containing TEA and in 25 of a total of 64 products not containing TEA. However, products with no TEA may have contained DEA or MEA. These findings suggest the possibility that TEA may lead to the formation of NDELA in some cosmetics.

Bronaugh et al.[61,62] investigated the percutaneous absorption of NDELA through excised human skin. NDELA was dissolved in water, propylene glycol, and isopropyl myristate, and the permeability constants were 5.5×10^{-6}, 3.2×10^{-6}, and 1.1×10^{-3} cm/h, respectively. The permeability of NDELA through ex-

TABLE 3. Association of NDELA with TEA in Cosmetics Analyzed by the FDA.

Cosmetic product samples reported to contain	*NDELA detected*	*No NDELA detected*
TEA	110	142
No TEA	25	39
Incomplete or no Ingredient information	5	14
	(Total) 140	(Total) 195

Data from Refs. 51–55.

cised human skin was greatly increased when applied from sufficiently lipoidal formulations. The major route of elimination after oral and topical administration of NDELA to rats was the urine.[63] NDELA was applied to the skin of monkeys and pigs and, afterwards, was detected in their urine.[64] NDELA was detected in rat urine following epicutaneous and intratracheal administration of NDELA and following percutaneous administration of DEA and oral administration of nitrite in drinking water.[65] After application of an NDELA-contaminated cosmetic. NDELA was detected in human urine.[66]

NDELA, in concentrations of 5–15 mg/plate, was mutagenic to *Salmonella typhimurium* strains TA1535 and TA100 in the presence of hamster liver S-9 but not in the presence of rat liver S-9.[67] NDELA is carcinogenic to rats after oral administration[68-70] and to hamsters after subcutaneous injections, skin painting, and oral cavity swabbing.[71,72] Although no epidemiological data were available, the International Agency for Research on Cancer[73] has suggested that "NDELA should be regarded for all practical purposes as if it were carcinogenic to humans."

Nitrites have been found in cosmetic raw materials.[13,49,74] TEA and DEA can be nitrosated to NDELA with 2-bromo-2-nitropropane-1,3-diol (BNPD), an antimicrobial agent used in cosmetics.[75-77] A report on the safety assessment of BNPD recommended against its usage in cosmetics where its actions with amines or amides could result in the formation of nitrosamines or nitrosamides.[75] Ong et al.[78] discovered that NDELA could be formed from the peroxidation and subsequent nitrosation of DEA. They found that peroxides could result from the autoxidation of compounds such as polysorbate 20 and that the addition of antioxidants prevented this. Under the same experimental conditions, TEA and MEA did not yield NDELA.

Noncosmetic Uses

The ethanolamines are 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. They are intermediates for resins, plasticizers, and rubber chemicals. They are used as lubricants in the textile industry, as humectants and

softening agents for hides, as alkalizing agents and surfactants in pharmaceuticals, as absorbents for acid gases, and in organic syntheses.[5,6]

TEA, at a concentration not exceeding 2 ppm, and MEA, at a concentration not exceeding 0.3 ppm, may be used in flume water for washing sugar beets prior to slicing (21 CFR 173.315). TEA, DEA, and MEA, at no specific concentration limits, may be components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food[79] except that TEA and DEA may not exceed 5% by weight of rubber articles intended for repeated use.[80] TEA and DEA may be used as adjuvants for pesticide chemicals and are exempt from the requirement of tolerances[81] except that DEA maleic hydrazide may not be sold in the United States.[82]

GENERAL BIOLOGY

Antimicrobial Effects

TEA, DEA, and MEA inhibit the growth of a wide variety of microorganisms. The concentration of ethanolamine required to inhibit growth varies with genus and species.[8,83-87] DEA and MEA have some antimycotic activity when applied on the skin of guinea pigs.[88-90]

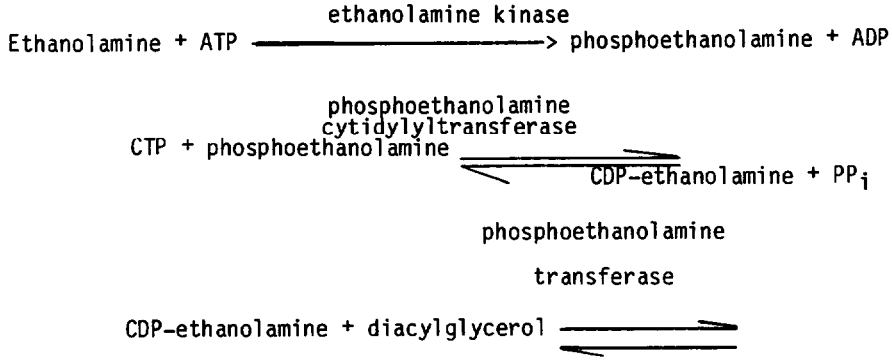
Effects on Chick Embryo

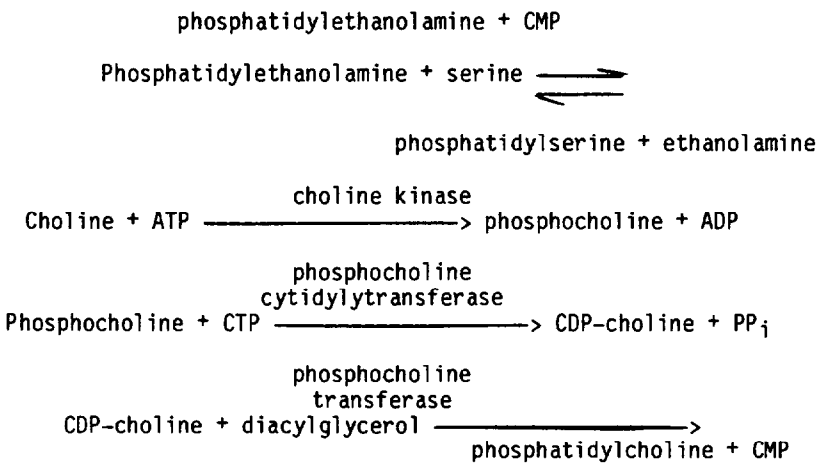
The incubation of chicken eggs with 0.03% MEA for 18 h increases the number of eggs with visible blastodisks, increases the synthesis of proteins, fats, and carbohydrates, and increases the number of hatching chicks.[91]

Effects on Enzymatic Activity

Effects on Enzymes Involved in Lipid Biosynthesis

TEA, DEA, and MEA affect the biosynthesis of lipids. Reactions of particular interest in mammals are those involved in the synthesis of the phosphoglycerides, phosphatidylethanolamine (PE), phosphatidylcholine (lecithin) (PC), and phosphatidylserine (PS):[92]





The administration of MEA at a dose of 60 mg/kg/day for 30 consecutive days to albino rats with experimentally-induced coarction of the aorta resulted in elevated levels of PE, PS, and PC in the rat myocardium. Metabolic changes produced by MEA action may have inhibited the development of cardiac insufficiency in these animals.[93] Hale et al.[94] grew chicken embryo fibroblasts in standard media with 40 mg/ml of choline in delipidated media without choline, and in delipidated media without choline and with 40 mg/ml of MEA. The PE content of the cells was increased in both delipidated media and hexose transport was slowed in the MEA supplemented medium. The authors suggested that some property of MEA other than its accompanying increase in PE must be responsible for the drop in hexose transport in these cells. Upreti[95] injected intraperitoneally approximately 168 mg/kg of MEA into male albino mice every day for four days. Mice were sacrificed at 6, 12, 24, 48, and 96 h. At all times from 12 to 96 h, the liver ethanol kinase levels of the treated mice were significantly higher than control mouse liver levels.

Barbee and Hartung[96] investigated the effect of the administration of DEA on the in vivo incorporation of MEA and choline into rat liver and kidney. They found that the administration of 250 mg/kg of labeled DEA in a single injection to male albino rats did not change the amount of injected labelled MEA and choline incorporated into liver or kidney. However, when labelled DEA was administered to male albino rats at a dose of 320 mg/kg/day in drinking water for up to three weeks, the results were different. Rats were sacrificed at 0, 1, 2, and 3 weeks, and the amounts of injected labeled MEA and choline incorporated in the liver and in the kidney were lower at 1, 2, and 3 weeks than at time 0. MEA and choline phospholipid derivatives were synthesized faster and in greater amounts, and were catabolized faster than DEA phospholipid derivatives. This may favor accumulation of DEA-containing phospholipids during chronic exposure. These researchers also investigated the effects of DEA on mitochondrial function in the male albino rat.[97] Administration of neutralized DEA at doses of 490 mg/kg/day for three days or of 160 mg/kg/day for one week in drinking water produced alterations of hepatic mitochondrial function. Barbee and Hartung hypothesize

that DEA phospholipids are formed and incorporated into mitochondrial membranes with subsequent disruption of mitochondrial metabolism.

The activity of glucosyltransferase, isolated from *Streptococcus mutans* culture supernatant solutions, was stimulated by TEA at a concentration of 50 m*M* and a pH of 6.5.[98] Glucosyltransferase catalyzes the formation of glucocerebroside, a sphingolipid, from ceramide and UDP-D-glucose.[92]

Effects on Other Enzymes

MEA inhibits the action of purified acetylcholinesterase from bovine erythrocytes.[99] Acetylcholinesterase catalyzes the reaction of acetylcholine and water to acetic acid and choline. This enzyme functions in the activity of the nervous system.[92]

DEA administered intraperitoneally or orally may affect directly or indirectly the serum enzyme levels, isozyme patterns, and concentrations of some amino acids and urea in the male rat liver and kidney. These changes were observed concomitant with or just after organ damage was histologically detectable.[100,101] Subchronic DEA administration in drinking water increased male rat hepatic mitochondrial ATPase and altered mitrochondrial structure and function.[97]

MEA stimulates the activity of purified aspartate transaminase from porcine heart[102] and intraperitioneal or intravenous administration of MEA decreases aspartate transaminase activity in rabbit kidney and heart.[103] The reversible reaction of L-aspartate and α-ketoglutarate to oxaloacetate and L-glutamate is catalyzed by aspartate transaminase.[92] Kotogyan et al.[104] found that the intravenous administration of MEA to rabbits for seven days increased the level of aspartate and glutamate in the kidneys and decreased the levels in the brain.

The intraperitoneal or intravenous administration of MEA to rabbits decreased the activity of alanine transaminase in the kidney and the heart.[103] Alanine transaminase is the enzyme involved in the reversible reaction that converts L-alanine and α-ketoglutarate to pyruvate and L-glutamate.[92]

Intraperitoneal administration of MEA to rats inhibited alcohol dehydrogenase. Ostroviskii and Bankovskii[105] suggested that this was the reason for the hepatic accumulation of endogenous ethanol and taurine.

Peroxidase activity and number of organic peroxide molecules in the blood, liver, and homogenate of chick embryos were decreased when chicken eggs were incubated with MEA.[91] Peroxidase acts in reactions in which hydrogen peroxide is an electron acceptor.

MEA can inactivate and partially dissociate β-galactosidase from *Escherichia coli*.[106] Beta-galactosidase catalyzes the formation of D-glucose and D-galactose from lactose and water.[92]

Effects on Hormones

MEA can affect the metabolism of catechol amines. The conversion of interest is as follows:

L-tyrosine → dihydroxyphenylalanine (DOPA) → dopamine → norepinephrine → epinephrine

Epinephrine and norepinephrine are hormones secreted by the adrenal medulla. They act in the regulation of heart rate and blood pressure. Epinephrine also activates glycogen breakdown to glucose in the liver and in muscle through its stimulation of adenylate cyclase.[92] Intraperitoneal injection of MEA into rats at 10 mg/kg increased norepinephrine and decreased epinephrine in the heart. A 25 mg/kg injection of MEA had the opposite effect. At the higher MEA dose, after three days the heart norepinephrine concentration remained altered and the DOPA concentration increased.[107] A 25 mg/kg intraperitoneal injection of MEA increased mouse heart muscle content of epinephrine and DOPA and decreased the content of norepinephrine.[108] Goncharenko et al.[109] found increased dopamine concentrations in rats following injection of MEA. DOPA decreased or remained unchanged.

Okano[110] reported that the in vitro conversion of proparathyroid hormone formed in the parathyroid gland to parathyroid hormone was strongly inhibited by the action of MEA. Parathyroid hormone is involved in the metabolism of calcium and phosphorus by the body.

Effects on Protein, Nucleic Acids, and Other Cellular Substances

Subchronic oral administration of MEA to castrated rams increased serum albumin concentrations and total protein concentrations.[111]

The administration of MEA to rabbits, either intraperitoneally or intravenously, increased RNA concentrations in the kidney, heart, and brain, decreased DNA concentrations in the heart and brain, and had no effect on total nitrogen or protein in any of the three tissues.[103]

Intraperitoneal administration of MEA to rats increased glycogen, ATP, and ascorbic acid concentrations in the liver, kidney, brain, and heart.[112]

Effects on Liver Structure

Grice et al.[100] assessed morphological damage to rat liver and kidney four and 24 h after intraperitoneal injection of DEA at 100 and 500 mg/kg. At both times, after both doses and in both organs, cytoplasmic vacuolization was observed. In addition, mitochondria of the hepatocytes were swollen and less dense than in the control animals, and after 24 h, liver nuclei were more deeply basophilic than normal. At both times at the high dose of DEA, there was some renal tubular degeneration and some cells were necrotic. Barbee and Hartung[97] found that the mitochondria from rats treated with 3 mg/kg/day of DEA for two weeks in their drinking water were consistently spherical and also appeared larger than mitochondria from control animals. Korsud et al.[101] administered 100 to 6400 mg/kg of DEA orally to rats. They discovered that liver and kidney weights and damage to the liver and kidney increased as dose increased. They confirmed the observations of Grice et al.[100] except that they found no morphological differences in mitochondria from control and treated rats.

Effects on the Heart

MEA, administered to rats with experimentally-induced coarction of the aorta, at doses from 5 to 50 mg/kg enhanced myocardial contractility. Thirty-day

administration of MEA in a dose of 10 mg/kg stimulated and 60 mg/kg of MEA inhibited the development of myocardial hypertrophy.[93] Increasing doses of MEA from 9.6×10^{-7} *M* to 1.2×10^{-5} *M* increased the atrial rate and force of contraction in the isolated rabbit atria.[113]

Effects on the Bovine Rhodopsin Chromophore

MEA bleached the visual pigment, rhodopsin, from water-washed bovine retinal rod chromophores, which are responsible for vision in dim light.[114]

ABSORPTION, METABOLISM, STORAGE, AND EXCRETION

MEA is the only naturally occurring ethanolamine in mammals and is excreted in the urine.[10] Much of the available scientific literature on the metabolism of the ethanolamines is concerned with the effect on phospholipid biosynthesis of the intraperitoneal and intracerebral or in vitro administration of MEA to intact mammals or mammalian tissue, respectively. Ansell and Spanner[115] have performed a respresentative experiment. Labeled MEA was administered intraperitoneally to adult female rats, the rats were sacrificed, and incorporation of MEA into phospholipids was traced in the liver, the blood, and the brain. They discovered that MEA was converted to phosphatidylethanolamine (PE) in all the tissues. However, the step-wise methylation of PE that converts it to phosphatidylcholine (PC), which occurs rapidly in the liver and less rapidly in extrahepatic tissues, did not occur at all in the brain. Morin[116] found that labelled MEA was incorporated into PE and also into PC in isolated human peripheral arteries. This suggests that the enzyme system for transmethylation of PE to PC may be active in human arteries. Researchers have found labeled respiratory carbon dioxide after intraperitoneal administration of labeled MEA to rats.[117] Further sources are available that corroborate these findings on the effect of MEA on lipid biosynthesis in mammals.[105,118-140]

In vitro administration of MEA had no effect on the incorporation of labeled phosphate into phospholipids in swine coronary and pulmonary arteries[141] or in rabbit or human endometria.[142] However, in both cases TEA did inhibit the incorporation of labeled phosphate into phospholipids.

Babior[143] labeled purified MEA from an unspecified source and demonstrated a coenzyme-B_{12}-dependent ethanolamine deaminase mediated conversion of MEA to acetaldehyde and ammonia. Ostrovskii and Bankovskii[105] administered MEA intraperitoneally to rats and observed an increase in blood urea and brain glutamine. They suggested that ethanolamine was an ammonia source. Sprinson and Weliky[144] labeled MEA and administered it in feed to rats. They detected labeled acetate in the urine of the rats. They suggested that MEA is phosphorylated by ATP in vivo, converted to acetaldehyde, ammonia, and inorganic phosphate and then the acetaldehyde is oxidized to acetate. These researchers hypothesize that the removal of phosphorylated MEA by its conversion to acetate may exert a regulatory effect on PE biosynthesis.

Labeled MEA was administered to dogs. The route of administration was unspecified. After 24 h, the total blood radioactivity as a percentage of dose was

1.69%. There was a persistence of low levels of radioactivity in dog whole blood samples; the half-life was 19 days. Excretion in urine of radioactivity as a percentage of dose was 11%.[145]

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

The acute oral toxicity of TEA, DEA, MEA, and a hair preparation containing DEA and MEA has been studied in guinea pigs[146-149] and in rats.[149-159] The animals were administered the material by gavage, and then were observed for 14 days. Table 4 presents data from the experiments. The LD50 values for rats of TEA, DEA, and MEA ranged from 4.19 g/kg to 11.26 g/kg, 0.71 ml/kg to 2.83 g/kg, and 1.72 g/kg to 2.74 g/kg, respectively. The LD50 values for DEA and MEA are quite similar and are lower than the LD50 values for TEA. In the Hodge and Sterner[160] classification of single-dose oral toxicity for rats, TEA, DEA, and MEA would be classified as practically nontoxic to slightly toxic, slightly toxic, and slightly toxic, respectively.

Oral Corrosivity

A study was conducted on rabbits to determine the oral tissue corrosivity potential of a hair preparation containing 1.6% DEA, 5.9% MEA, and 3.2% sodium borate.[161] The undiluted test material at a dose of 0.229 g/kg (0.210 ml/kg) was placed on the posterior tongue surface of four rabbits and they were allowed to swallow. Two rabbits were sacrificed at 24 h and two at 96 h. Gross and microscopic examinations of the tongue, adjacent pharyngeal structures, larynx, esophagus extending to the cardiac incisure, and stomach revealed no observable abnormalities. The hair preparation was not an irritant and was not corrosive in these tests.

Subchronic and Chronic Toxicity

Long-term oral toxicity of TEA, DEA, MEA or a composite of hair dyes and bases has been studied in guinea pigs,[149] in rats[149,155,156,162-165] and in dogs.[166] Table 5 presents data from the experiments. Considerably less data are available for DEA and MEA than for TEA. However, it does appear that DEA is the most toxic ethanolamine. Workers at the Mellon Institute[154] have suggested that this may be because MEA has a normal function in the lipid metabolism of the body and DEA is structurally similar enough to MEA to act in competition with it and interfere in lipid metabolism. TEA may be so sufficiently unlike MEA that it does not act in competition and therefore is less toxic than DEA.

Dermal Studies

Acute Toxicity

Undiluted TEAs, 91.8% and 88.1% active and both containing slightly more than 6% of DEA, were each applied to the intact skin of three rabbits and to the

TABLE 4. Acute Oral Toxicity.

Material tested	*Conc. of material tested (%) and vehicle*	*Dose of ethanolamine*[a]	*No. and species of animal*	*LD50*	*Comments*	*Ref.*
TEA, 99+ Percent	20 in water; 100	4.0; 5.0, 6.3 g/kg	2 rats at each dose level		0/2, 1/2, 2/2 deaths, moderate liver and kidney damage at all dose levels.	150
TEA, 99+ Percent	In gum arabic solution	0.6–7.0 g/kg	2–3 (unspecified) guinea pigs at each dose level		All survived 0.6 and 1.4 g/kg; None survived 7.0 g/kg.	146
TEA, 78.6% (DEA, 8.6%; MEA, 1.7%)	25 in water	2.6–7.4 ml/kg TEA	10 rats at each of 4 dose levels	4.03 ml/kg (4.19 g/kg)	No unusual observations.	151
TEA, 91.8% (DEA, 6.5%)	100	3.64–14.00 ml/kg	10 rats at each of 5 dose levels	7.11 ml/kg	Slight to moderate degrees of hemorrhagic rhinitis in rats dosed at ≥7.14 ml/kg.	152
TEA, 88.1% (DEA, 6.1%)	100	3.64–10.00 ml/kg	10 rats at each of 4 dose levels	5.39 ml/kg	Slight to moderate degrees of hemorrhagic rhinitis in rats dosed at ≥7.14 ml/kg.	152
TEA, Commercial or high purity grade	100	1.0–26.0 g/kg	10 guinea pigs at LD50 and at 1 g < LD50 estimated from single feedings	8 g/kg	Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals. Some were paralyzed in their hind quarters.	149
TEA, Commercial grade	100	1.0–12.0 g/kg	10 rats at LD50 and at 1 g < LD50 estimated from single feedings	8 g/kg	Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals.	149

TABLE 4. (Continued.)

Material tested	*Conc. of material tested (%) and vehicle*	*Dose of ethanolamine*[a]	*No. and species of animal*	*LD50*	*Comments*	*Ref.*
TEA, high purity grade	100	1.0–12.0 g/kg	10 rats at LD50 and at 1 g < LD50 estimated from single feedings	9 g/kg	Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals.	149
TEA	in water		6 male rats at each dose level	9.11 g/kg		156
TEA, produced from 1939–1960	20 in water/100		rats	8.54–9.85 ml/kg or 7.3–11.26 g/kg		154,155
DEA, 99+ Percent	in gum arabic solution	0.6–5.0 g/kg	2–3 (unspecified) guinea pigs at each dose level		All survived 6.0 and 1.0 g/kg; None survived 3.0 g/kg.	147
DEA	in water		6 male rats at each dose level	1.82 g/kg		156
DEA	100		5 female rats at each dose level	0.80 ml/kg		157
DEA	100		5 female rats at each dose level	0.71 ml/kg		158
DEA, produced from 1939–1949	20 in water		90–120 (unspecified) rats	1.41–2.83 g/kg		154

MEA, 99+ Percent	in gum arabic solution	0.64–1.4 g/kg	2.3 (unspecified) guinea pigs at each dose level		All survived 0.6 g/kg; None survived 7.0 g/kg.	148
MEA	in water		6 male rats at each dose level	2.74 g/kg		156
MEA			male rats	1.97 g/kg		159
MEA			female rats	1.72 g/kg		159
MEA, produced from 1939–1949	20 in water		90–120 (unspecified) rats	2.14–2.74 g/kg		154
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	100	8.72–17.4 g/kg (8.00–16.0 ml/kg) of undiluted preparation	10 rats at each of 4 dose levels	14.1 g/kg (12.9 ml/kg) for undiluted preparation	Animals receiving ≥ 13.8 g/kg of product had signs of melanuria, diarrhea, polyuria, and discoloration of stomach, intestinal mucosa, and gastrointestinal contents.	167

[a]Adjusted for concentration tested and material activity, when known.

TABLE 5. Subchronic and Chronic Toxicity.

Material tested	*Dose and vehicle*	*Length of study*	*No. and species of animals*	*Results*	*Ref.*
TEA	0–2.61 g/kg/day in food	90 days	10 rats at each dose level	No effects observed at ≤0.08 g/kg/day. Decreased weight gain at 1.27 g/kg/day. Heavy livers and kidneys produced when dose was ≥0.17 g/kg/day. Major pathology of small intestine, kidney, liver, or lung rare at ≤0.73 g/kg/day. Most major pathology observed was fatty degeneration of the liver. Some deaths at ≥0.73 g/kg/day.	154,156
TEA, 88.5% (DEA, 6%)	0–1.0 g/kg/day in food	91 days	20 rats of each sex at each of 4 dose levels	Increased weight gain in female rats receiving 0.25 g/kg/day. Increased feed consumption in female rats receiving 0.5 g/kg/day. No significant differences noted in organ to body weight ratios. No gross or histopathologic indications of a treatment related effect. No significant hematologic effects.	163
TEA, commercial or high purity grade	0.2–1.8 g/kg/day in food	60, 120 days	8 rats of each dose level for each time	Peripheral optic nerves showed scattered degeneration in the myelin of individual fibers at all doses for both 60 and 120 days. Liver changes were observed at ≥0.4 g/kg/day for 60 or 120 days. Kidney changes were observed at 0.2 to 0.225 g/kg/day for 120 days and at 0.4–0.45 g/kg/day for 60 or 120 days. Kidney damage was observed at ≥0.8 g/kg/day for 60 or 120 days. No kidney damage was severe enough to interfere with organ function.	149

TEA, commercial or high purity grade	0.2–1.8 g/kg/day in food	120 days and then, ~3 months without TEA	8 rats at each dose level	Kidney regeneration was observed after organ damage.	149
TEA, commercial or high purity grade	0.2–1.6 g/kg/day by pipette 5 days/week	60, 120 doses	8 guinea pigs at each dose level for each number of doses	Peripheral optic nerves showed scattered degeneration in the myelin of individual fibers at all doses for both 60 and 120 days. Liver and kidney damage was observed at ≥0.8 g/kg/day. No kidney or liver damage was severe enough to interfere with organ function.	149
TEA, commercial or high purity grade	0.2–1.6 g/kg/day by pipette 5 days/week	120 doses and then, ~3 months without TEA	8 guinea pigs at each dose level	Liver and kidney regeneration was observed after organ damage.	149
TEA, 99%	1.4 mg/l in drinking water; TEA in drinking water and 6.5% TEA solution applied to skin caudally for 1 h 5 days/week; TEA in drinking water and 13% TEA solution applied to skin caudally for 1 h	6 months	10 rats in each group	No toxic effect observed from 6.5 percent topical TEA and 1.4 mg/l TEA in drinking water. Changes observed after 1 month in the functions of the liver and central nervous system in animals receiving 13% topical TEA and 1.4 mg/l TEA in drinking water. Increase seen in number of segmented neutrophils after 3 months and increase seen in number of lymphocytes after 4 months.	165

TABLE 5. (Continued.)

Material tested	*Dose and vehicle*	*Length of study*	*No. and species of animals*	*Results*	*Ref.*
	5 days/week.				
DEA, neutralized salt (labeled)	1.0, 2.0, 3.0 m*M*/kg/day orally	11 days (5th–15th day after birth)	Neonatal rats	No changes observed in heart or brain. Moderate cloudy swelling seen in kidney proximal tubule. Periportal cloudy swelling and vacuolization seen in liver. Swollen hepatic mitochondria observed.	162
DEA, neutralized	4 mg/ml in drinking water	7 weeks	Male rats	Many deaths observed. There was liver and kidney damage and a pronounced normocytic anemia without bone marrow depletion or obvious increase in number or reticulocytes.	164
DEA	0–0.68 g/kg/day in food	90 days	10 rats at each dose level	No effects observed at ≤0.020 g/kg/day. Heavy livers and kidneys produced at ≥0.090 g/kg/day. Major pathology of small intestine, kidney, liver, or lung observed at ≥0.17 g/kg/day. Major pathology included cloudy swelling and degeneration of kidney tubules and liver fatty degeneration. Some animals died at 0.17 and 0.35 g/kg/day and all died at levels greater than that.	154,156
MEA	0–2.67 g/kg/day in food	90 days	10 rats at each dose level	No effects observed at ≤0.32 g/kg/day. Heavy livers and kidneys produced at ≥0.64 g/kg/day. Some deaths and major pathology at ≥1.28 g/kg/day.	154,156
Composite hair dyes and bases (MEA, 22 percent)	0–0.0975 g/kg/day of composite in food	2 years	12 beagle dogs at each of 3 dose levels.	No toxic effects observed.	166

abraded skin of three rabbits. The test was a 24 h closed patch test and the TEAs were applied to yield a rabbit exposure of 2 g/kg of actual TEA. The 88.1% TEA elicited mild erythema and no edema at 24 h and the skin returned to normal by Day 6. The 91.8% TEA produced moderate erythema and no edema at 24 h and the treated sites were normal by Day 10. The animals were observed for 14 days. All rabbits gained weight and none died.[168]

Subchronic and Chronic Toxicity

Kindsvatter[149] applied commercial and high purity grades of TEA each to the shaved skin of 10 guinea pigs. The test was a closed patch continuous exposure test in which 8 g/kg was applied daily for five days a week to guinea pigs. Deaths occurred at from 2 to 17 applications. No guinea pigs survived 17 applications. Adrenal, pulmonary, hepatic, and renal damage was observed.

Kostrodymova et al.[165] applied TEA caudally to rats for 1 h, five days per week, for six months. No toxic effects were observed with a 6.5% solution of TEA. A 13% solution of TEA did effect changes in the liver and central nervous system function. The toxic effect of TEA was not increased when rats were given 1.4 mg/l of TEA in their drinking water in addition to the dermal application of the 13% solution of TEA.

The percutaneous application of MEA to rats at a dose of 4 mg/kg/day resulted in nonspecific histological changes in the heart and lung. Hepatoxic manifestations included fatty degeneration of the liver parenchyma and subsequent focal necrosis.[169]

Groups of 16 rabbits had a cosmetic formulation containing 14% TEA stearate and 1% methycellulose, applied to one of two clipped sites on their backs that were alternated weekly, at doses of 1 and 3 ml/kg five times per week for 13 weeks. Mild to moderate skin irritation which cleared within 72 h was observed and this was followed by moderate to heavy skin scaling. No toxic effects were seen in any rabbits. The control rabbits received 3 mg/ml of 1% methylcellulose in water. The low dose group had significantly lower kidney weights and the high dose group gained less weight and had significantly greater kidney weights than the control rabbits.[153]

Burnett et al.[170] applied three hair dyes containing 0.10%–0.15% TEA, 1.500% TEA, or 2.0% DEA to the backs of groups of 12 rabbits for 13 weeks. The doses were 1 mg/kg twice weekly and two clipped sites were alternated. The skin of half the rabbits was abraded. The dye was placed on the skin, the rabbits were restrained for 1 h, then shampooed, rinsed and dried. Control rabbits were treated identically except that no dye was applied to their skin. No systemic toxicity was observed and there was no histomorphologic evidence of toxicity in the treated rabbits after 13 weeks.

Primary Skin Irritation

Rabbits were used in primary skin irritation studies for TEA,[171,172] DEA,[173,174] and MEA.[175-177] Data from these experiments are presented in Table 6. These data suggest that MEA is irritating to rabbit skin, and that TEA and DEA are much less irritating to rabbit skin than MEA.

TABLE 6. Primary Skin Irritation.

Material tested	*Concentration (%)*	*Method*	*Number of rabbits*	*Results*	*Ref.*
TEA, 99+ percent	100	10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the intact shaved abdomen.	Unspecified	Slight hyperemia after 7 applications. "Slight to moderately irritating, prolonged or repeated exposure may be irritating."	171
TEA, 99+ percent	100	3 24-hour semioccluded patch applications to the abraded shaved abdomen.	Unspecified	Moderate hyperemia, edema, and necrosis. "Slight to moderately irritating, prolonged or repeated exposure may be irritating."	171
TEA	100	1 24-hour occluded patch application to clipped back. Erythema (0 to 4), edema (0 to 4), and necrosis (0 to 15) evaluations are made at 24 and 72 hours and are added and divided by 2 to yield a primary irritation score (scale = 0 to 24). Total possible score for 22 laboratories was 400.	8 male/each laboratory	Primary irritation scores ranged from 0 to 5.5 for 22 laboratories. Total score for all 22 laboratories was 27.3.	172

DEA, 99+ percent	100	10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the shaved abdomen.	Unspecified	Some denaturation on ear after 10 doses and on belly after 3 doses. "Moderately irritating."	173
DEA, 99+ percent	10 in water		Unspecified	No irritation observed.	173
DEA, 99+ percent	50	Semioccluded patch applications to intact and abraded shaved skin. Erythema and edema reactions are evaluated at 24 and 72 h and values are averaged to yield a primary irritation score (scale = 0 to 8).	6	Essentially no irritation of the skin. Primary irritation score = 0.17. "Not a primary irritant."	174
DEA, 99+ percent	30		6	Essentially no irritation of the skin. Primary irritation score = 0.29. "Noncorrosive to skin."	174
MEA, 99+ percent	85, 100	Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 h.	1	Visible destructive alteration of the tissue at the site of application. "Corrosive."	176
MEA, 99+ percent	30	Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 and at 24 h.	6	Visible destructive alteration of the tissue at the site of application at 4 h. Necrosis observed at 24 h. "Corrosive to skin."	177
MEA, 99+ percent	1–100	10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the shaved abdomen.	Unspecified	10 percent or higher was corrosive to the skin, >1% was extremely irritating to the skin and 1% was irritating to the skin. "Extremely corrosive to skin."	175

Phototoxicity

The phototoxicity of a suntan lotion containing 1% TEA was evaluated by applying the lotion to the stripped ears of six guinea pigs. A known photosensitizer was used as a positive control in four other guinea pigs. Each animal was then exposed to ultraviolet (UVA) from two GE F8T5-BL lamps at a distance of 4–6 cm for 2 h. No erythema or edema was observed in any of the guinea pigs treated with suntan lotion. Results of the positive controls are unavailable.[178]

Skin Sensitization

Pairs of guinea pigs were treated dermally with 5%–100% TEA in water for 6 h with occlusion, and the treated sites were scored for erythema at 24 and 48 h. Since use of undiluted TEA resulted in only one erythemic reaction at 24 h, 100% TEA was used in both induction and challenge procedures in the subsequent sensitization test. Twenty guinea pigs received dermal applications of undiluted TEA once per week for three weeks. A challenge patch was applied after 14 days and again seven days later. One erythemic reaction occured in each of three animals during the induction procedure, in two other animals during the first challenge, and in one other animal during the second challenge. All the guinea pigs remained healthy and made normal weight gains during the test. There was no evidence of any skin sensitizing activity of undiluted TEA for guinea pigs.[179]

TEA from four different suppliers was evaluated in guinea pig skin sensitization tests.[180-183] The tests were conducted with 10 control and 20 treated guinea pigs. The induction patches were applied once a week for up to six hours for three weeks. Two weeks later challenge patches were applied to both control and treated guinea pigs. One test was conducted with undiluted TEA at induction and 90% TEA at challenge[181] and all the other tests were conducted with 50% TEA at induction and 90% TEA at challenge.[180,182,183] None of the animals showed clinical symptoms during or after the treatment period and no guinea pigs showed signs of primary irritation of the skin. Challenge reactions were measured with a reflectometer and average readings between control and experimental animals were compared. TEA was not a guinea pig skin sensitizer in these studies.

Patches containing a 25% active TEA solution and 10% and 5% TEA in aqueous solution were applied to the backs of four clipped guinea pigs. No irritation was observed in this preliminary study. Induction patches containing the 25% TEA solution were applied to the backs of 20 clipped guinea pigs for 6 h once per week for three weeks. One week later, a challenge patch containing 25% TEA was applied for 6 h to the clipped backs of the 20 treated and 10 control guinea pigs. Challenge reactions were read at 24 h and at 48 h. No irritation was observed. No positive primary irritation or sensitization responses were observed under the test conditions with the 25 percent active TEA solution.[184]

Eye Irritation

The eye irritation potential of TEA, DEA, MEA, or cosmetic products containing the ethanolamines has been studied in rabbits[171,172,174,177,185-187] and in rhesus monkeys.[188] Data from these experiments are presented in Table 7. In high concentrations and with long contact time, TEA, and DEA may be irritating to the rabbit eye and MEA is irritating to the rabbit eye.

TABLE 7. Eye Irritation.

Material tested	*Concentration (%)*	*Method*	*No. and species of animals*	*Results*	*Ref.*
TEA, 99+ percent	100	0.1 ml of test material instilled into conjunctival sac of both rabbit eyes. Left eye unwashed. After 30 sec. exposure, right eye washed for 2 min with tap water.	Rabbits	Moderate pain and swelling in unwashed eye. Slight conjunctival irritation which subsided in 48 h. No irritation observed in the washed eye. "Slight to moderately irritating, no corneal damage likely."	171
TEA, 99+ percent	10 in water		Rabbits	Essentially no irritation observed in washed or unwashed eyes.	171
TEA	100	0.005, 0.02 ml of test material applied to corneal center while eyelids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18–24 h.	Rabbits	0.005 ml yielded a score of ≤ 5.0, 0.02 ml yielded a score of >5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75% of the surface of the cornea.	185
TEA, 98 percent	100	0.01, 0.03, 0.10 ml of test material applied directly to cornea and eyelids released immediately. Eyes scored at days 1, 3, 7, 14 and 21 by the method of Draize, et al.[193] (scale = 0 to 110).	6 rabbits at each dose level	0.01 ml gave a 0 score on all days eyes were examined. 0.03 ml gave a score of 1 on Day 1 and 0 thereafter. 0.10 ml yielded a score of 4 on Day 1, 2 on Days 3 and 7, and 0 on Days 14 and 21. The median number of days for eyes to return to normal was 1 for 0.01 and 0.03 ml and 3 for 0.10 ml.	187
TEA	100	0.1 ml of test material was placed inside the lower eyelid. Lids were held together for a few seconds. Eyes were examined at 1, 24, and 72 hours and 7 days after application. Scoring was according to the scale of Draize et al.[193] (scale = 0 to 110).	6 male rabbits	Eye irritation scores ranged from 0–10 for 24 laboratories.	172

TABLE 7. (Continued.)

Material tested	*Concentration (%)*	*Method*	*No. and species of animals*	*Results*	*Ref.*
DEA, 99+ percent	30 in water	~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.	6 rabbits	The material was essentially nonirritating to the eye. "Noncorrosive to eye".	174
DEA, 99+ percent	50 in water		6 rabbits	Moderate to severe conjunctival irritation and corneal injury with slight reddening of the iris was observed. The eye essentially healed in 7 days. "Severe irritant".	174
DEA	100	0.005, 0.02 ml of test material applied to corneal center while eyelids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18 to 24 hours.	Rabbits	0.005 ml yielded a score of ≤5.0, 0.02 yielded a score of >5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the cornea.	185
MEA, 99+ percent	30 in water	~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.	6 rabbits	Slight discomfort, slight conjunctival irritation, and slight corneal clouding which healed in 48 hours was observed. "Moderately irritating."	177
MEA	1,5,100	0.005 ml of undiluted or diluted test material applied to corneal center while lids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18 to 24 h.	Rabbits	1% solution yielded a score ≤5.0; 5 and 100% solutions yielded scores >5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the cornea.	185

Shampoo (TEA, 12.6%)	100 of the shampoo	0.1 ml of the shampoo was instilled into the conjunctival sac of the left eye. Held closed for 1 sec. After 15 sec, rinsed with 50 ml tap water. Eyes were examined at 24, 48, and 72 hours and at 4 and 7 days post-instillation.	6 rhesus monkeys	Slit lamp examinations at 24 h revealed edematous cornea and slight sloughing of the corneal epithelium in the treated eyes of 2 animals. At 72 h, a slight positive fluorescein staining was observed in the eye of one monkey and at Day 7, a faint, diffuse positive staining was noted in one monkey.	188
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	100 of the hair preparation	0.1 ml of the hair preparation was placed into the conjunctival sac of one eye. The lids were held together for 1 sec. After 30 sec, the eyes of 3 animals were washed with 20 ml of deionized water. The eyes were examined at 24, 48, and 72 hours and at 4 and 7 days and were scored according to the method of Draize et al.[193] (scale = 0 to 110).	9 rabbits	Maximum average irritation scores for both washed and unwashed eyes was 0.7.	194

Vaginal Mucosa Irritation

A spermicidal preparation containing 1.92% TEA was tested for vaginal mucosa irritation using six female rats in the same stage of estrus. A 0.5 ml volume of the ointment was placed inside the vaginas of the rats at a depth of 0.6–0.8 cm daily for three days. On the fourth day, the vaginas were exposed and examined for erythema, exudate, and edema. The researchers classified the spermicidal preparation as a nonirritant to rat vaginal mucosa.[189]

Inhalation Studies

Respiratory difficulties and some deaths in male rats resulted from the short-term inhalation of 200 ppm DEA vapor or 1400 ppm DEA aerosols. Inhalation of 25 ppm DEA for 216 continuous hours resulted in increased liver and kidney weights. A workday schedule inhalation of 6 ppm DEA for 13 weeks resulted in growth rate depression, increased lung and kidney weights, and some deaths in male rats.[164]

Weeks et al.[190] reported that the dominant effects of continuous exposure of dogs, guinea pigs, and rats to 5–6 ppm MEA vapor were skin irritation and lethargy. The inhalation of MEA vapor at concentrations of 12–26 ppm for 90 days did not result in any mortality in dogs or rodents. Some deaths did occur after 25 days in dogs exposed to 102 ppm MEA vapor, and after 24–28 days in rodents exposed to 66–75 ppm MEA vapor. Exposure to 66–102 ppm MEA vapor caused behavioral changes and produced pulmonary and hepatic inflammation, hepatic and renal damage, and hematologic changes in dogs and rodents.

Parenteral Studies

The mouse acute intraperitoneal LD50s of TEA and MEA have been reported to be 1.450 and 1.050 g/kg, respectively.[191] Blum et al.[192] determined that the mouse acute intraperitoneal LD50 of DEA was 2.3 g/kg. This level of DEA produced hepatic steatosis, cellular degeneration and swollen hepatic mitochondria in the 24 h following the injection. After 24 h, survivors were apparently normal. The livers of mice that survived over 48 h appeared to have returned to normal. Other information can be found in the literature on the intraperitoneal administration of the ethanolamines to mice and rats.[164,195,196]

SPECIAL STUDIES

Mutagenesis

The Ames assay has been used to investigate the mutagenic potential of the ethanolamines.[197] TEA, 99+ percent, with or without metabolic activation, was not mutagenic at concentrations of 0.001 to 100 mg/plate to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538.[198] The National Toxicology Program (NTP) tested 0–3.333 mg/plate of TEA and DEA in their preincubated *Salmonella* mutagenicity assay in strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation and reported both

chemicals to be negative.[199] Hedenstedt[200] tested DEA and MEA with and without metabolic activation by liver preparations from rats induced with a polychlorinated biphenyl mixture in *S. typhimurium* strains TA100 and TA1535. There was no observed increase in the number of mutants per plate with either DEA or MEA.

The mutagenicity of TEA, sodium nitrite, and a mixture of the two, with and without metabolic activation by liver S-9, was tested with *Bacillus subtilis*. Only the mixture of TEA and sodium nitrite was mutagenic to the bacteria. N-nitrosodiethanolamine (NDELA) was found in this mixture, but NDELA does not induce mutations in *B. subtilis* without metabolic activation. Some other reaction mixture product must be mutagenic and this product loses its mutagenic activity in the presence of liver enzymes.[201]

Fresh primary rat hepatocyte cultures were treated simultaneously with TEA and ^{3}H-thymidine in an unscheduled DNA synthesis test. DNA repair was quantitated by microautoradiographic evaluation of the incorporation of ^{3}H-thymidine into nuclear DNA. The concentrations of TEA tested ranged from 10^{-8}–10^{-1} *M* and three cultures were tested per concentration. The authors reported that TEA did not appear to cause DNA-damage inducible repair.[202]

Carcinogenesis

Kostrodymova et al.[165] used a total of 560 male mice, strain CBA × $C_{57}Bl_6$, in a series of three experiments to study the possible carcinogenic and cocarcinogenic effects of pure TEA, 99+ percent, and industrial TEA, 80+ percent, and the combined effect of TEA and syntanol DC-10, applied cutaneously. The experiments ran for 14–18 months, and they found no evidence of TEA carcinogenicity or cocarcinogenicity.

Hoshino and Tanooka[201] fed a diet containg 0.01%, 0.03%, or 0.3% TEA to groups of 40 ICR-JCL male and 40 ICR-JCL female mice throughout the life-span of the animals. The malignant tumor incidence in females was 2.8%, 27%, and 36%, and in males was 2.9%, 9.1%, and 3.6% for the mice fed diets containing 0.0%, 0.03%, and 0.3% TEA, respectively. Treated females showed a much higher incidence of thymic and nonthymic tumors in lymphoid tissues than treated males. The mice fed TEA in their diet survived as long as the control mice.

DEA is currently being tested in an NTP carcinogenesis bioassay program. It is being administered in drinking water to rats and mice.[199]

Teratogenesis and Reproduction Studies

Hair dyes containing 0.10%–0.15% TEA, 1.5% TEA, or 2.0% DEA were topically applied to the shaved skin of groups of 20 pregnant rats on Days 1, 4, 7, 10, 13, 16, and 19 of gestation. On Day 20, the rats were sacrificed and comparisons were made with control rats. No significant soft tissue or skeletal changes were noted in the fetuses. The mean number of corpora lutea, implantation sites, live fetuses, resorptions per pregnancy, and number of litters with resorptions were not significantly different in the dye-treated and control rats.[170]

A composite hair dye and base containing 22% MEA was given to 60 female rats at concentrations of 0 to 7800 ppm in the diet from Day 6 to 15 of gestation.

The rats were sacrificed at Day 19 and there was no evidence of any adverse effects on the rats or their pups. No differences were observed in the average number of implantation sites, live pups, early or late resorptions per litter, or females with one or more resorption sites. Thirty male rats were fed diets containing 0–7800 ppm composite for eight weeks prior to mating and during mating to 60 female rats on a basal diet. Sixty female rats were fed 0–7800 composite-containing diets eight weeks prior to mating through Day 21 of lactation. They were mated with 30 male rats on the basal diet. In both experimental designs, there were no dose-related significant differences in male and female fertility, length of gestation, number of females with resorption sites, live pups per litter, pup body weights, and pup survival. The composite hair dye and base was also administered at a dose of 0–19.5 mg/kg/day by gavage to 48 artificially inseminated female rabbits from Day 6 to 18 of gestation. The rabbits were sacrificed at Day 30. There was no evidence of any teratologic effects. Fetal survival was not adversely affected and no grossly abnormal fetuses or soft tissue defects were seen.[166]

CLINICAL ASSESSMENT OF SAFETY

Dermal Studies

Patch tests can be used to measure skin irritation and sensitization by a chemical substance in human subjects. However, caution should be exercised in the interpretation of patch tests. Patches will elicit positive reactions in cases where the test material is a primary irritant or when the human subject has been sensitized by previous contact with the chemical, either in a past patch or in the course of his daily life.[203] In addition, patch tests may elicit positive responses because the threshold irritating concentration of a chemical has decreased after repeated exposure of the skin to irritants; this would be a fatigue response. The population from which the subjects are drawn is also important. Certain skin types may be predisposed to react more intensely to chemical insult.[204]

Triethanolamine is the only ethanolamine for which human skin irritation and sensitization data are presented. The results of six patch test experiments with triethanolamine and details of those experiments are presented in Table 8. TEA produced minimal irritation in 1143 "normal" subjects and was more irritating to subjects chosen because they were "hyper reactors" to skin irritants or because they were suffering from eczema.

The cosmetic industry has conducted studies on the skin irritation, sensitization, and photosensitization of a variety of products containing the ethanolamines. Data from these unpublished experiments are presented in Table 9. There was some evidence of irritation by some products.

Inhalation Studies

MEA inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma[205] and clinical symptoms of acute liver damage and chronic hepatitis.[169]

TABLE 8. Skin Irritation and Sensitization by Triethanolamine.

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
TEA, 88.6% (DEA, 6%)	0.5 ml of 1% active TEA	24 h semiocclusive induction patches were applied on the dorsal surface of the upper arm 3 times per week for 3 weeks. 14 days later, challenge patches were applied to the same site and the other arm and these were graded at 48 and 96 h on a scale of 0–6.	64	No irritation (0) in 451 inductions. Mild irritation (1) in 420 and moderate irritation (2) in 3 inductions (includes residual reactions). 188 and 68 scores of 0 and 1 at challenge, respectively. "No sensitization."[a]	214
TEA	5%	Patch test, 1979–1980	479	9 (2%) positive reactions for contact dermatitis observed. (Sensitizing)	215
TEA	2% in water	Patch tests, 1974–1976, Marseille, France	500	23 (4.6%) positive reactions for contact dermatitis observed. (Sensitizing)	216
TEA	5% in petrolatum	Patch tests	100	2 positive reactions for allergic contact dermatitis were observed. (Sensitizing)	217
TEA	100%; 10 and 5% in ethanol	Test material applied in an aluminum chamber containing a cotton disk once daily for 3 days, after light scarification of the forearm site with a needle. Readings on a scale of 0–4 at 72 h 30 min after chamber removal.	5–10 (unspecified) caucasian "hyper reactors" (gave brisk inflammatory reaction to 24 h forearm exposure of 5% aqueous sodium lauryl sulfate in an aluminum chamber.)	100% TEA was required to produce an irritant reaction on nonscarified skin. 10% TEA was a marked irritant (2.5–4.0) and pustules were observed and 5% TEA was a slight irritant (0.5–1.4) on scarified skin.	218
TEA	5%, 1% in eucerin with water	24 h patch tests. Readings after 24 and 48 h.	22 subjects suffering from different types of eczemas	4 and 3 positive reactions to 5% and 1% TEA, respectively. (Irritating)	219

[a]Conclusions of the researchers are in quotations. Interpretations of the Expert Panel are in parentheses.

TABLE 9. Skin Irritation, Sensitization, Phototoxicity, and Photosensitization by Products Containing the Ethanolamines.

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Shaving preparation (TEA, 4.2%)	100%	2 24-hour patches applied 10 to 14 days apart on the same site.[203] Simultaneous closed patch on back and open patch on arm. Scoring scale was + to + + +.[220] Additionally, there was UV exposure of the second patch.	508	46 weak (nonvesicular) (+) reactions to the first closed patch, 42 + and 7 strong (edematous or vesicular) (+ +) reactions to the second closed patch. 67 + reactions after UV (Hanovia Tanette Mark 1 lamp, 360 nm at 12 in for 1 min) exposure of the second patch. "Nonirritating." (Irritating. Either mildly phototoxic or UV enhancement of an irritation response).[a]	222
Shaving preparation (TEA, 4.2%)	100%	10 24-hour induction patches with 24-hour recuperative periods in between. After 2 to 3 weeks rest, a 48-hour challenge patch (modification of Ref. 221). Simultaneous closed patch on back and open patch on arm. Scoring scale was + to + + +.[220] Additionally, there was UV exposure of induction patches 1,4,7, and 10, and the challenge patch.	260	Between 31 and 64 + reactions were observed to closed induction patches 1 through 10. 1,3,3,4, and 4 strong + + reactions to closed induction 60 + and 2 + + reactions to the closed challenge patch. Following UV (Hanovia Tanette Mark 1 lamp, 360 nm at 12 inches for 1 min.) exposure, 7,6,1,4, and 8 + reactions were observed at induction patches 1,4,7, and 10, and the challenge patch, respectively. "Nonsensitizing and nonphotosensitizing." (Irritating)	222
Shaving preparation (TEA, 4.2%)	Normal use	Used on the face for 4 weeks and scored each week.	52 male	No reactions were observed. "Nonirritating."	223
Sun cream (TEA, 3.75%)	100%, ~0.1 ml	24-hour occlusive induction patches applied to the upper back 3 times a week for 3 weeks. After 2 weeks rest, a 24-hour occlusive challenge patch was applied to a previously unpatched site. Reactions were scored 24 and 48 hours after patch removal on a scale of 0 to 4.	48	1 barely perceptible (±) reaction; minimal faint (light pink) uniform or spotty erythema at induction patch 2. "No potential for inducing allergic sensitization."	186

Shaving cream (TEA, 3.3%)	100%	12-hour occlusive induction patches applied to the medial surface of the upper arm 4 times a week for 2 weeks and scored at patch removal on a scale of 0 to 4. After 2 weeks rest, a 24-hour occlusive challenge patch was applied. Reactions were scored at 24, 48, and 72 hours.	54	5, 16, and 14 very slight erythema (±), slight erythema (1), and well defined erythema (2) reactions, respectively, were observed to the 8 induction patches. Number of positive reactions increased with each induction. No reactions to the challenge patch. (Irritating)	224
Shaving cream (TEA, 3.3%)	100%		57	104, 36, 5, and 2 slight erythema (1), moderate erythema (2), severe erythema (3), and edema with or without erythema (4) reactions, respectively, were observed to the 8 induction patches. Number of positive reactions generally increased with each induction. 6 1+ and 1 2+ reactions were observed on challenge at 24 hours. At 48 hours, 4 1+ and 1 2+ reactions were observed, and at 72 hours, 2 1+ reactions were observed. (Irritating)	225
Shaving cream (TEA, 2.6%)	100%		51	27 slight erythema (1) and 1 moderate erythema (2) reactions were observed to the 8 induction patches. 1 1+ reaction was observed on challenge at 24 hours. (Mildly Irritating)	226
Mascara formulation (TEA, 2.1%)	100%, 0.2 ml	23-hour patches applied to the back every day for 21 days. Reactions were scored daily on a scale of 0 to 4.	15	7, 42, 2, and 3 questionable erythema (±), erythema (1), erythema and papules (2), and erythema, papules, vesicles, and possibly edema (3) reactions, respectively, to the 21 patches. (Irritating)	227
Mascara formulation (TEA, 2.1%)	100%, 0.2 ml		15	5, 54, and 6 ±, 1, and 2 reactions, respectively, to the 21 patches. (Irritating)	227
Mascara formulation (TEA, 2.1%)	100%	1 48-hour occluded patch was applied to the arm or back; 24-hour aqueous sodium lauryl sulfate occluded patch on arm or back, then 5 alternate day 48-hour occluded patches of the test material. After a 10-day rest, 5-10 percent sodium lauryl sulfate was applied to another test site for 1 hour and followed by a 48-hour occluded patch of the test material. Reactions were observed at patch removal and 24 hours later.	25	No reactions observed to challenge. "No sensitization."	228
Mascara formulation (TEA, 2.1%)	100%		25	No reactions observed to challenge. "No sensitization."	229

TABLE 9. (Continued.)

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Suntan lotion (TEA, 1.0%)	100%	48-hour occlusive induction patches were applied 3 times a week for a total of 10 times. Patches 1,5,6, and 7 were on the left shoulder, the others on the right. The sites were scored 24 to 48 hours after patch removal. After 8 days rest, a challenge patch was applied to a virgin back site and scored 24 hours after patch removal. The skin sites where patches 1,4,7, and 10 and the challenge patch had been were exposed to UV light (Hanovia Tanette Mark I Lamp) at a distance of 12 inches for 1 min and scored 48 hours later.	26 female	No reactions observed. "Not a photo-toxicant."	230
Mascara (TEA, 20.04%)	100%, ~0.1 ml/cm²	2 times/week for 3 weeks, duplicate 24-hour occlusive induction patches applied to the back. Then, one site and a control site (no test product) irradiated with 3 times the individual's "minimal erythema dose" (MED) using a Xenon arc solar simulator (290–400 nm). 48 hours later, both sites were read. There was a 10-day rest and then, duplicate challenge patches were applied at fresh sites. 24 hours later one site and a control site exposed to 3 min. of irradiation from the solar simulator (Schott W345 filter). Sites graded at 15, 24, 48, and 72 hours after light exposure.	26 female	2 slight reactions upon challenge to test product alone. One doubtful and one erythema reaction before irradiation. "No sensitization." (Irritation)	231
Mascara (TEA, 2.8%)	100%, ~0.1 ml/cm²		23	No reactions observed. "Not phototoxic or photoallergenic."	232

Skin lotion (TEA, 0.83%)	100%, ~0.2 ml	Sites on both forearms were tape-stripped several times. Duplicate 24-hour occlusive patches applied to each forearm. Then, one site irradiated with UV light for 15 min. at a distance of ~10 cm (~4,400 μW/cm^2 UVA). Sites scored after patch removal, after irradiation, and 24 and 48 hours after irradiation. Examined for tanning after 1 week. Scored on a scale of 0–4.	10	One subject had minimal erythema (±) at both sites at all readings except for the irradiated site at the 24-hour before and after irradiation readings. Another subject had minimal erythema (±) at the irradiated site at the 72-hour reading. No tanning was observed. "Not phototoxic." (Irritating)	233
Skin lotion (TEA, 0.83%)	100%, ~0.2 ml		10	One subject had minimal erythema (±) at both sites at all readings. Another subject had minimal erythema (±) at the irradiated site at the 48- and 72-hour readings. No tanning was observed. "Not phototoxic." (Irritating)	234
Skin lotion (TEA, 0.83%)	100%, ~0.2 ml	24-hour occlusive induction patches were applied 3 times a week to both forearms for a total of 10 times. At the end of 24 hours the sites were scored and 1 site was irradiated with nonerythrogenic UV radiation for 15 min. at a distance of 10 cm (~4,400 μW/cm^2 UVA) and then scored again. After 10 to 14 days rest, challenge patches were applied to virgin adjacent sites. 24 hours later, the sites were scored, 1 site was irradiated and scored. The challenge sites were also read 48 and 72 hours later. Scored on a scale of 0–4.	30	Among 300 induction readings for the nonirradiated sites, there were 13 minimal erythema (±) and 2 erythema (1) readings. There was 1 minimal erythema (±) challenge reading at 48 hours. Among 600 induction readings for the irradiated sites, there were 8 and 9 minimal erythema (±) readings before and after irradiation, respectively, and 4 erythema (1) readings after irradiation. There was 1 minimal erythema (±) reading after irradiation at 24 hours. "Does not induce photoallergy or contact allergy." (Irritating)	235
Skin lotion (TEA, 0.83%)	100%, ~0.2 ml		30	Among 300 induction readings for the nonirradiated sites, there were 15 minimal erythema (±) and 3 erythema (1) readings. There were 2 minimal erythema (±) challenge readings, one at 24 and one at 48 hours. Among 600 inductions for the irradiated sites, there were 7 and 10 minimal erythema (±) readings before and after irradiation, respectively, and 5 erythema (1) readings after irradiation. There was one erythema reading (1) after irradiation at 24 hours. "Does not induce photoallergy or contact allergy." (Irritating)	236

TABLE 9. (Continued.)

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Shaving cream (TEA, 2.1%)	100%	10 48- to 72-hour occlusive induction patch applications to the same site, readings before the application of the succeeding patch, followed by a rest period of about 3 weeks and then a final challenge patch on a fresh site. Modified Draize test.[193]	104	Among 1040 induction readings, there were 172 ± readings, 11 (1) readings and one (3) reading. There were 16 (?) challenge readings. (Irritating)	237
Shaving cream (TEA, 2.4%)	100%	9 8-hour "semi-open" induction applications, scored 48 to 72 hours later just before application of the next patch, a 2-week rest followed by challenge patches scored at 48 and 96 hours after application. Challenge patches were applied to the original and to virgin sites. Reactions were scored on a scale of 0–6.	76	Among 684 induction readings there were 231, 83, and 1 reaction of (1) (slight erythema), (2) (marked erythema) and (3) (erythema and papules), respectively. There were 28 (1), 4 (2), and 3 (E) (erythema and possibly also edema) reactions upon challenge at the original site and 23 (1) reactions at the virgin site among 304 challenge readings. "Moderately irritating following initial and repeated application. Very little cumulative irritation. No evidence of sensitization." (Sensitizing)	238
Shaving cream (TEA, 2.1%)	100%		76	Among 684 induction readings there were 222 and 101 reactions of (1) and (2), respectively. Among 304 challenge readings there were 33, 13, and 2 reactions of (1), (2), and (E), respectively, at the original site and 20, 2, and 1 reactions of (1), (2) and (E), respectively, at the virgin site. "Moderately irritating following initial and repeated application. Very little cumulative irritation. No evidence of sensitization." (Sensitizing)	238

Shaving cream (TEA, 2.1%)	100% 0.5 ml	9 24-hour "semi-open" patch induction applications scored 48 to 72 hours later just before application of the next patch a 2-week rest followed by challenge patches scored at 48 and 96 hours after application. Challenge patches were applied to original and virgin sites. Reactions were scored on a scale of 0–6.	63	Among 567 induction readings, there were 106, 4, 2, and 4 reactions of 1, 2, 3 and 4 (erythema, edema, and papules), respectively. Among 252 challenge readings there were 28, 6, 1, 9, and 1 reactions of 1, 2, 3, 4, and 6 (strong reaction spreading beyond test site), respectively, at the original site and 9, 4, and 2 reactions of 1, 2, and 3, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hour. "Proably skin fatigue."	239
Shaving cream (TEA, 2.1%)	100%, 0.5 ml		63	Among 567 induction readings, there were 144, 20, 8, and 12 reactions of 1, 2, 3, and 4, respectively. Among 252 challenge readings, there were 42, 8, 5, 19, and 1 reactions of 1, 2, 3, 4, and 6, respectively, at the original site and 19, 8, and 2 reactions of 1, 2, and 4, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hours. "Probably skin fatigue."	239

TABLE 9. (Continued.)

Material tested	Concentration and dose	Method	Number of subjects	Results	Ref.
Shaving cream (TEA, 2.1%)	100%, 0.5 ml		63	Among 567 induction readings, there were 131, 23, 2, and 14 reactions of 1, 2, 3, and 4, respectively. Among 252 challenge readings, there were 34, 16, 6, 18, and 1 reactions of 1, 2, 3, 4, and 6 respectively, and 19, 5, 1, and 1 reactions of 1, 2, 3, and 4, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hours. "Probably skin fatigue."	239
Shaving cream (TEA, 2.1%)	100%	Every other day for a total of 20 days (10 open-patch applications) a 1 in. square of gauze was dipped in sample and applied to the subjects' arm (the same site was used each time). 24 hours after application the sites were scored. A 10-day rest was followed by a challenge open patch which was observed 24 and 48 hours later. Reactions were scored on a scale of +1 to +4.	60	Among 600 induction and 120 challenge readings, there were no reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 2.6%)	100%		60	Among 600 induction readings there were 5 (1+) (mild erythema) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 2.1%)	100%		60	Among 600 induction readings there were 5 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 2.1%)	100%		60	Among 600 induction readings, there were 3 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 1.9%)	100%		60	Among 600 induction readings, there was 1 (1+) reaction. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240

Shaving cream (TEA, 2.3%)	100%		60	Among 600 induction readings there were 2 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Sunscreen product (TEA, 0.45%)	100%, ~0.2 g	10 24-hour occlusive patch applications with 24- to 48-hour rest periods in between. Sites scored just prior to next patch application. An 11- to 15-day rest followed by a 24-hour challenge patch on a virgin site. Sites scored at 24 and 48 hours after application. Scored on a scale of 0–4.	52	Among 520 induction readings, there were 7 ± (minimal erythema) scores. Among 104 challenge readings, there were 2 ± scores. "No irritation or sensitization."	241
Sunscreen product (TEA, 0.45%)	100%, ~0.2 g	Forearms were tape-stripped to remove cornified epithelium. 24-hour occlusive patch applications to both arms, patches removed, sites scored, and one site subjected to 15 minutes of UV light (~4,400 $\mu W/cm^2$ UVA) at a distance of 10 cm and rescored. Additional readings were made 48 and 96 hours after application. Scored on a scale of 0–4.	10	There was 1 ± reaction at 24 hours and 1 ± reaction at another site after irradiation at 24 hours. "No phototoxic response."	241
Sunscreen product (TEA, 0.45%)	100%, ~0.2 g	10 24-hour occlusive patch applications to both arms with 24- to 48-hour rest periods in between. Sites scored at patch removal and then irradiated for 15 min at a distance of 10 cm (~4,400 $\mu W/cm^2$ UVA) and re-scored. An 11- to 15-day rest period, 24-hour challenges to virgin sites, patches removed and sites scored, irradiated, scored again and scored 24 and 48 hours later. Scored on a scale of 0–4.	26	Among 260 induction readings of the non-irradiated site, there were 5 ± scores. Among 78 challenge readings, there were 3 ± scores. Among 520 induction readings of the irradiated site there were 5 ± scores before and 5 ± scores after irradiation. Among 104 challenge readings, there were 2 ± scores. "No photoallergic response."	241
Shaving cream (TEA, 2.4%)	100%, ~0.1 ml/cm^2	10 48- to 72-hour nonocclusive induction patch applications. Sites scored at patch removal. 10th patch also scored 24 hours later, 11-day rest period, followed by a 48-hour challenge patch to a virgin site. Challenge site scored at patch removal and 24 hours later.	100	Among 1100 induction readings, there were 2 (doubtful reaction, very mild erythema, barely exceeding that of the untreated skin) reactions. There were no challenge reactions. "No irritation or sensitization."	242
Shaving cream (TEA, 2.1%)	100%, ~0.1 ml/cm^2		100	Among 1100 induction and 200 challenge readings, there were no reactions. "No irritation or sensitization."	242

TABLE 9. (Continued.)

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Dyeless Base Formulation (DEA, 2%), non-commercial product	0.3 ml, 10% in distilled water	24-hour semioccclusive patches applied to upper arm 3 times a week for 3 weeks. Scored 24 to 48 hours after patch removal. Challenge patches on the same site and a virgin site after 15 to 17 days. Challenges scored at 24 and 72 hours after patch removal on a scale of 0 to 5.	165	No reactions observed. "No contact sensitization."	243
Shave gel (DEA, 2.7%)	100%, ~0.1 ml/cm^2	10 48- to 72-hour nonocclusive induction patch applications. Sites scored at patch removal. 10th patch also scored 24 hours later, 11-day rest period, followed by a 48-hour challenge patch to a virgin site. Challenge site scored at patch removal and 24 hours later.	100	Among 1100 induction readings, there were 2 (doubtful reaction, very mild erythema, barely exceeding that of the untreated skin) reactions. There were no challenge reactions. "No irritation or sensitization."	242
Dyeless Base Formulation (MEA, 11.47%), non-commercial product	0.3 ml, 5% in 25% alcohol	24-hour semiocclusive patches applied to upper arm 3 times a week for 3 weeks. Scored 24 to 48 hours after patch removal. Challenge patches on the same site and a virgin site after 15 to 17 days. Challenges scored at 24 and 72 hours after patch removal on a scale of 0 to 5.	165	19, 1, 1, and 1 scores of mild erythema (1), definite papular response (2), definite edema (3), and definite edema and papules (4), respectively, during induction. No reactions observed at challenge. "No contact sensitization." (Irritating)	243
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	~0.2 ml, 100%	23-hour patches applied to the back every day for 21 days. Reactions were scored daily on a scale of 0 to 7.	12 female	4,3, and 225 scores of minimal erythema, barely perceptible (1), definite erythema, readily visible (2), erythema and papules (3). "Experimental cumulative irritant."	244
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	0.3 ml, 100%	48-hour occluded patch on the forearm; 5 48-hour occluded induction patches, a 10-day rest, then a 48-hour occluded challenge patch. Reactions scored at patch removal and 24 hours later on a scale of 0 to 3.	25	Test material was irritating during a pre-test. No reactions observed during the induction and challenge procedures. "No contact sensitization."	245

[a]Conclusions of the researchers are in quotations. Interpretations of the Expert Panel are in parentheses.

An eight-year-old female developed a nasal allergic reaction to a detergent containing TEA. The prick test was positive for 10^{-7}–10^{-4} *M* TEA and not for any of the other ingredients in the product. Sneezing was relieved after removal of the detergent from the clothes by extensive washing and recurred upon re-exposure.[206]

Potential hazards from inhalation of TEA and DEA are probably minimized by their low vapor pressures.[10]

Occupational Exposure

Information on vascular, neurologic, and hepatic disorders and respiratory and skin allergies of people who come in contact with the ethanolamines in their work environment can be found in the literature.[207-213]

SUMMARY

TEA, DEA, and MEA are amino alcohols and as such, are chemically bifunctional, combining the properties of alcohols and amines. The pHs of 0.1 N aqueous solutions of TEA, DEA, and MEA are 10.5, 11.0, and 12.05, respectively. Ethanolamine soaps and ethanolamides are used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. In 1981, TEA, DEA, and MEA were reported to be ingredients of 2757, 18, and 51 cosmetic products, respectively. Most products contained TEA, DEA, and MEA in concentrations less than or equal to 5%. The nitrosation of the ethanolamines may result in the formation of N-nitrosodiethanolamine (NDELA) which is carcinogenic in laboratory animals. Traces of NDELA (below 5 ppm) have been found in a variety of cosmetic products.

The LD50 values for rats of TEA, DEA, and MEA ranged from 4.19 g/kg to 11.26 g/kg, 0.71 ml/kg to 2.83 g/kg, and 1.72 g/kg to 2.74 g/kg, respectively. In single-dose oral toxicity for rats, TEA is practically nontoxic to slightly toxic, and DEA and MEA are slightly toxic. Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney. Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage. TEA and DEA showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semioccluded patch application and at a greater than 10% concentration in 10 open applications over a period of 14 days. A lotion containing 1% TEA was not phototoxic to guinea pigs, and TEA was not a guinea pig skin sensitizer. With long contact time TEA, DEA, and MEA are irritating to the rabbit eye at concentrations of 100%, 50%, and 5%, respectively.

The ethanolamines have been shown to be nonmutagenic in the Ames test and TEA is also nonmutagenic to *Bacillus subtilis*. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test.

TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months. There was a higher incidence of malignant lymphoid tumors in female mice fed diets containing TEA for their whole lifespan than in male mice on the same diet or in control mice.

Clinical skin testing of TEA and cosmetic products containing TEA and DEA showed mild skin irritation in concentrations above 5%. There was very little skin sensitization. There was no phototoxicity and photosensitization reactions with products containing up to 20.04% TEA. A dyeless base formulation containing 11.47% MEA and a hair preparation containing 1.6% DEA and 5.9% MEA were irritating to human skin in patch tests.

COMMENTS

In the presence of N-nitrosating agents, TEA and DEA may give rise to N-nitrosodiethanolamine, a known animal carcinogen.

TEA and DEA are mild skin and eye irritants and irritation increases with increasing ingredient concentration.

Animal studies with MEA indicate that it is both a skin and eye irritant and clinical studies with formulations containing MEA indicate that it is a human skin irritant. The longer MEA stays in contact with the skin the greater the likelihood of irritation. MEA is primarily used in rinse-off hair products.

CONCLUSION

The Panel concludes that TEA, DEA, and MEA are 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 ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used in products containing N-nitrosating agents.

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