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Final Amended Report on Safety Assessment on Aminomethyl Propanol and Aminomethyl Propanediol

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Abstract

Aminomethyl propanol and aminomethyl propanediol are substituted aliphatic alcohols that function as pH adjusters in cosmetic products at concentrations less than 10%; additionally, aminomethyl propanediol is a fragrance. Extensive oral toxicity data are reviewed, with fewer inhalation toxicity data. Dermal toxicity data are presented that demonstrate, for example, that a mascara with 1.92% aminomethyl propanediol does not cause dermal irritation or allergic contact sensitization, suggesting that the maximum reported use concentration of 2% in mascara would be safe. Although these ingredients are primary amines that are not substrates for N-nitrosation, they may contain secondary amines as impurities in finished products that may undergo N-nitrosation. These ingredients should not be included in cosmetic formulations containing N-nitrosating agents. The Cosmetic Ingredient Review Expert Panel concludes that aminomethyl propanol and aminomethyl propanediol are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

Keywords

aminomethyl propanol, aminomethyl propanediol, cosmetics, safety

A safety assessment for aminomethyl propanol (AMP) and aminomethyl propanediol (AMPD) was published by the Cosmetic Ingredient Review (CIR) in 1990.[1] At that time, the CIR Expert Panel concluded that "at concentrations not exceeding 1%, aminomethyl propanol and aminomethyl propanediol are safe for use in cosmetics." New data were provided suggesting the safety of these ingredients at concentrations higher than 1%. This report is a compilation of new data and data from the original safety assessment on AMP and AMPD that are relevant to the assessment of these chemicals as used in cosmetics.

In 1987, a safety assessment for isopropanolamine, a close analog of AMP, was published with the conclusion from the CIR Expert Panel that this ingredient is safe as used in the practices of use and concentration but should not be used in products containing N-nitrosating agents.[2] This conclusion was confirmed during a subsequent review of new published literature.[3]

Chemistry

Definition and Structure

AMP (CAS 124-68-5) is defined in the *International Cosmetic Ingredient Dictionary and Handbook* as a substituted aliphatic alcohol that conforms to the formula in Figure 1.[4]

AMPD (CAS 115-69-5) is defined in the *International Cosmetic Ingredient Dictionary and Handbook* as a substituted aliphatic diol that conforms to the formula in Figure 2.[4]

Synonyms and trade names for these ingredients can be found in Table 1. Both AMP and AMPD are in the general chemical groups of alkanolamines (also, alcohol amines).

Properties

Chemical and physical properties for AMP and AMPD are described in Table 2.

Method of Manufacture

Both AMP and AMPD can be synthesized by the condensation of the corresponding nitroparaffins with formaldehyde and reduction to the β-aminoalkanols.[5] The reduction to the alkanolamine is accomplished by hydrogenation in the presence of a Raney nickel catalyst.

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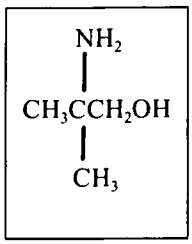

Figure 1. Structure of aminomethyl propanol.

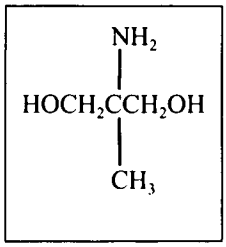

Figure 2. Structure of aminomethyl propanediol.

Table 1. Synonyms and Trade Names for Aminomethyl Propanol (AMP) and Aminomethyl Propanediol (AMPD)[95]

Ingredient	Synonyms	Trade Name	Trade Name Mixtures
Aminomethyl propanol	2-Aminoisobutanol	AMP-95	Cerasynt IP
	2-Amino-2-methyl-1-propanol	AMP-Regular	FZ-3148
	2-Hydroxymethyl-2-propylamine		FZ-3158
	Isobutanolamine		Hair gloss polymer A
	1-Propanol, 2-amino-2-methyl-		
Aminomethyl propanediol	2-Amino-2-methylpropane-1,3-diol	AMPD	
	2-Amino-2-methyl-1,3-propanediol		
	AMPD		
	1,3-Dihydroxy-2-methyl-2-propylamine		
	1,3-Propanediol, 2-amino-2-methyl-		

Table 2. Chemical and Physical Properties of Aminomethyl Propanol (AMP) and Aminomethyl Propanediol (AMPD)[5,20,96,97]

	AMP	AMPD
Physical description	Colorless liquid or crystals; crystals are odorless, but liquid has slight amine odor.	Colorless liquid or crystals; crystals are odorless, but liquid has slight amine odor.
Molecular weight	89.14	105.14
Empirical formula	$C_4H_{11}NO$	$C_4H_{11}NO_2$
Melting point, °C	30-31	109-111
Boiling point, °C	165 (760 mm Hg)	151-152 (10 mm Hg)
Flash point, °C	67	—
Vapor density	3.04	3.63
Specific gravity	0.934 at 20/20 °C	—
pH in 0.1 M solution	11.3	10.8
Solubility	Miscible in water, soluble in alcohols, slightly soluble in aromatic hydrocarbons, and insoluble in aliphatic hydrocarbons	Soluble in water and alcohols, slightly soluble in aromatic hydrocarbons, and insoluble in aliphatic hydrocarbons and mineral oil

Analytical Methods

Infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS) have been published for AMP.[6] The IR spectrum of commercial AMP closely matches the standard spectrum, with no evidence of foreign materials.[7] For AMPD, the infrared spectrum has been published.[6] Alkanolamines such as AMP and AMPD can be determined in hair spray formulations, after acetylation, by gas-liquid chromatography.[8]

Impurities

Angus Chemical Company reported that AMP may have up to 6.8% of secondary amine impurity. AMPD has impurity levels below 0.5%.[9] Analysis of AMP by this company found no nitrosamines at the limit of detection, 50 ppb. Ultra PC grades of AMP and AMPD meet European Union Cosmetics Directive standards that require a minimum purity of 99%, a secondary amine content no greater than 0.5%, and a nitrosamines content no greater than 50 ppb.

Chemical Reactions

Alkanolamines can react with copper, brass, and aluminum but not with steel or iron.[5]

Alkanolamines react with the methyl ester of an organic acid in the presence of an alkaline catalyst, and at low temperatures and pressures they form amides. When this reaction is carried out at higher temperatures, oxazolines are produced. The alkanolamines react with acid anhydrides to form imides. The

substituted ethyleneimine is formed by the reaction of AMP with excess mineral acids at temperatures above 75°C, followed by reaction with a caustic agent. Oxazolidines are formed by reaction of the alkanolamines with aldehydes.[10]

Use

Cosmetic Uses

AMP functions as a pH adjuster in cosmetic products.[4] AMPD functions as a pH adjuster and is also a fragrance ingredient.[4] As reported to the US Food and Drug Administration (FDA) by industry, AMP is used in a total of 853 cosmetic products, primarily aerosol hair sprays and hair dyes, whereas AMPD is used in a total of 47 cosmetic products, most frequently in mascara.[11] Table 3 presents the product formulation data for AMP and AMPD. Based on a survey conducted by the Cosmetic, Toiletry and Fragrance Association (CTFA), the highest use concentration reported for AMP is 7% in hair dyes and colors and the highest use concentration for AMPD is 2% in mascara.[12]

Products containing AMP or AMPD may come into contact with the skin, eyes, and mucous membranes. Contact with the ingredient may be temporary or prolonged. Products containing either ingredient may be used repeatedly over a period of time.

AMP and AMPD are unlikely to exist as the free bases in cosmetic products but rather as salts as the result of neutralization of acidic components of the cosmetic formulation.[13]

AMP and AMPD are not included among the substances listed as prohibited, restricted, or provisionally allowed in the use of cosmetic products marketed in Japan.[14,15] In the European Union, monoalkanylamines, monoalkanolamines, and their salts are listed under Annex III, Part 1 of the Cosmetics Directive with the following restrictions: maximum secondary amine content in finished products and raw materials of 0.5%, must not be used with nitrosating systems, minimum purity of 99%, maximum nitrosamine content of 50 μg/kg, and must be kept in nitrite-free containers.[16]

Aerosol use. AMP and AMPD also are used in hair sprays, which may be inhaled. Jensen and O'Brien[17] reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question. These authors reported a mean aerodynamic diameter of 4.25 ± 1.5 μm for respirable particles that could result in lung exposure.[17]

Bower[18] reported diameters of anhydrous hair spray particles of 60 to 80 μm and pump hair sprays with particle diameters of 80 μm or greater. Johnsen[19] reported that the mean particle diameter is around 38 μm in a typical aerosol spray. He stated that in practice, aerosols should have at least 99% of particle diameters in the 10 to 110 μm range.

Noncosmetic Uses

AMP and AMPD have a variety of uses in the synthesis of surface-active agents, vulcanization accelerators, and pharmaceuticals. They are also used as emulsifying agents in mineral oil and paraffin wax emulsions, leather dressings, textiles, cleaning compounds, polishes, and soluble oils and as absorbents for acidic gases.[20] AMPD can be used to stabilize emulsions, although stability depends on the concentration of AMPD, the length of storage, and temperature.[21]

Alkanolamines can be used in pigment dispersion, resin solubilizers, catalysts, boiler water treatment, formaldehyde scavenging, applications in oil and gas production, biomedical applications, and synthetic applications.[5] In cutting fluids, AMP is useful as an antimicrobial agent.[22] AMP is also listed as an indirect food additive for use, without restrictions, as a component of adhesives.[23]

General Biology

Absorption, Distribution, Metabolism, and Excretion

Skin absorption. Musial and Kubis[24] evaluated the interaction of AMP and AMPD along with several other alcoholamines with model skin sebum for potential use in topical treatments and prevention of acne. This study found that AMP and AMPD penetrated the artificial sebum and that reaction product accumulated above the sebum layer (sebum thickness not defined). The depth of penetration increased as a function of time and plateaued after 48 hours at approximately 2.7 mm for AMP and at approximately 3.6 mm for AMPD. After 72 hours, the penetration of AMP and AMPD was about 3.1 mm and 4.1 mm, respectively.

Metabolism. AMP is incorporated into phospholipids.[25] AMP inhibits incorporation of ethanolamine and diethanolamine in phospholipids. This, in turn, may limit the conversion of ethanolamine (in the phospholipids) to choline.[26] No metabolism data were available for AMPD.

Distribution and excretion. Yue et al[27] studied the fate of [^{3}H]AMP (dose not reported) injected intraperitoneally in young male Sprague-Dawley rats on choline-adequate and choline-deficient diets. The rats receiving the choline-deficient diets started the diet 24 hours before the injection of [^{3}H]AMP and continued on this diet until they were killed at 30 minutes or 1, 2, 3, 6, 24, or 96 hours post injection. The rats fed the choline-adequate diet (ad libitum) followed the same protocol. Thirty minutes after the intraperitoneal injection, [^{3}H] appeared in the serum, with radioactivity disappearing shortly after its initial uptake. Radioactivity in the serum was consistently lower in the rats fed the choline-deficient diet, with

Table 3. Current Cosmetic Product Uses and Concentrations for Aminomethyl Propanol (AMP) and Aminomethyl Propanediol (AMPD)[11,12]

Product Category (Total No of Products in Each Category)	Ingredient Uses in Each Product Category	Use Concentrations, %
Aminomethyl propanol		
Bath products		
Soaps and detergents (594)	7	0.03-0.2
Other (276)	—	2
Eye makeup		
Eyebrow pencils (124)	—	0.7
Eyeliners (639)	—	0.7
Eye shadow (1061)	—	0.7
Eye lotions (32)	1	0.5-0.7
Eye makeup remover (114)	2	0.7
Mascara (308)	6	0.3-1
Other (229)	1	0.7
Fragrance products		
Colognes and toilet waters (948)	2	0.03-0.3
Perfumes (326)	—	0.2-0.3
Powders (324)	—	0.3
Sachets (28)	—	0.3
Other (187)	4	0.04-0.3
Noncoloring hair care products		
Conditioners (715)	24	0.02-2
Sprays/aerosol fixatives (294)	219	0.3-3
Straighteners (61)	1	0.2
Permanent waves (169)	—	0.2
Rinses (46)	—	0.2
Shampoos (1022)	9	0.0001-1
Tonics, dressings, etc. (623)	124	0.5-3
Wave sets (59)	6	1
Other (464)	144	0.3-1
Hair coloring products		
Dyes and colors (1600)	245	0.5-7[a]
Tints (56)	1	0.5
Rinses (15)	5	0.5
Shampoos (27)	7	—
Color sprays (4)	—	0.5
Lighteners with color (14)	—	0.5
Bleaches (103)	—	0.5
Other (73)	—	0.5
Makeup		
Blushers (459)	—	0.5
Face powders (447)	—	0.5
Foundations (530)	—	0.5-0.6
Makeup bases (273)	—	0.5
Makeup fixatives (37)	—	0.5
Other (304)	1	0.3-0.5
Nail care products		
Basecoats and undercoats (43)	—	0.1
Cuticle softeners (20)	—	0.1
Creams and lotions (13)	—	0.0009-0.1
Nail extenders (1)	—	0.1
Nail polishes and enamels (398)	—	0.1
Nail polish and enamel removers (39)	—	0.1
Other (58)	—	0.1
Personal hygiene products		
Underarm deodorants (281)	10	0.0009-0.4
Douches (8)	—	0.2
Feminine deodorants (7)	—	0.2
Other (390)	1	0.08-2
Shaving products		
Aftershave lotions (260)	6	0.5-0.8
Shaving creams (135)	—	0.2-2
Shaving soaps (2)	—	0.2

(continued)

Table 3 (continued)

Product Category (Total No of Products in Each Category)	Ingredient Uses in Each Product Category	Use Concentrations, %
Other (64)	—	0.2
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	4	0.1-1
Depilatories (49)	—	0.5
Face and neck creams, lotions, powders, and sprays (546)	2	0.07-0.5[b]
Body and hand creams, lotions, powders, and sprays (992)	5	0.05-1[c]
Foot powders and sprays (43)	1	0.03-0.5[d]
Moisturizers (1200)	6	0.5[e]
Night creams, lotions, powders, and sprays (229)	—	0.5[f]
Paste masks/mud packs (312)	2	0.5
Skin fresheners (212)	—	0.1-0.5
Other (915)	7	0.09-2[g]
Suntan products		
Suntan gels, creams, liquids, and sprays (138)	—	0.4
Total uses/ranges for aminomethyl propanol	853	0.0001-7
Aminomethyl propanediol		
Eye makeup		
Eyebrow pencils (124)	—	1
Eyeliners (639)	—	0.1
Eye makeup remover (114)	—	0.5
Mascara (308)	37	0.2-2
Other (229)	1	—
Noncoloring hair care products		
Sprays/aerosol fixatives (294)	1	—
Shampoos (1022)	1	—
Other (464)	3	—
Makeup		
Blushers (459)	—	1
Face powders (447)	—	1
Foundations (530)	—	1
Makeup bases (273)	—	0.8-1
Makeup fixatives (37)	—	1
Other (304)	1	1
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	1	1
Depilatories (49)	—	1
Face and neck creams, lotions, powders, and sprays (546)	1	1[h]
Body and hand creams, lotions, powders, and sprays (992)	—	1[i]
Foot powders and sprays (43)	—	1
Moisturizers (1200)	1	1[j]
Night creams, lotions, powders, and sprays (229)	—	1[k]
Paste masks/mud packs (312)	—	1
Skin fresheners (212)	—	1
Other (915)	—	0.1-1[l]
Suntan products		
Suntan gels, creams, liquids, and sprays (138)	—	1
Total uses/ranges for aminomethyl propanediol	47	0.1-2

[a] 7% before dilution.
[b] 0.5% in face and neck sprays; 0.07%-0.5% in face and neck creams, lotions, and powders.
[c] 0.1%-0.5% in body and hand sprays; 0.05%-1% in body and hand creams, lotions, and powders.
[d] 0.4% in foot cream; 0.03%-0.5% in foot powders and sprays.
[e] 0.5% in moisturizing sprays; 0.5% in moisturizing creams, lotions, and powders.
[f] 0.5% in night sprays; 0.5% in night creams, lotions, and powders.
[g] 0.09% in an antibacterial hand soap; 0.2% in a hand sanitizer; 2% in pore strips; 2% in a body polish.
[h] 1% in face and neck sprays; 1% in face and neck creams, lotions, and powders.
[i] 1% in body and hand sprays; 1% in body and hand creams, lotions, and powders.
[j] 1% in moisturizing sprays; 1% in moisturizing creams, lotions, and powders.
[k] 1% in night sprays; 1% in night creams, lotions, and powders.
[l] 0.1% in exfoliating scrubs (hand and body; foot).

the exception of the 6-hour value, at which time the activity was approximately equal for both dietary groups.

Radioactivity in the urine followed the same pattern as that in the serum, with the rats on the choline-adequate diet excreting a greater amount of radioactivity in their urine than the rats on the choline-deficient diet. Paper chromatography results suggested that the radioactivity in the urine was the [^{3}H]AMP, which had been excreted unchanged, as indicated by samples of [^{3}H]AMP that were chromatographed concurrently.

From 0.5 to 6 hours, the uptake of radioactivity by the brain, skeletal muscle, heart muscle, intestine, and spleen was greater in the rats fed the choline-adequate diet. At 6 hours, this trend was completely reversed and remained so until the end of the study. In the liver, uptake of radioactivity was greater in the choline-deficient group throughout the study. By 96 hours, the radioactivity in the liver of both groups had decreased considerably, but that in the liver of the choline-deficient group remained higher than that in the choline-adequate diet group.

The distribution of the radioactive AMP in the phospholipids of the liver was also examined. At 0.5 hours, the amount of free radioactive AMP in hepatic mitochondria from rats fed the choline-adequate diet was approximately 72%, the remaining 28% being incorporated into phospholipids. In the choline-deficient rats, about 29% of the AMP was free; the remaining 71% was present in the phospholipids. This same trend was seen in hepatic microsomes, with the exception that a greater amount of the AMP (81%) in rats fed the choline-deficient diet was incorporated into phospholipids. There was no indication that the AMP had been phosphorylated.

At all times, the livers of the choline-deficient rats had a higher amount of [^{3}H]AMP in all subcellular fractions. The cytosol of both the liver and kidneys cells contained the most [^{3}H]AMP. In the rats receiving a choline-adequate diet, the radioactivity in the kidneys and liver decreased with time, whereas the opposite was true for rats fed the choline-deficient diet; radioactivity increased in the hepatic subcellular fractions and remained constant in the renal subcellular fractions.

In the choline-deficient rats, this change was most pronounced in the liver microsomal fraction. The authors also noted that the radioactivity found in the cytosol was not free AMP because no free AMP was identified after 30 minutes, and that the radioactive AMP was redistributed among several phospholipid fractions. This latter observation indicated that incorporation of AMP into phospholipids may occur with other derivative forms of AMP other than the phosphatidyl derivative.[27]

No distribution or excretion data on AMPD were found.

Animal Toxicology

Acute Oral

Aminomethyl propanol. A review by Power[28] described an acute oral toxicity study in young adult male fasted rats (strain not specified; 5 groups of 10 rats each) that received a single oral dose of AMP diluted in an equal volume of saline. Doses were 2200, 2400, 2800, 3600, or 4000 mg/kg. Animals were observed closely for 4 hours immediately following dosing and then daily for 14 days after treatment. Rats receiving 3600 or 4000 mg/kg experienced rapid absorption into the circulatory system that resulted in gross damage to the liver, kidney, spleen, and respiratory system that was followed by respiratory collapse. Irritation to the stomach and duodenum was observed in rats receiving 2800 mg/kg or more. The LD_0, LD_{50}, and LD_{100} were 2200, 2900 $\pm$ 140, and 4000 mg/kg, respectively.

An acute toxicity study of a hair spray containing 0.25% AMP was performed using 10 albino rats, 5 of each sex.[29] After fasting overnight, the animals received a dose by gavage of 5.0 mL/kg of the undiluted hair spray (sprayed into glass beakers to collect test material) and then were observed for 14 days thereafter, during which they were allowed feed and water ad libitum. One female rat died during the second week of observation. Most of the rats had either slightly decreased activity or decreased activity up to 3 hours after administration of the test material, and all appeared normal from the 6-hour point until the end of the study. All of the survivors gained weight during the study. At necropsy, no abnormalities were observed in the survivors or in the rat that died during the study.

The same protocol was also performed with a hair spray (specific gravity 0.81) containing 0.58% AMP.[30] All rats survived the 14-day oral observation period. The rats had severely decreased activity an hour after administration of the test material. Their activity remained decreased through the 6-hour observation point and then returned to normal for the remainder of the study. All animals gained weight during the study, and no gross abnormalities were noted at necropsy.

Using the same protocol as the previous study, a hair spray (specific gravity 0.74) containing 0.59% AMP was tested for oral toxicity in albino rats.[31] All rats had some degree of decreased activity for the first 24 hours. All of the rats died before the end of the study, and 7 of the 10 rats died on or before day 2. The 3 rats that survived through day 2 appeared normal on the second day but had recurring slightly decreased activity on day 3. These 3 rats all died within the first week. The following observations were noted at necropsy: the 3 rats that died within 1 hour had severely reddened pyloric mucosae, the 2 rats that died at 24 hours had moderately reddened pyloric and duodenal mucosae, the 2 rats that died on day 2 had severely reddened pyloric and duodenal mucosae, the rat that died on day 5 had necrosis of the pyloric mucosa, the rat that died on day 6 had consolidation of the superior and inferior lobes of the right lung, and the rat that died at 1 week had moderately reddened pyloric and duodenal mucosa and gas-filled stomach and intestines.

A fourth test following the same protocol was performed with 3 cosmetic formulations containing either 0.58% or 0.59% AMP (0.59% AMP at specific gravity of 0.80, 0.58% AMP at specific gravity of 0.79, and 0.58% AMP at specific gravity of 0.85).[32] No animals in the 3 test groups died during the study, and all rats gained weight. All of the test animals had varying degrees of decreased activity; in no case did the decreased activity last beyond 24 hours. No gross abnormalities were observed at necropsy, and the 3 formulations containing 0.58% or 0.59% AMP were not toxic to rats by the oral route

under the conditions of the study. Predicated on the different specific gravity values for the tested materials, these materials are different formulations. Because no control formulations without AMP were tested, it is not possible to conclude that any adverse reactions are related to AMP.

The oral LD_{50} values in Cox strain albino mice for both AMP and AMP-95 (95% AMP solution) were estimated at 2.15 ± 0.2 g/kg and 2.4 ± 0.089 g/kg, respectively, but no experimental details were provided.[13]

Aminomethyl propanediol. Bio-Test Laboratories tested an aerosol spray containing 0.40% AMPD for acute oral toxicity using Charles River albino rats.[33] The rats were divided into groups of 2 males and 2 females for each of 4 dosage groups (no control group was described). The rats received the test material undiluted at the following doses: 10.2, 15.4, 23.1, and 34.6 g/kg. The pH of the test material was 8.7. The animals were observed for 14 days following administration of the test material, at which time all surviving animals were killed and necropsied. Animals that died during the study were also necropsied. One rat in the 15.4 g/kg group died during the study, and none of the rats of the low-dose group died. All rats in the 2 high-dose groups died, with those in the 23.1 g/kg group dying within the first week and those in the high-dose group dying 45 minutes to 3 hours after administration of the test material. The 7- and 14-day LD_{50} doses were both 17.0 ± 1.7 g/kg. Schafer and Bowles[34] reported an approximate oral LD_{50} for AMPD in the deer mouse of 0.140 g/kg, and CTFA[35] stated that albino mice all survived an oral dose of 5.0 g/kg.

Inhalation

Aminomethyl propanol. A group of 10 Wistar rats, equally divided by sex, were exposed for 1 hour to an atmosphere containing 200 mg/L of a hair spray (particle size not available) containing AMP at a concentration of 0.59%.[36] The test animals were observed for 2 weeks following the exposure. All but 1 rat survived the duration of the study. All survivors gained weight during the study, and all, including the rat that died, appeared normal during the observation period. At necropsy, the left lung of the rat that died (day 3) was adhered to the dorsolateral body wall; none of the other rats had any abnormalities.

In a second study following the above protocol, 3 cosmetic formulations containing 0.58%, 0.59%, and 0.58% AMP (groups 1, 2, and 3, respectively) were tested.[37] All rats survived the 2-week observation period, and all but 1 gained weight (1 rat maintained a steady weight). The rats of groups 1 and 2 appeared normal throughout the observation period, whereas those of group 3 had slightly decreased activity at hour 1 and were normal thereafter. The only abnormality noted upon necropsy was in 1 rat of group 2; all lobes of the right lung were consolidated and had adhered to the ventral body wall. The formulations containing 0.58%, 0.59%, and 0.58% AMP were not toxic by inhalation to rats under the conditions of the study.

A group of 20 Sprague-Dawley rats, 10 of each sex, were exposed for 1 hour to an atmosphere containing 168.2 mg/L of a spray (particle size not available) containing AMP at a concentration of 0.26%.[38] Except for the hour during which they were exposed to the test material, the rats were allowed feed and water ad libitum. After exposure to the test material, the rats were rinsed, dried, and placed in clean cages. The rats were observed during the exposure, and half of the rats of each sex were killed 24 hours later. The remainder of the test animals were observed for 14 days.

During exposure to the test material, all rats had decreased activity and exhibited labored respiration, squinting, and ataxia. The decreased activity, labored/slow respiration, and squinting continued after the exposure; in addition, the rats had depressed righting and placement reflexes. One female rat had tremors and prostration upon removal from the test chamber; another female had intermittent tremors. All rats, with the exception of 1 male rat with a slight nasal discharge, appeared normal at 24 hours. One male rat was wheezing on days 2, 3, and 14. All of the remaining rats appeared normal through the remainder of the observation period. One female rat in the control group was wheezing on days 13 and 14; all other control rats appeared normal.

There were no differences in weights and weight gains between the control and test animals. The kidney weights and ratios of kidney to body weight were significantly higher for the treated rats. No treatment-related lesions were observed at necropsy. One hour of exposure to an atmosphere containing 168.2 mg/L of a spray containing 0.26% AMP caused no significant histopathological changes in rats.[38]

No deaths occurred when rats were exposed for 1 hour to atmospheres containing 200 mg/L of an aerosol (particle size not available) containing AMP at concentrations of 0.25% or 2.5% in alcohol and propellant.[13]

In a study of the effects of metal working fluid components, Detwiler-Okabayashi and Schaper[39] exposed a group of 4 male Swiss-Webster mice to aerosolized AMP (concentration range of 185-1160 mg/m^3; mass median aerodynamic diameter range of 1-2 μm) for 3 hours. The exposure period was followed by a 20-minute recovery period. The mice were observed for sensory irritation and pulmonary irritation during the exposure period and for recovery response and mortality for a week following the exposure. Sensory irritation and pulmonary irritation (measured by evaluating the individual breathing patterns of mice) occurred during the exposure period and recovery response was poor. No deaths occurred in the test group.

Aminomethyl propanediol. An acute inhalation toxicity study of a hair spray containing 0.50% AMPD was performed using 10 male Sprague-Dawley rats.[40] The rats were exposed for 1 hour to an aerosol atmosphere containing approximately 200 mg/L of the hair spray formulation (particle size not available). The animals were observed during exposure and for 14 days thereafter. The rats were weighed before the study and on days 7 and 14. At the end of the study, the rats were necropsied, and tissues were examined microscopically. All rats survived the duration of the study, and body weights and weight gains were normal. The animals had no pharmacotoxic signs during or after exposure to the test material. There was no evidence of toxicity with respect

to organ weights and gross lesions. The results of the microscopic evaluations were unavailable.

Dermal

Aminomethyl propanol. Parekh[41] performed an acute dermal toxicity study of 99.19% AMP using rabbits (strain unknown). Twelve rabbits (3.0 ± 0.5 kg) were divided into 3 groups, with each group consisting of 2 males and 2 females. The abdomens were shaved and 1 of each sex in each group was abraded on the shaved site. Rats received 1000, 1500, or 2000 mg/kg body weight applied to the shaved abdomen and covered with gauze and rubberized cloth. After 24 hours, the patches were removed and the exposure area was cleaned and observed for skin irritation. The animals were further observed for 2 weeks for toxicity. The test was repeated with 8 more rabbits (2.5 ± 0.2 kg, 4 of each sex). After the abdomens were shaved, the skin was abraded in all rabbits and each was topically treated with 2000 mg/kg body weight for 24 hours. After the exposure period, the rabbits were observed for an additional 2 weeks. Upon completion of the observation period, all rabbits from both tests were weighed, killed, and necropsied. After the 24-hour exposure, all intact and abraded skin sites were severely irritated and black in color. The sites became necrotic in 2 to 3 days and remained necrotic for the rest of the observation period. Severe eschar formation was observed by day 14. Rabbits in all treatment groups experienced a loss in body weight over the 2 weeks. No systemic toxicity was observed and the organs at necropsy appeared normal. AMP was determined to be systemically nontoxic but a severe skin irritant. The LD_{50} was greater than 2000 mg/kg.

Short-Term Toxicity

Oral

Aminomethyl propanol. The International Research and Development Corporation (IRDC) conducted a study in which Charles River CD-1 mice were fed AMP in the diet for 8 weeks.[42] Concentrations were 0, 200, 400, 800, 1600, or 3200 ppm; 10 mice of each sex were in each diet group. The mice were observed daily, and weights and feed consumption were recorded weekly. At the end of the study, all mice appeared normal. Livers and gross lesions found in test animals were examined (all of the 3200 ppm mice and 4 mice from each of the other dosage groups). No compound-related gross lesions and no microscopic lesions in the liver were observed.

A similar study was undertaken with Charles River CD rats.[43] The test protocol was the same as in the mouse study except that the dietary concentrations were 0, 1000, 2000, 4000, 8000, or 16 000 ppm.[42] At study termination, the rats of the 16 000 ppm group were emaciated and had rough hair coats, small skin lesions, and loss of hair. Two female rats in the highest dose group died before the end of the study. Alopecia and focal skin erosions were observed in the rats of the 16 000 ppm group, and these were considered compound induced. Microscopically, hepatocyte vacuolation was noted in all rats of 16 000 and 8000 ppm groups and 4 from each of the remaining dose group. This change was considered compound-induced.

Eight beagle dogs were used in a study of the toxic effects of AMP over a 28-day period.[44] AMP was administered in the diet at concentrations of 600, 1800, 5400, or 16 200 ppm to 2 dogs, 1 of each sex for each dose. Feed consumption was recorded daily, and the dogs were weighed once weekly. Hematologic evaluations and urinalyses were performed once before the administration of AMP and at week 4 during the study. Both of the dogs in the 1800 and 16 200 ppm groups, as well as the female dog in the 5400 ppm group, had frequent soft stools or diarrhea. High-dose dogs had marked weight loss and anorexia, and at week 2, both had dry noses and mouths. The male dog of the 5400 ppm group had similar but less severe reactions. All dogs survived the duration of the study. Urinalyses were normal throughout the study. The hematologic changes at 4 weeks included elevated hemoglobin, packed cell volume, and erythrocyte count for the female high-dose dog. The male dogs of the 5400 and 16 200 ppm groups had slight neutropenia. For all dogs, except those of the 600 ppm group, serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase activities were moderately to markedly increased; for the dogs of the 5400 and 16 200 ppm groups, serum glutamic oxaloacetic transaminase (SGOT) activity was slightly to moderately increased.

No gross lesions attributable to the AMP treatment were found at necropsy. Microscopic lesions in the liver included hepatocytic vacuolation, necrosis of hepatocytes, pigment deposits, centrilobular inflammatory infiltrate, and fibrosis and atrophy of centrilobular parenchymal tissue; these were observed in all dogs except the male exposed to 600 ppm. The damage to the liver, as well as a decrease in liver weight, was dose dependent.

Inhalation

Aminomethyl propanol. An inhalation study was performed with a hair spray containing AMP at a concentration of 0.58%.[45] A group of 16 Wistar rats, 8 of each sex, was exposed to an atmosphere containing 200 mg/L of the hair spray for 1 hour per day, 5 days per week for 2 weeks. Four rats were killed at the end of the first week, another 4 at the end of the second week, and the remainder after a 1-week recovery period. All rats were examined for gross lesions, and the respiratory tissues were preserved for possible microscopic examination. None of the rats died as a result of exposure to the test material. All rats had slightly decreased activity 1 hour after exposure that returned to normal by 3 hours and once again had slightly decreased activity at 24 hours. The rats in the 1-week recovery group appeared normal by day 14 of the study. No gross changes were noted at necropsy, and weight gains were comparable between the test animals and the control group.

Aminomethyl propanediol. No short-term inhalation studies on AMPD were found.

Subchronic Toxicity

Oral

Aminomethyl propanol. In a 90-day study, AMP solutions (pH 7 and 11+) were administered to rats by gavage.[46] At each pH, the AMP solution was administered at doses of 0.5, 0.75, 1.1, or 1.7 g/kg/d. The dosage groups consisted of 20 rats, divided equally by sex. The rats were observed daily, and body weights and feed consumption were recorded weekly. All rats that died during the study were necropsied, and those that survived to the end of the study were killed and necropsied after samples were taken for hematologic, urologic, and clinical chemistry measurements. Because the pH 11+ AMP solution is so different from cosmetic preparations, these results are not discussed here.

The noted behavior changes were hyperventilation and hyperirritability. All surviving rats gained weight and consumed feed in a normal manner, although the test rats did appear to drink more water.

In the pH 7 group, some occurrences of increased SGPT and OCT activities were noted, and the males of the 1.7 g/kg group had significant decreases in packed cell volume and hemoglobin. Urinalyses were performed only on the rats from the pH 11+ group; some samples contained protein. No gross lesions were found at necropsy.[46]

In a 3-month study by Parekh,[47] AMP-hydrochloride (pH 7) was administered to groups of 20 male and 20 female rats (strain unknown) in their diet at concentrations of 0, 2.5, 15, 25, or 250 mg/kg (0, 25, 150, 250, or 2500 ppm). Prior to administration and at 1 and 3 months of the treatment period, urinalyses, hematology, and plasma chemistries were monitored. A complete histopathological examination was performed at study completion (no further details were available). No physical or ophthalmoscopic changes due to treatment with AMP-hydrochloride were observed. Body weight gains, food consumption, hematology, and urinalysis were comparable to the control animals. Rats in both the control and treatment groups became infected with a virus at weeks 5 and 6 of the study, but it was determined that the infection had no effect on the outcomes of the study. At the 1-month observation, animals in the 250 mg/kg dose group had increases in total serum proteins, immunoglobulins, and alkaline phosphatase activity. At the 3-month observation, this same treatment group had increases in SGOT, SGPT, and LDH activities. Livers of 3 males and 4 females in the 250 mg/kg dose group exhibited patchy hepatocellular vacuolization.

For 3 months, groups of 4 male and 4 female beagle dogs were fed diets containing 0.63, 15.0, or 62.5 mg AMP/kg.[48] The AMP was used as AMP-hydrochloride, pH 7.0. The physical conditions and feed consumptions of the dogs were monitored, and urinalyses, hematology, and clinical chemistries were obtained at the start of the study and at 1 and 3 months. At the end of the study, some tissues were examined microscopically (further details not provided in this study). Except for the high-dose group, body weight gains were normal during the study. The high-dose group also had increased activities of SGOT, SGPT, and alkaline phosphatase at 1 and 3 months. The liver weights and ratio of liver to body weight were slightly increased in the dogs of the high-dose and mid-dose groups at necropsy. In addition, 2 females and 1 male of the high-dose group had tan and mottled livers. At microscopic examination, vacuolization, lipid deposits, and bile duct hyperplasia were found in the livers of all of the high-dose dogs and in 1 of the mid-dose dogs. The author stated that no other organs appeared to be affected. No other comments were made about the effects in dogs of 90 days of dietary consumption of AMP.

Inhalation

Aminomethyl propanol. A 90-day inhalation toxicity study of 2 pump sprays (mass median diameters ranging from 4.82 to 7.45 μm), each containing 0.40% AMP, was performed using cynomolgus monkeys.[49] The test animals were divided into groups consisting of 3 males and 6 females each. One group (group 2) was exposed to the test material under static conditions by automatic dispensation of 1 pump sprayer every 7.5 seconds per 10-minute period per day, for a total of 800 sprays per day. The monkeys of group 3 were exposed to the test material following the same spraying regimen but under dynamic conditions (in an air flow of 622 L/min) for the first 25 days, followed by static exposure for the remaining 64 days. The other 2 groups of monkeys were the control group and a group exposed to a different test material. The monkeys were fed after the daily exposure, and water was available ad libitum. All monkeys tested negative for tuberculosis and had clear chest X-rays prior to the start of the study.

The monkeys were weighed prior to the start of the study and weekly thereafter. They were observed daily during and after exposure for signs of behavioral abnormalities or toxicity. Prior to the start of the study and after 89 days, the following respiratory function parameters were assessed: distribution of ventilation, diffusion capacity, mechanics of respiration, mid-maximum expiratory flow, and spontaneous anesthetized tidal volume and respiratory rate. These tests were accomplished by anesthetizing the monkeys and placing them on a whole-body respirator. Hematology and clinical chemistry values were performed on blood samples from each monkey prior to the start of the study and at 30 and 89 days. After 89 days of exposure, the monkeys were killed and necropsied; organ weights were obtained and various organs were preserved for microscopic examination. The monkeys in group 2 were exposed to a mean gravimetric concentration of 6.63 $\pm$ 1.50 μg/L, and the monkeys in group 3 were exposed to a mean gravimetric concentration of 6.06 $\pm$ 1.99 μg/L during the study.

All animals survived the study, and no exposure-related clinical signs were noted. Only the monkeys in group 3 failed to gain weight during the study (body weights were slightly but significantly lower for weeks 3-12). Monkeys in group 3 required a significantly greater number of breaths and cumulative tidal volume to wash out to 2% nitrogen and had a significantly higher pulmonary flow resistance. No significant

hematological differences were noted. The test animals had decreased blood urea nitrogen values and increased SGPT activities compared with the controls at weeks 4 and 13. These differences were not considered significant, because the values were still within the normal range for the species and because there was no microscopic evidence of damage to the affected organs. An increase in serum CO_2 was noted for all test groups, but because there was no evidence of hyperventilation, the authors stated that the cause was believed to be ingestion of the acidic resin, causing a nonrespiratory acidosis.

Group 3 monkeys had increased ratios of liver to body weight that resulted from increased mean liver weights coupled with decreased average body weights. No compound-related alterations were found upon histopathological evaluation of the tissues in the monkeys of groups 2 and 3. No other compound-related adverse effects were reported after 89 days of exposure to atmospheres containing either 6.06 or 6.63 µg/L of hair spray containing 0.40% AMP.

In another 90-day study, groups of 8 cynomolgus monkeys, divided equally by sex, were exposed for 1 hour per day to a hair spray formulation (particle size not available) containing 0.21% AMP.[50] Groups were exposed to high and low concentrations of the hair spray, as well as to the vehicle control. There was a room air control group. The 90-day high and low mean values for the hair spray concentrations were 27.0 ± 3.1 µg/L and 2.73 ± 0.56 µg/L, respectively. No treatment-related effects were noted in body weights, weight gains, organ weights, ratios of organ to body weight, ratios of organ to brain weight, hematology, clinical chemistry, neurologic and ophthalmic parameters, or at necropsy. Histopathologic examination of the pulmonary tissues indicated increased numbers of free macrophages and macrophage aggregates in the alveolar spaces as well as foci of interstitially located particle-laden alveolar macrophages. Inflammation or interstitial fibrosis was not evident. Pulmonary alveolitis was noted in the high-dose hair spray group, and a slight to moderate increase in hepatocellular lipid was noted in all test animals.

In a 13-week inhalation study, CD-Crl:CS(SD)BR Charles River albino rats, 11 of each sex, were exposed to an aerosolized form of a pump hair spray (particle size not available) containing 0.44% AMP for 4 hours per day, 5 days per week for a total of 67 exposures.[51] The control group was a chamber control. The exposure concentration was 0.23 mg/m^3 (calculated to be a 100-fold increase over normal human exposure). The animals were observed daily and weighed weekly, and blood and urine samples were obtained on weeks 7 and 13. The animals were killed after the 67th exposure, gross observations were made, and various tissues and organs were removed for weighing and microscopic study. All animals survived the duration of the study. There were decreases in body weight gains for female rats during weeks 1 to 3 compared with controls, but they were considered within normal limits for the species in this laboratory.

Statistically significant hematologic changes included increased packed cell volume and erythrocyte counts for males at weeks 7 and 13, increased hemoglobin values for males at week 7, and increased packed cell volume for females at week 7. Although these differences were significant with respect to the controls, they were still within the normal range established by the laboratory for the strain of rat used. Male rats had a statistically significant increase in serum glucose concentration at week 7, and females had a significant decrease in blood urea nitrogen at week 13. The authors stated that these differences were not considered toxicologically significant when included with the other study results. No abnormalities were noted in urinalyses, and no lesions were found at necropsy. Female rats had a significant decrease in uterine and lung weights; there were also significant increases in heart- and liver-to-body weight ratios for the females.

No treatment-related microscopic changes were found in the heart or liver; frequency and severity of noted changes were equivalent for both the treated and control rats. The authors stated that microscopic changes observed in the lungs and upper respiratory tract of both the treated and control rats were consistent with chronic murine pneumonia in rats and were unrelated to treatment. The authors concluded that the pump hair spray formulation containing 0.44% AMP was safe under the exaggerated inhalation conditions of the test.

Aminomethyl propanediol. A 13-week inhalation toxicity study in female Chr/CD Charles River albino rats and female outbred Syrian golden hamsters was performed with 2 hair spray formulations (particle size not available) containing 0.135% AMPD.[52] One hair spray formulation also contained 3.00% ethylene maleic anhydride copolymer, 50%; this formulation was referred to as the hair spray, whereas the second formulation, without the ethylene maleic anhydride copolymer, was labeled the hair spray vehicle. Dosage groups consisted of 16 animals of each species. All animals were allowed feed and water ad libitum. The following concentrations were used: 10 mg/m^3 hair spray, 100 mg/m^3 hair spray, 100 mg/m^3 vehicle, and controls. Animals were exposed to the formulations 4 hours per day, 5 days per week for 13 weeks. The aerosol concentrations in the inhalation chambers were monitored hourly and adjusted as necessary; the temperature, pressure, and humidity were also closely monitored. After 32 exposure days, 5 animals of each species from each group were killed. The remaining test animals were killed starting 3 days after the last day of exposure. Blood analyses were performed on all of the test animals. Gross and microscopic examinations were also performed.

During the study, 5 animals either died or were killed when moribund (1 rat and 1 hamster of the low-dose hair spray group, 1 hamster of the high-dose hair spray group, and 1 animal of each species of the vehicle group). The authors stated that none of the deaths were the result of the aerosol treatment. The low- and high-dose hair spray group hamsters had a decreased body weight gain; these values were statistically significant for the hamsters of the high-dose group. The high-dose hair spray hamsters also had lower body weights at the end of the study, but this result was not statistically significant. There were no significant body weight changes in the rats.

In both species, there were scattered incidences of statistically significant differences in various hematology and clinical chemistry parameters, but no dose- or exposure-dependent trends were noted, and so these differences were not considered toxicologically significant. The same was true for the gross observations made at necropsy. The organ weights and histopathological findings did not include any comments on the animals exposed to the hair spray vehicle. The authors concluded that exposure of female Chr/CD Charles River rats and Syrian golden hamsters to atmospheres containing 144 mg/m^3 of a hair spray vehicle containing AMPD at a concentration of 0.135% was not harmful.

Chronic Toxicity

Aminomethyl propanol. A chronic oral toxicity study of AMP in beagle dogs was reported by Griffin.[53] Male and female dogs (number not specified) received 0, 1.1, 11.0, or 110.0 ppm AMP in their diets for a period of 1 year. The dogs were observed daily for general pharmacologic or toxicologic effects. Ophthalmology, hematology, and urinalysis evaluations were performed and serum chemistry was measured before dosing began and after 3, 6, 9, and 12 months of treatment with AMP. Two dogs of each sex and treatment group were killed after 6 months and the remaining animals were killed after the year-long treatment. All dogs were necropsied. No effects in appearance, behavior, food consumption, body weights, vision, blood chemistry, or urine attributable to AMP were observed in the dogs at any dose level. No gross or microscopic effects were observed. An amendment to the study in 1993 reported the details of seizures that occurred in 2 female dogs during the study. The authors stated that because the breed of dogs used is prone to primary epilepsy, AMP likely was not the cause of the seizures. The no observable effect level (NOEL) was reported to be 110.0 ppm or greater.

Aminomethyl propandiol. No chronic toxicity studies on AMPD were found.

Dermal Irritation and Sensitization Irritation

Aminomethyl propanol. A group of 6 rabbits was tested for primary skin irritation to AMP at a concentration of 0.25% in ethanol.[54] This single-insult, occlusive patch test was modified to include abraded and nonabraded skin. The test sites were graded for erythema and edema 24 and 72 hours after patch removal. Neither the abraded nor the nonabraded skin of any of the rabbits had a reaction during the study. The 0.25% AMP in ethanol was not irritating to rabbit skin.

The primary skin irritation potential of 2 formulations containing 0.26% AMP was determined in albino rabbits.[55] The test formulations (0.5 mL) were applied under an occlusive patch to the intact and abraded skin (2 rabbits of each sex per test formulation; 1 rabbit of each sex in each group was abraded). The patch was removed 24 hours later and the sites were graded at 25 hours (1 hour after patch removal) and 72 hours.

With the first formulation, all of the rabbits had erythema at both sites at both time points, with slight desquamation at the 72-hour time point. One rabbit also had edema at the abraded site; this reaction had subsided by 72 hours. The reactions of the rabbits tested with the second formulation were essentially the same. All rabbits had erythema at both time points, with slight desquamation at 72 hours. One rabbit had edema at the abraded site at 25 hours but was negative at 72 hours.

The primary irritation indices (PIIs) for the 2 formulations containing 0.26% AMP were 1.13 and 1.31 (maximum possible score = 8), respectively. The reactions to the second formulation were slightly more severe than those to the first formulation, accounting for the differences in the PIIs. The formulations containing 0.26% AMP were considered mildly irritating to intact and abraded rabbit skin.

Dermal irritation studies were performed on 3 cosmetic formulations containing AMP.[56-58] In each test, 0.5 mL of the formulation was applied under an occlusive patch to the abraded and nonabraded skin of 6 rabbits (3 per sex). After 24 hours, the patch was removed. The test sites were graded upon patch removal and at 72 hours.

A hair spray containing 0.25% AMP caused no irritation to either the intact or abraded skin of rabbits; the PII was 0.0.[56]

The PII of a hair spray containing 0.58% AMP was 0.38.[57] At the 24-hour grading, 3 of the rabbits had erythema at both the intact and abraded sites, whereas the other 3 rabbits had erythema at the abraded sites only. All of the reactions had cleared by 72 hours.

The PII for a hair spray containing 0.59% AMP was 0.35.[58] Four of the 6 rabbits had erythema at both the intact and abraded skin sites at the 24-hour grading. All reactions at 72 hours were negative. The authors concluded that the hair spray containing 0.59% AMP was not a primary dermal irritant.

A study was conducted using the same procedure as described above, in which 3 products containing 0.58, 0.59, and 0.58% AMP had PIIs of 0.75, 1.40, and 0.35, respectively.[59] With the first formulation (0.58% AMP), 5 of the 6 rabbits had erythema at both the abraded and intact sites at 24 hours and the irritation persisted through the 72-hour grading period, with 1 rabbit having edema in addition to the erythema at both sites. With the second formulation (0.59% AMP), 4 rabbits had both erythema and edema at 24 hours. A fifth rabbit had erythema alone, which had subsided by 72 hours. Of the other 4 rabbits with reactions, 1 had no reaction at 72 hours, 1 had erythema only, 1 had increased erythema and continued edema, and the last had increased erythema and edema. All of the reactions noted occurred at both the intact and abraded sites. With the third formulation (0.58% AMP), 1 rabbit had erythema at the abraded site, and 2 rabbits had erythema and edema at both sites at the 24-hour grading. All of the reactions had subsided by 72 hours. None of the formulations were considered primary dermal irritants under the conditions of the test.

In a limited summary, CTFA stated that AMP at concentrations of 0.25% and 2.5% in aqueous and alcoholic vehicles caused no irritation in single insult occluded patch tests in rabbits, but no details were available.[13]

In another study, an unspecified cosmetic formulation containing AMP-95 at a concentration of 0.22% was tested for primary skin irritation potential in a group of 9 rabbits using a single-insult, occlusive patch test procedure.[60] The skin reactions were graded 2 and 24 hours after patch removal. Three rabbits had erythema 2 hours after patch removal; of these 3, 1 had undiminished erythema 24 hours after patch removal. A fourth rabbit had erythema at the 24-hour grading. The group PII for the formulation containing AMP-95 at a concentration of 0.22% was 0.56 (maximum 8.00), leading the authors to conclude that the formulation was minimally irritating.

Aminomethyl propanediol. A hair care product containing 0.715% AMPD was tested in 4 New Zealand albino rabbits for primary dermal irritation.[61] The undiluted test material, 0.5 mL, was applied under an occlusive patch to the intact and abraded skin of each rabbit, where it remained for 24 hours. The sites were graded 1 hour after patch removal and at 72 hours. No adverse reactions were noted. The authors stated that the hair care product containing 0.715% AMPD was nonirritating when applied to intact and abraded rabbit skin.

A hair spray formulation containing 0.50% AMPD was tested for irritation following the protocol outlined in the previous paragraph.[62] Two rabbits had erythema and edema at the intact skin site; the reactions had cleared by 72 hours. One rabbit had erythema persisting through 72 hours at the intact site. The fourth rabbit had no reaction at the intact skin site. At the abraded skin sites, 3 rabbits had erythema and edema; the erythema persisted through 72 hours whereas the edema subsided in all but 1 of the rabbits. The fourth had continuing erythema and no edema. The PII for the hair spray was 1.38.

Sensitization

Aminomethyl propanol. The intradermal sensitization potential of AMP was studied in guinea pigs.[63] Three groups of 10 male guinea pigs each were used in the study: negative control (saline), positive control (0.3% dinitrochlorobenzene, or DNCB), and test group receiving 0.1% AMP. The backs and flanks of the guinea pigs were shaved, and 0.05 mL of the appropriate solution was injected intradermally. The injection sites were graded 24 hours later. At 48 hours, 0.1 mL of the appropriate solution was injected, and the injections were repeated 2 to 3 times a week for a total of 10 injections. Two weeks after the last injection, the animals received challenge injections at a previously untreated site. The challenge injections for the test and control groups consisted of 0.1 mL each of 0.01% and 0.05% solutions of AMP. The challenge sites were chemically depilated 24 hours after the injection; grading of the sites was performed 3 hours later and again at 48 hours. During the first 2 injections of the induction phase, 1% and 0.5% AMP solutions, respectively, caused necrotic lesions, and so the remainder of the induction injections were made with a 0.1% AMP solution. One guinea pig of the test group had a slight reaction at the 24-hour grading of the 0.05% AMP challenge site. This reaction had cleared by 48 hours. No reactions were noted in the test group at the second challenge. At the second challenge with AMP solutions, 4 guinea pigs of the saline control group had reactions to 0.05% AMP and 1 had a reaction to 0.01% AMP. All of these reactions had cleared by 48 hours. The positive control animals had the expected reactions. The authors concluded that AMP was not a sensitizer in guinea pigs.

Another sensitization potential study of AMP in guinea pigs was performed by the International Minerals & Chemicals Corporation.[64] The test was conducted in 3 groups of 10 male guinea pigs (250-300 g).[65] The test group was topically treated on shaved backs and flanks with 0.5 mL of 10% AMP solution applied under an occlusive patch. The positive control group received 0.5 mL of 0.3% DNCB and the negative control received 0.5 mL of saline in the same manner. The patches were removed from all animals 24 hours after the application, the skin was cleaned, and the patch sites were scored for reaction at 24 and 48 hours post application. The procedure was repeated every 48 hours, 2 to 3 times a week, with each group of animals for a total of 10 applications. Following a 2-week rest period, the guinea pigs received challenge patches on virgin sites. The test group and the negative control group were patched with 0.5 mL of 2.5% and 5.0% AMP solution. The positive control group and the negative control group were patched with 0.3% and 0.03% DNCB. After 24 hours, the patches were removed and the sites were cleaned and depilated. Three hours after depilation and 48 hours later, the challenge sites were scored for skin reactions. During the first 2 patches of the induction phase, the 10% AMP solution was found to be mildly irritating to all the animals in the test group. Because of this, the concentration of AMP was lowered to 5% for the remaining 8 topical application. In the positive control group, DNCB caused mild to strong skin reactions at all 10 applications. One animal in the positive control group died on day 6 from a lung infection. During the challenge phase, the test group and the negative control did not have any observable skin reactions from the AMP solution at 24 hours; however, at the 48-hour scoring, 2 animals in the negative control group had mild skin reactions. In the positive control group that was patched with 0.3% DNCB, 9 animals at the 24-hour scoring and 7 animals at the 48-hour scoring had skin reactions. The negative control group had 4 animals at the 24-hour scoring period with skin reactions and none at the 48-hour scoring. It was concluded that AMP was nonsensitizing under these conditions.

Ocular Irritation

Aminomethyl propanol. An ocular irritation study of AMP-Regular and AMP-95 was conducted using Draize techniques.[66] The eyes of 6 rabbits (strain not specified) were instilled with an unspecified amount and concentration of the test materials and were not rinsed. The eyes were scored at 110, the highest score possible, in all rabbits at both the 3-hour and 24-hour evaluation. Vision was destroyed in all the rabbits. Another test group of 6 rabbits received 0.1 mL of materials for either a 15-second or 30-second exposure period followed by a 30-second wash. Scores for AMP-Regular were

69.3 and 89.3 for the 15-second and 30-second exposures, respectively. Scores for AMP-95 were 69.6 and 82.6 for the 15-second and 30-second exposures, respectively. It was concluded that flushing had little beneficial effect following exposure to these materials and that AMP-Regular and AMP-95 were severe ocular irritants.

Twelve New Zealand White rabbits received a single 1-second spray, from a distance of 4 inches, of a hair spray containing 0.25% AMP.[67] The eyes of 6 of the rabbits were rinsed 30 seconds after the spraying. The animals were observed for 3 days. Two of the 6 rabbits of the no-rinse group had signs of irritation. One had slight iritis and conjunctivitis on day 1, with the conjunctivitis continuing through day 2 and clearing by day 3. The second rabbit had slight corneal opacity, iritis, and conjunctivitis; the corneal opacity had cleared by day 2 and the remainder of the irritation had cleared by day 3. Three rabbits of the rinsed group had slight conjunctivitis on day 1, which was cleared by day 2.

A second test following the protocol described in the previous paragraph was performed with a hair spray containing 0.58% AMP.[68] Of the rabbits that did not have their eyes rinsed, 3 had slight conjunctivitis on day 1; the conjunctivitis had cleared by day 2 in 2 of the rabbits and by day 3 in the third. The remaining 3 rabbits of the group had no reactions. Of the rabbits receiving a rinse, 1 had slight corneal opacity and conjunctivitis on day 1. The opacity had cleared by day 2, and the conjunctivitis cleared by day 3. None of the other rabbits of the rinsed group had adverse reactions.

Five New Zealand White rabbits received a single spray of a formulation (pH 8.3) containing 0.26% AMP.[69] The spray was directed from a distance of 6 inches from the left eye; the right eye was untreated and served as a control. Observations of the eyes were made at 1 and 24 hours and at 3, 4, and 7 days post exposure. At 1 hour, 2 rabbits had slight conjunctivitis and dull corneas that cleared by 24 hours. A third rabbit had slight conjunctivitis at 1 hour that also cleared by 24 hours. The fourth rabbit had slight conjunctivitis that persisted through 24 hours and was cleared by day 3. The fifth rabbit had no reaction. All rabbits had negative fluorescein stains 7 days after exposure to the test material. Details pertaining to the control eyes were not available. The spray containing 0.26% AMP was minimally irritating when not rinsed from sprayed rabbit eyes.

A hair spray containing 0.59% AMP was instilled into the eyes of 12 New Zealand White rabbits.[70] The volume of the material tested was 0.1 mL. Six of the rabbits received no eye rinse, whereas the eyes of the other 6 were rinsed 30 seconds after instillation of the test material. The rabbits were observed for 3 days after the instillation. Of the rabbits that did not receive eye rinses, 1 had scattered areas of opacity over most of the cornea as well as slight redness and chemosis on day 1. On day 2, this rabbit had obvious translucent areas over a small part of the cornea, and by day 3 the eye appeared normal. The remaining rabbits in the test group had no ocular reaction. Of the rabbits that received eye rinses, 1 rabbit had scattered areas of opacity over a small portion of the cornea and moderate chemosis, both of which had cleared by day 2. None of the other rabbits had adverse reactions. The hair spray containing 0.59% AMP was considered a mild ocular irritant to rabbits under the conditions of the test. Rinsing reduced the extent of the irritation.

In a limited summary, CTFA stated that AMP at a concentration of 0.25% in an aqueous vehicle caused slight transient irritation when instilled in the eyes of rabbits with and without rinsing.[13] The irritation had cleared by days 2 and 4, respectively.

A cosmetic formulation containing 0.22% AMP-95 was tested in 6 rabbits for eye irritation potential.[71] The test material was not rinsed from the eyes of the rabbits, and the reactions were graded on days 1 to 4 and on day 7 after instillation. Three different rabbits had conjunctivitis, 1 each on days 1 to 3. No reactions were observed on days 4 and 7. The formulation containing 0.22% AMP-95 had a mild eye irritation potential according to the Draize classification system.

A bovine corneal opacity and permeability test was performed using a waving gel containing 6.3% AMP.[72] Five bovine corneas were treated with 0.75 mL of test product. Opacity measurements and sodium fluorescein permeability were determined. A corrected mean opacity score was calculated to be 0.5. The corrected mean optical density (permeability measurement) was 0.008. The in vitro score was 0.62 (mild ocular irritant) for the test material. No further details are available.

Because these studies lacked a vehicle control, the irritation cannot be conclusively attributed to AMP. In the absence of other data, however, these results need to be considered.

Aminomethyl propanediol. A hair spray containing 0.40% AMPD was sprayed into the left eye of each of 5 New Zealand White rabbits for a duration of 1 second.[73] The right eyes served as controls. The eyes were observed for signs of irritation at 1 and 24 hours and on days 2, 3, 4, and 7. All of the rabbits had severe iritis and slight conjunctivitis at 1 hour. In 4 of the rabbits this was reduced at 24 hours and cleared by day 2. In the fifth rabbit, the severe iritis persisted, along with the slight conjunctivitis, through day 2 and was cleared by day 3.

A hair care product (0.1 mL) containing 0.715% AMPD was instilled into the left eye of each of 10 New Zealand White rabbits.[74] Half of the rabbits had their eyes rinsed 4 seconds after instillation of the test material. Ocular reactions were graded at 1 and 24 hours and on days 2, 3, 4, and 7. Sodium fluorescein examinations were performed on day 7 as well as at other times during the study as necessary. One rabbit of the nonrinsed group had moderate conjunctivitis at 1 hour, clearing by 24 hours. Two rabbits had moderate conjunctivitis that diminished steadily and was cleared by day 3. One rabbit had moderate iritis and conjunctivitis at 1 hour; the iritis had cleared by 24 hours and the conjunctivitis by day 2. The fifth rabbit had moderate iritis at 1 hour, clearing by 24 hours. In addition, this rabbit had moderate conjunctivitis at 1 hour; this reaction gradually diminished through day 4 and was clear by day 7. Two of the rabbits of the rinsed eye group had moderate iritis and conjunctivitis, with the iritis clearing by 24 hours and

the conjunctivitis diminishing at 24 hours and clearing by day 2. Two rabbits had moderate conjunctivitis at 1 hour, clearing by 24 hours. The fifth rabbit had moderate conjunctivitis, which had diminished at 24 hours and cleared by day 2. The rabbits of both test groups had negative fluorescein dye examinations on day 7.

Reproductive and Developmental Toxicity

Aminomethyl Propanol

A reproductive and developmental toxicity study of AMP hydrochloride salt was performed on groups of 12 male and 12 female CD rats, 8 weeks of age.[75] AMP was administered to rats via diet at doses of 0, 100, 300, or 1000 mg/kg of body weight per day. The males were dosed 2 weeks prior to breeding, during breeding, and after until necropsy on day 38. The females were dosed 2 weeks before breeding and during breeding and gestation until day 4 postpartum. They were killed and necropsied on day 5 postpartum. General toxicity and reproductive effects were evaluated (cage side observations twice daily, clinical examinations weekly), with body weights and food consumption monitored throughout the study. Organ weights were measured, and a histopathological examination of tissues was conducted at necropsy in the adult rats. Litters were measured for size, pup survival, weight, and physical abnormalities after delivery.

No mortalities were observed in any groups. The male rats that received 1000 mg/kg/d in their diet had increases in absolute and relative liver weights. Very slight microvacuolation of periportal hepatocytes was also observed, with and without vacuolization of hepatocytes consistent with fatty change. The male rats in this dose group also had increased absolute and relative kidney weights, but there were no histopathological effects. The female rats in all test groups had increased incidences of microvacuolization of the hepatocytes when compared with the controls, but there were no significant changes in the liver weights. No effects on mating or conception were observed. However, a dose-related increase in embryo resorption was noted. The NOEL for general toxicity in males was 300 mg/kg/d; the NOEL for general toxicity in females could not be determined because of the effects on the liver. Complete litter resorption was seen in all females in the 1000 mg/kg/d dose group. In the 300 mg/kg/d dose group, resorption was 70%. In the control group, resorption was 10%. The 300 mg/kg/d dose group also had decreased litter size, increased pup body weight, and decreased gestation body weight and body weight gain. No treatment-related fetal effects were observed in the 100 mg/kg/d dose group. Litters had no visible morphologic alterations.

Carney and Thorsrud[76] performed a dermal developmental toxicity study of 94.85% AMP in CRL:CD(SD) female rats. AMP (pH ~9.5) was administered once daily (dose volume of 1 mL/kg body weight; each exposure was ~6 hours) to 4 groups of 26 time-mated females (10-11 weeks old, 200-250 g) via dermal wrapping at dose levels of 0, 30, 100, or 300 mg/kg/d from gestation days 6 to 20. The rats were observed twice daily, and body weights and food consumption were monitored. After the wrapping material was removed each exposure period, test sites were graded for erythema, edema, scaling, and fissuring. On the last day of dosing (3 hours after exposure), blood samples were collected from 4 rats in each dose group in order to determine the amount of dermal absorption of AMP. All rats were killed on gestation day 21 and necropsied. The reproductive organs were studied in detail, and the number and position of implantations, viable fetuses, dead fetuses, and resorptions were recorded. Fetuses were examined and measured for variations or malformations, and the sex and fetal body weights were recorded. No signs of systemic toxicity were noted during the treatment period. There also were no significant differences in body weight and feed consumption in the dose groups compared with the control group. Blood sampling indicated that dermal absorption of AMP occurred in a dose-responsive manner. A disproportional increase in mean blood concentration at 300 mg/kg/d was thought to be due to a compromised skin barrier. Localized dermal effects were most pronounced in the 300 mg/kg/d dose group: 1 female had very slight edema from gestation days 6 to 13, and almost all of the rats (92%) in this dose group had slight scaling, with 36% of the rats having moderate to severe scaling during the last half of the treatment period. One, 2, and 7 rats in the 0, 30, and 100 mg/kg/d dose groups, respectively, had slight scaling that was not considered adverse. Scabbing was mainly observed in the 300 mg/kg/d dose group, with 77% of the rats in this group having scabs on up to 25% of the test site. Rats in the lower dose groups did not have scabbing that was considered to be toxicologically significant. At necropsy, there were no significant gross findings. One rat in the 300 mg/kg/d dose group had a hemorrhagic placenta in the right uterine horn that correlated with the occurrence of red vulvar discharge on gestation day 19. No other adverse effects were observed in this rat, which produced a normal litter, so the finding was considered not related to treatment. There were no significant treatment effects on reproductive parameters and fetal development. The small number of malformations observed in the fetuses did not follow a pattern consistent with treatment. The maternal no observable adverse effect level (NOAEL) was 100 mg/kg/d and the NOEL for fetuses was 300 mg/kg/d.

Genotoxicity

Microbial Assays

Aminomethyl propanol. A plate assay mutagenicity test, with and without metabolic activation, was performed using AMP and *Saccharomyces cerevisiae* strain D4 and *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100.[77] Positive activation and nonactivation controls were used; the controls were positive for either frameshift or base-pair substitution mutations. AMP was tested over a range of concentrations from 0.01 to 5 μL. The high dose produced some toxic effects, and the low dose was below a toxic level.

The results indicated that AMP was not mutagenic, with and without metabolic activation, under the conditions of the test.

Wagner and Bonvillain[78] tested the mutagenicity of AMP (98.81% pure) in a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA. The assays were performed with and without the presence of Aroclor-induced rat liver S9.[78] The study was performed in 2 phases: a preliminary toxicity assay, which established the dose ranges used in the second phase, and a mutagenicity assay. Both phases used the plate incorporation method. In both phases, water served as the solvent at 100 mg/mL. In the first phase, the maximum dose of AMP was 5000 µg per plate. No precipitates or significant toxicity was observed in this phase of the study, with and without the metabolic activation. In the second phase, 5000 µg AMP per plate was again the maximum dose. The assay consisted of both an initial and a confirmatory stage. Neither precipitates nor significant toxicity was observed in either stage of this phase, with and without metabolic activation. It was concluded that AMP was negative for mutagenic activity.

Aminomethyl propanediol. RCC NOTOX tested AMPD for mutagenic potential using *S typhimurium* strains TA1535, TA1537, TA98, and TA100 to detect frameshift and base-pair substitution-type mutations.[79] AMPD was tested at concentrations of 100, 333, 1000, 3330, or 5000 µg per plate, with and without metabolic activation. The test was performed twice. There were no dose-related increases in the number of revertants in either study over the concentration range tested, and AMPD was not considered mutagenic under the conditions of the study.

Mammalian Cell Assays

Aminomethyl propanol. The mutagenic potential of AMP was studied by San and Clarke[80] in an L5178Y/TK$^{+/-}$ mouse lymphoma assay with and without metabolic activation. The study was performed in 2 phases, with the first phase, a preliminary toxicity assay, establishing the dose range for the mutagenesis assay of the second phase, which was made up of an initial mutagenesis assay and an independent repeat assay. The maximum concentration of AMP in the first phase was 5000 µg/mL, where substantial toxicity (growth was $\leq$50% of the solvent control) was observed, with and without metabolic activation. The dose range in the second phase was 500 to 5000 µg/mL. In the initial and the independent repeat mutagenesis assay, no treated cultures had mutant frequencies that were at least 55 mutants per 10^6 clonable cells over the control. There was no dose-response trend in either assay. Cloned cultures exhibited toxicity at doses 1500 µg/mL or greater without activation and at 3500 µg/mL with activation in the initial assay. Toxicity in the independent repeat assay was observed at 2500 µg/mL or greater without activation and at 3500 µg/mL with activation. AMP was concluded to be negative in this mutagenesis assay.

Animal Assays

Aminomethyl propanol. Gudi[81] studied the mutagenic effects of AMP (>95% pure) in a mouse micronucleus assay.[81] The assay was performed in 2 phases: phase I consisted of a pilot assay and toxicity study to set the doses for phase II, the micronucleus assay. In both phases of the study, test and control material were administered at a volume of 20 mL/kg body weight by a single intraperitoneal injection. In the pilot assay, male mice (species and number not specified) were dosed with 1, 10, 100, or 1000 mg of AMP per kilogram of body weight, and both male and female mice were dosed with 2000 mg/kg. Mortality occurred in 2 of 2 male mice in the 1000 mg/kg dose group and in all mice (5/5 of each sex) in the 2000 mg/kg dose group.

In the toxicity assay, male and female mice were dosed with 200, 400, 600, or 800 mg of AMP per kilogram of body weight. Mortality occurred in all mice (5/5 of each sex) in the 400, 600, and 800 mg/kg dose groups and in 3 of 5 males and 5 of 5 females in the 200 mg/kg dose group. Clinical signs following dosing were lethargy in both sexes at all dose levels and piloerection in males and females and crusty eyes in males in the 200 mg/kg dose group. From this toxicity assay, the high dose for the micronucleus test was set at 60 mg/kg (80% of $LD_{50/3}$). Male and female mice were dosed with 16, 30, or 60 mg of AMP per kilogram of body weight in the micronucleus assay. No mortality was observed. Lethargy was observed in both sexes at 60 mg/kg. Bone marrow cells were collected at 24 and 48 hours post treatment and were examined microscopically for micronucleated polychromatic erythrocytes (PCE). Reductions of up to 10% in the ratio of PCE to total erythrocytes were observed in some AMP-treated groups compared with the controls. No significant increases in micronucleated PCE in any AMP treatment groups of either sex were observed ($P > .05$). It was concluded that AMP was not a mutagen in a mouse micronucleus assay.

Clinical Assessment of Safety

Irritation

Aminomethyl propanol. The skin irritation potential of a cosmetic formulation containing 0.22% AMP-95 was examined in a single-insult, occlusive patch test using 15 panelists.[82] One panelist had an equivocal reaction ($\pm$), resulting in a group PII of 0.03 (8.0 maximum). The cosmetic formulation containing 0.22% AMP-95 had a negligible primary skin irritation potential.

Aminomethyl propanediol. A hair spray containing 0.40% AMPD was tested for primary irritancy in 15 human subjects.[83] The patches were applied to the arms of the panelists. The test was referred to as a 5-hour, 4-day test with the test beginning on Monday and the readings being made on the mornings of Tuesday, Wednesday, Thursday, and Friday. Four panelists had no reactions. There were scattered instances of questionable responses in 9 panelists, with 7 having 1 questionable response and the remainder having 2 questionable responses. In addition,

1 panelist had slight redness on day 4, and 1 panelist had slight redness on days 2 to 4.

Sensitization

Aminomethyl propanol. A conditioning hair mousse containing 0.22% AMP-95 was tested for allergic contact sensitization potential in 97 panelists.[84] None of the panelists (86 females and 11 males) had skin conditions or medical histories that would interfere with the purpose of the study.

Ten formulations were tested simultaneously; 5 patches were placed on either side of the upper back, next to the midline. Only if there was a severe reaction was a patch removed. Approximately 0.1 mL of the test material was applied to the patch. The patches were applied every Monday, Wednesday, and Friday for 3 weeks. The patches were removed by the panelists 24 hours after application, and the patch sites were graded prior to the application of the new patch. The final induction patch sites were graded prior to the challenge phase of the study, which began week 6 of the study. The challenge sites were graded 24 and 48 hours after patch removal. Thirteen panelists had reactions during the induction phase of the test. Of these 13, 9 had single reactions, 2 had 2 reactions each (patches 4 and 7; 1 and 8), 1 had 3 reactions (patches 1, 6, and 7), and 1 had 4 reactions (insults 2, 3, 8, and 9). All of the reactions that occurred during the induction phase were recorded as barely perceptible. Another panelist had a barely perceptible reaction at the 24-hour grading of the challenge phase; the results of the 72-hour grading were not available. The conditioning hair mousse containing 0.22% AMP-95 did not have allergic contact sensitization potential.

TKL Research, Inc[85] performed a repeated insult patch test (RIPT) in 50 volunteer subjects using a hairstyling gel containing 3.8% AMP. During the induction phase, 0.02 mL was applied to the infrascapular region of the subjects' backs with an occlusive Finn Chamber patch.[85] The patches were removed after 48 hours, the sites were evaluated, and new patches were reapplied until a total of 9 consecutive applications were recorded. During the induction phase, 1 subject had a minimal to doubtful response for patches 6 to 9 and another subject had a minimal to doubtful response for patch 6. After the last patch application, the subjects were given a 10- to 15-day rest period. The challenge phase began in the sixth week of the study, with patches applied to the induction phase sites as well as to virgin sites on the subjects' backs. The patches were removed after 48 hours and the application sites were scored at 48 and 72 hours post application. There was no evidence of sensitization from the hairstyling gel formulation containing 3.8% AMP.

AMA Laboratories, Inc[86] reported on an RIPT evaluating a hair dye base containing 3.5% AMP in 108 subjects. The test material was diluted 50% in distilled water to a final concentration of 1.75%. During the induction phase, semiocclusive patches with 0.2 mL of the test material were applied to the infrascapular region of the back of the subjects for 24 hours. The applications were made every Monday, Wednesday, and Friday until a total of 9 applications were made during 3 consecutive weeks. Following a 10- to 14-day rest period, a challenge patch was applied to a virgin site on the subjects' backs for 24 hours. Reactions were scored 24 and 48 hours after the application for signs of sensitization. No reactions were observed, and it was concluded that the test material was a nonprimary irritant and a nonprimary sensitizer.

Harrison Research Laboratories, Inc[87] performed an RIPT evaluating a hair dye containing 1.5% AMP. Of 120 initial subjects, 108 completed the investigation. In the induction phase of the study, a Webril patch with 0.2 g of the test material was affixed occlusively to the left back of the subjects for 24 hours. Another patch was affixed after a 24-hour rest period (48 hours on weekends) for 9 applications over 3 consecutive weeks. A 2-week resting phase preceded the challenge phase patch that was adhered to the right (virgin) side of the subjects' backs for 24 hours. The site was scored for irritation reactions at patch removal and again at 48, 72, and 96 hours post patching. During the induction phase, 1 subject had a 1+ edema reaction in 2 different patch sites. The remaining patch applications for the induction phase were suspended for this subject. In the challenge phase, this subject exhibited erythema and edema at 72 hours and erythema and dryness at 96 hours. The subject was then given an open patch test with the test material and breakdown products. Dermal sensitization was not sustained during this procedure. Other subjects exhibited a low-level, transient ($\pm$/1) reaction during the induction phase. Another subject had faint, minimal erythema at the 48- through 96-hour observation periods of the challenge phase.

Another RIPT conducted on a body polish (rinse-off) containing 1.625% AMP was reported by Consumer Product Testing Co.[88] Of 114 initial subjects, 105 completed the study. The test material was prepared as a 1% dilution using distilled water. During the induction phase, approximately 0.2 mL of the prepared material was applied to the interscapular region of the subjects with an occlusive patch for 24 hours. The patches were applied 3 times a week for a total of 9 applications. After the final induction patch, subjects were given a 2-week rest period before a challenge patch was applied to a virgin site adjacent to the induction site. The patch was removed after 24 hours, and the site was scored for reaction at 24 and 72 hours post application. It was concluded that the test material containing AMP did not indicate potential for dermal irritation or allergic contact sensitization.

Harrison Research Laboratories, Inc[89] performed an open RIPT with the dyeless base of a hair dye product containing 7% AMP. Of 121 initial subjects, 99 completed the investigation. In the induction phase, approximately 0.2 g of the test material was applied to a test site on the left side of the subjects' backs and allowed to air dry. The subjects were instructed to keep the test area dry and untouched for 24 hours. Another application of test material was made 48 hours after the previous application (72 hours if the application was performed on a Friday) until a total of 9 applications were made. The test sites were observed following each application, and any reactions were scored and recorded. There was a 2-week rest period between the induction and challenge phases of the

study. In the challenge phase, approximately 0.2 g of test material was applied to a virgin site on the right side of the subjects' backs and allowed to air dry. Again, the subjects were instructed to keep the site dry and untouched. The challenge sites were observed 24, 48, 72, and 96 hours post application, and any reactions were scored and recorded. One subject had faint, minimal erythema (±) at the ninth induction reading. This subject did not have any reaction in the challenge phase. No other reactions were observed in any of the other subjects during the induction and challenge phases. It was concluded that the test material containing 7% AMP was not a dermal sensitizer in humans.

The Consumer Product Testing Company[90] performed an RIPT with a body polish (rinse-off) containing 1.65% AMP on 113 subjects (108 subjects completed the study). The test material was prepared as a 1% dilution using distilled water. Approximately 0.2 mL of the prepared material was applied to the interscapular region of the subjects with a semiocclusive patch for 24 hours. The patches were applied 3 times a week for a total of 9 applications during the induction phase of the study. Following a 2-week rest period after the final induction patch, a challenge patch was applied to a virgin site adjacent to the induction patch site. The patch was removed after 24 hours, and the site was scored for reaction at 24 and 72 hours post application. The study did not indicate a potential for dermal irritation or allergic contact sensitization in a test material containing 1.65% AMP.

Aminomethyl propanediol. A cosmetic formulation containing 0.073% AMPD was tested for sensitization potential in a group of 30 human test subjects using an open RIPT.[91] The test material was applied to the arm daily, 4 days per week for 2 weeks, alternating arms daily. In addition, an occlusive patch was applied on the first day of the test. After the 2-week application period, there was a 2-week nontreatment period. After this 2-week period, the test subjects were challenged with a reapplication of the formulation to the test site along with an occlusive patch at an adjacent site. The original patch, challenge patch, and open challenge test sites were read at 24, 48, and 96 hours. No reactions were observed in any of the test subjects. The formulation containing 0.073% AMPD was neither a primary irritant nor a sensitizer, and the formulation was safe under the conditions of the study.

A modified RIPT of a cosmetic formulation containing 0.50% AMPD was performed on a panel of 39 women and 20 men.[92] The test material (0.5 mL) was applied to a semiopen patch on the arm of each panelist every Monday, Tuesday, Wednesday, and Thursday for 2 weeks. The patch sites were graded approximately 24 hours after application. In addition, a closed patch was applied to each panelist on the first day of the study and on the day of challenge. No patches were applied for 2 weeks after the induction phase. On the Monday following the nontreatment period, challenge patches were applied to the original test site and an adjacent site; the second closed patch was also applied at this time. The challenge sites were graded 1, 2, and 4 days after application. Slight erythema was noted at 1 adjacent application site at each of the grading times, but it was not clear whether these reactions occurred in the same panelist. The formulation containing 0.50% AMPD was not a sensitizer under the conditions of the test.[92]

A RIPT study by Consumer Product Testing Company[93] tested for the irritation and sensitization potential of a mascara containing 1.92% AMPD using 113 subjects (107 subjects completed the study). A semioccluded patch was used to apply 0.2 mL of the test material to the interscapular region of the subjects, and the patch was affixed 24 hours before removal. The induction phase consisted of patch applications 3 times a week for a total of 9 applications. Following a 2-week rest period, a challenge patch was applied to a virgin site adjacent to the induction patch site. The challenge patch was removed after 24 hours, and the site was scored for reaction at 24 and 72 hours post application. No indication of potential dermal irritation or allergic contact sensitization by the test material containing AMPD was observed.[93]

Case Studies

Aminomethyl propanol. Two cases of airborne contact dermatitis were described by Cipolla et al[94] in patients who were exposed to AMP 100 in a cosmetic company during production of a hair dye. The patients had periorbital erythema and itching skin, which improved when they were away from their workplace (weekends and holidays). Patch testing with AMP 100 and other substances in the production line was performed on the 2 patients and on 8 asymptomatic subjects from the same company (2 of the 8 were on the same production line as the 2 patients). The dilutions were 0.1%, 0.5%, 1%, 2%, 5%, 10%, and 20% in distilled water and in ethyl alcohol, respectively. The patch tests proved positive (+/++) in the 10% and 20% dilutions of both distilled water and ethyl alcohol in all the subjects.[94]

Summary

AMP and AMPD are substituted aliphatic alcohols used as cosmetic ingredients. Isopropanolamine is another cosmetic ingredient and is a close structural analog to AMP. A CIR safety assessment of isopropanolamine found the ingredient safe as used as long as it was not used in products containing N-nitrosating agents.

AMP and AMPD occur in solid and liquid forms. AMP is miscible in water and soluble in alcohols, whereas AMPD is soluble in both water and alcohols.

Both AMP and AMPD function as pH adjusters in cosmetic products. AMPD is also a fragrance ingredient. AMP is used in concentrations up to 7%, and AMPD is used in concentrations up to 2%.

Several acute inhalation studies were performed with cosmetic formulations containing AMP as well as with AMP in alcohol and propellant. The study results indicated that AMP was nontoxic by inhalation. A hair spray containing 0.50% AMPD was also nontoxic to rats.

When rats were exposed to atmospheres of a hair spray containing 0.58% AMP 1 hour per day, 5 days per week over a period of 2 weeks, no toxic effects resulted from the treatment.

When AMP solutions with pHs of 7 or 11+ were administered to rats by stomach tube, it was found that any mortality was due to the alkalinity of the AMP solutions.

In a subchronic oral toxicity study of AMP in beagle dogs, only the high-dose group (62.5 mg/kg) did not gain weight during the study. There were changes in some clinical chemistry parameters in the dogs of the high-dose group. Liver and liver-to-body weight ratios were increased, and tan and mottled livers were observed at necropsy in some dogs of the high-dose group. Microscopic lesions included vacuolation, lipid deposits, and bile duct hyperplasia in the livers of the dogs in the high-dose group as well as in 1 dog of the low-dose (0.63 mg/kg) group.

Cynomolgus monkeys were exposed to hair sprays containing 0.40% AMP under static and dynamic conditions in a 90-day subchronic inhalation toxicity study. The only compound-related adverse effects were that the monkeys exposed under dynamic conditions did not gain weight during the study and the monkeys exposed under either condition had lowered serum CO_2 levels.

In another 90-day study, cynomolgus monkeys exposed 1 hour per day to a hair spray containing 0.21% AMP showed some histopathologic changes in the pulmonary tissues. A slight to moderate increase was found in hepatocellular lipids in all test animals. Pulmonary alveolitis was noted in the high-dose monkeys.

In a subchronic inhalation study, rats were exposed to an aerosolized form of a pump hair spray containing 0.21% AMP for 4 hours per day, 5 days per week. The hair spray was not toxic under the exaggerated inhalation conditions of the test.

When both albino rats and Syrian Golden hamsters were exposed in a 13-week subchronic inhalation toxicity study to hair spray formulation containing 0.1350% AMPD for 4 hours per day, 5 days per week, no significant compound-related adverse effects were observed.

The NOEL in a chronic dietary toxicity study of AMP in beagle dogs was 110.0 ppm or greater.

In numerous primary irritation studies, cosmetic formulations containing varying concentrations of AMP were nonirritating to minimally irritating to abraded and nonabraded rabbit skin. AMP (0.25%) in an ethanol vehicle was nonirritating to rabbit skin. Cosmetic formulations containing AMPD were also nonirritating to minimally irritating to rabbit skin.

In an intradermal study, 0.1% AMP was not a sensitizer in guinea pigs. In a topical sensitization study, 5.9% AMP was not a sensitizer in guinea pigs.

An unspecified concentration of AMP was found to be a severe ocular irritant in rabbits. At concentrations ranging from 0.22% to 0.59%, AMP in cosmetic formulations or in an aqueous vehicle was a minimal to mild ocular irritant. The degree of irritation was reduced by rinsing the eyes after exposure to the formulations. A bovine corneal opacity and permeability test classified a waving gel containing 6.3% AMP as a mild ocular irritant. Cosmetic formulations containing 0.40% AMPD were moderate ocular irritants.

In an oral reproductive and developmental toxicity study of AMP hydrochloride salt in rats, the NOEL for general toxicity in males was 300 mg/kg/d. The NOEL for general toxicity in females could not be determined because of effects on the liver. Dose-related increases in embryo resorption were noted. The NOEL for fetuses was 100 mg/kg/d.

A dermal developmental toxicity study of 94.85% AMP in rats indicated a maternal NOAEL of 100 mg/kg/d and a NOEL for fetuses of 300 mg/kg/d.

AMP was not mutagenic, with and without metabolic activation, in *S cerevisiae* strain D4, in *E coli* strain WP2 uvrA, and in *S typhimurium* strains TA 1535, 1537, 1538, 98, and 100. AMPD was not mutagenic, with and without metabolic activation, in *S typhimurium* strains TA 1535, 1537, 98, and 100. AMP was also not mutagenic in a mouse lymphoma mutagenesis assay and in a mouse micronucleus assay.

In a clinical study, a cosmetic formulation containing AMP-95 was not a primary dermal irritant. In a primary irritancy test of a cosmetic formulation containing AMPD, scattered incidences of questionable responses were observed in two thirds of the panelists. In addition, 2 of 15 panelists had slight redness at least once during the observation period.

A cosmetic formula containing 0.22% AMP-95 was not an allergic contact sensitizer when tested using a panel of 97 subjects. Sensitization did not occur in other RIPT studies of cosmetic formulations containing AMP ranging from 1.5% to 7.0%. A cosmetic formulation containing 0.073% AMPD was not a primary irritant, and it was neither a fatiguing agent nor a sensitizer. In another study, a cosmetic formulation containing 0.50% AMPD was not a sensitizer.

Two cases of airborne contact dermatitis were reported in patients who were exposed to AMP 100 in the production line of a cosmetic company.

Discussion

The CIR Expert Panel considered that acute, short-term, subchronic, and chronic oral, inhalation, and dermal toxicity studies are adequate to support the safety of AMP and AMPD with respect to systemic toxicity end points. These ingredients did not produce significant toxicity to the reproductive systems or development of fetuses in animal studies. AMP and AMPD did not demonstrate genotoxicity in bacterial, mammalian cell, or animal assays.

In past ingredient safety assessments, the CIR Expert Panel has expressed concern over N-nitrosation reactions in ingredients containing amine groups. The 2 ingredients in this report, AMP and AMPD, are primary amines that are not substrates for N-nitrosation. However, these ingredients may contain secondary amines as impurities in finished products that may undergo N-nitrosation. Because of the possible presence of secondary amine contamination, the Expert Panel recommends that these ingredients should not be included in cosmetic formulations containing N-nitrosating agents.

In its earlier safety assessment, the Expert Panel determined that the available skin irritation and sensitization data at the time were able to support the safety of AMP and AMPD in cosmetic products up to a concentration of only 1%. The Expert Panel now has considered safety test data for a hairstyling gel containing 3.8% AMP; hair dye bases with 1.5%, 3.5%, and 7% AMP; and body polishes with 1.625% and 1.650% AMP and determined that these test materials did not cause dermal irritation or allergic contact sensitization in human subjects. In addition, the Expert Panel determined that a mascara with 1.92% AMPD did not cause dermal irritation or allergic contact sensitization. Although the reported use concentration of AMPD is 2% in mascara, the Expert Panel considers the new clinical data adequate to support safety to the higher concentration.

After reviewing inhalation toxicity data on AMP and AMPD, the Expert Panel determined that AMP and AMPD can be used safely in hair sprays because hair spray aerosols are nonrespirable.

Conclusion

The CIR Expert Panel concluded that AMP and AMPD are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment.

Authors' Note

The 2009 Cosmetic Ingredient Review Expert Panel members are Wilma F. Bergfeld, MD, FACP, Chair; Donald V. Belsito, MD; Curtis D. Klaassen, PhD; James G. Marks, Jr., MD, Ronald C. Shank, PhD; Thomas J. Slaga, PhD; and Paul W. Snyder, DVM, PhD. The CIR director is F. Alan Andersen, PhD. This report was prepared by Christina L. Burnett, CIR scientific analyst.

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036, USA.

Conflicts of Interest

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