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Final Report on the Safety Assessment of Aminomethylpropanol and Aminomethylpropanediol

AMP and AMPD are substituted aliphatic alcohols. AMP is used in cosmetic products at concentrations up to 10%, AMPD is used at concentrations up to 5%. AMP and AMPD when buffered, and orally administered, are practically nontoxic to rats and mice.[1]

In primary irritation studies, AMP and formulations containing AMP were, at most, minimally irritating to abraded and nonabraded rabbit skin. Cosmetic formulations containing AMPD were only minimally irritating to rabbit skin. AMP was not an intradermal sensitizer in guinea pigs. Cosmetic formulations containing AMPD and/or AMP were minimal to moderate ocular irritants.

AMP and AMPD were nonmutagenic, both with and without metabolic activation, in *Salmonella typhimurium* strains.

In clinical studies, AMP was neither a primary dermal irritant nor a contact sensitizer. AMPD was neither a primary irritant, fatiguing agent, nor sensitizer when tested in humans.

AMP and AMPD are highly alkaline in pure form, they are buffered in cosmetic formulations, and, therefore, the adverse reactions seen with the undiluted chemical would not be expected with the cosmetic product. The highest level of both AMP and AMPD for which test data were available was 1.0%, therefore the safe use of these two compounds should be limited to this test value. Neither ingredient should be used in cosmetic products containing nitrosating agents.

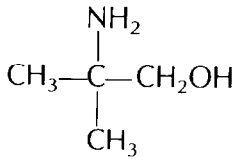
INTRODUCTION

The following report is a literature review on the chemistry, use, and toxicology of Aminomethylpropanol (AMP) and Aminomethylpropanediol (AMPD).

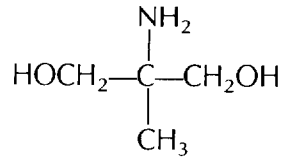
CHEMISTRY

Definition and Structure

Aminomethylpropanol (AMP) and Aminomethylpropanediol (AMPD) are substituted aliphatic alcohols with the following structures:[2]



AMP



AMPD

AMP (CAS No. 124-68-5) is also known as 2-amino-2-methyl-1-propanol[2] and isobutanolamine,[3] and commercially as AMP-Regular[2] and AMP-95 (a dilution of AMP-Regular, with 5% water),[4] while AMPD (CAS No. 115-69-5) is also known as 2-amino-2-methyl-1,3-propanediol,[2] aminobutylene glycol, and butanediolamine.[3]

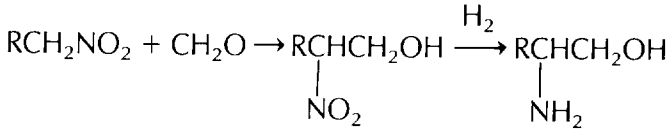
Properties

AMP is either a colorless liquid or a white crystalline solid,[3] though it may appear as a paste since its melting point is slightly above room temperature.[4] As a solid, AMP is odorless, while in liquid form it possesses a slight amine odor.[4] The molecular weight of AMP is 89.14, its melting range is 30–31°C and its boiling point is 165°C.[5] The flash point of AMP is 153°C.[6] At low temperatures, AMP has a low vapor pressure.[4] AMP has a density of 0.934 at 20°/20°C.[5] AMP is miscible with water, soluble in alcohols,[5] slightly soluble in aromatic hydrocarbons, and insoluble in aliphatic hydrocarbons.[4] The pH of a 0.1 M solution of AMP is 11.3.[3,5]

AMPD is either a white crystalline solid,[3] yellowish crystals,[7] or a clear liquid.[6] It has a molecular weight of 105.14, with melting and boiling ranges of 109–111°C and 151–152°C, respectively.[5] AMPD is soluble in water and alcohols,[5,7] and is insoluble in mineral oil.[7] The pH of a 0.1 M solution of AMPD is 10.8.[3,5]

Method of Manufacture

Both AMP and AMPD may be made by the condensation of the corresponding nitroparaffins with formaldehyde. After condensation, reduction is carried out to the β-aminoalkanols:[4]



The desired end product may then be isolated by distillation.[4]

Analytical Methods

Infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS) have been published for AMP.[8] The IR spectrum of commercial AMP closely matches the standard spectrum, with no evidence of foreign materials.[9] For AMPD, the infrared spectrum has been published.[8] Alkanolamines, both AMP and AMPD, can be determined in hair spray formulations, after acetylation, by gas-liquid chromatography.[10]

Impurities

No definitive report on impurities, including *N*-nitrosamines, was available.

Chemical Reactions

AMP can react with copper, brass, and aluminum, but will not react with steel or iron. With mineral acids, AMP can form ammonium salts; these salts are easily hydrolyzed by water, and will dissociate upon heating. Soaps containing AMP are important industrially as emulsifying agents.[4]

Aminohydroxy compounds react with the methyl ester of an organic acid in the presence of an alkaline catalyst, and at low temperatures and pressures to form amides. When this reaction is carried out at higher temperatures, oxazolines are produced. The aminohydroxy compounds 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 aminohydroxy compounds with aldehydes.[11]

USE

Cosmetic

Both AMP and AMPD are listed in the *Merck Index*[5] as emulsifying agents for cosmetic creams and lotions and, according to the *CTFA Cosmetic Ingredient Handbook*,[12] they are used as pH adjusters. In hair sprays, they are used as neutralizing agents to regulate the solubility, flexibility, and tackiness of the resin, usually in amounts of 2–15% of the resin.[10] They are used in gelling products where a polymer is required to function as a thickener, and they may also be used to form soaps in waterless hand cleaners, liquid hand soaps, shampoos, shave creams, and other creams and lotions.[13]

Data submitted to the Food and Drug Administration (FDA) in 1987 by cosmetic firms participating in the voluntary registration program indicated that AMP was used in a total of 161 cosmetic products (Table 1). Product types containing AMP included hair sprays, wave sets, other noncoloring hair preparations, hair dyes and colors (requiring a caution statement and patch test), face preparations, and eye area products, skin care preparations, and miscellaneous products. AMP was listed in a total of seven categories, with the greatest use in the categories of aerosol fixative hair sprays (83 products) and other hair preparations (38 products). AMP is used in concentrations ranging from ≤0.1% to >5–10% (3 products).[14]

AMPD was used in a total of 18 products (Table 2). Product types containing AMPD included aerosol fixative hair sprays, wave sets, and other noncoloring hair preparations, and makeup preparations including eye area makeup; a total of three product categories. The greatest use of AMPD was in aerosol fixative hair sprays (10 products). AMPD was used in concentrations of ≤0.1% (7 products), >0.1–1% (9 products), and >1–5% (2 products).[14]

The FDA cosmetic product formulation computer printout[15] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[16] Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic

TABLE 1. Product Formulation Data for Aminomethyl Propanol[14]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			>5–10	>1–5	≥1	>0.1–1	≤0.1
Hair sprays (aerosol fixatives)	174	83	—	2[a]	—	71	10
Wave sets	155	16	—	1[a]	—	14	1
Other hair preparations (noncoloring)	1185	38	—	1[a]	—	34	3
Hair dyes and colors (all types requiring caution statement and patch test)	915	6	3[a]	3[a]	—	—	—
Face preparations and eye area products	1013	5	—	—	5	—	—
Skin care preparations	1896	6	—	—	—	5	1
Miscellaneous products	291	7	—	—	7	—	—
1987 Totals		161	3	7	12	124	15

[a]According to voluntarily registered formulations, all uses above 1% involve neutralization of AMP with fatty acids of acidic polymer resins. Other uses also likely to involve neutralization.

formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to tenfold error in the assumed ingredient concentration.

Products containing AMP or AMPD may come into contact with the skin, eyes, and mucous membranes. Either ingredient may be inhaled when an aerosol hair spray is used. 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.

TABLE 2. Product Formulation Data for Aminomethyl Propanediol[14]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>1–5	>0.1–1	≤0.1
Hair sprays (aerosol fixatives)	265	10	—	4	6
Wave sets and other hair preparations (noncoloring)	337	5	—	4	1
Makeup preparations (including eye)	550	3	2[a]	1	—
1987 Totals		18	2	9	7

[a]According to voluntarily registered formulations, AMPD neutralized by reacting with excess of fatty acids. Other uses also likely to involve neutralization.

Noncosmetic

In industry, AMP and AMPD have a variety of uses. They are used in the synthesis of surface-active agents, vulcanization accelerators, and pharmaceuticals. They are also used as emulsifying agents in leather dressings, cleaning compounds and polishes, and as absorbents for acidic gases.[5] AMPD may be used to stabilize emulsions, though stability depends on the concentration of AMPD, the length of storage, and temperature.[17]

AMP also is used as an emulsifying agent in insecticides. Small amounts of AMP are used as pigment dispersers in water-based paints; in paints, AMP helps to stabilize pH, viscosity, and odor of the product. The salts of AMP and acidic polymers are used to make resins water soluble, and AMP salts are also used as catalysts for textile resins, coating resins, and adhesives. In boiler water, AMP provides protection for copper and steel, and absorbs CO_2 efficiently.[4] In cutting fluids, AMP is useful as an antimicrobial agent, especially against molds.[18] AMP is also listed as an indirect food additive for use, without restrictions, as a component of adhesives.[16]

GENERAL BIOLOGY

Biochemical Effects

In rats which were fed a choline-deficient diet, oxidative phosphorylation in the rat-liver mitochondria was uncoupled.[19] The explanation for the incidence of uncoupling was an increase in free fatty acids in the liver. When AMP was injected intraperitoneally in rats fed a choline-deficient diet, the uncoupling effect was reversed. The authors concluded that this reversal was due to the interference of AMP with the formation of free fatty acids from lipids. It was noted that the addition of AMP increased the fat content of the liver above that of rats fed a choline-deficient diet, suggesting that while choline deficiency inhibited "fat removal," AMP inhibited fat catabolism, resulting in an increase in the fat content of the liver. AMP appeared to interfere not only with lipid catabolism, but also with choline utilization and synthesis. The authors also cited evidence that AMP, or a metabolite of AMP, might become incorporated into phospholipids, and concluded that this may be the mechanism of action of AMP.

In another study in which rats were fed a choline-deficient diet, AMP (incorporated into the diet in micromolar amounts) increased the incidence of hemorrhagic kidneys and the amount of fat in the liver; the renal damage was dose dependent.[20] Ocular hemorrhages were noted in rats consuming the higher doses of AMP (actual amount not stated). Also at higher AMP doses, the amount of hepatic fat decreased; this was associated with a corresponding decrease in daily feed intake and body weight gain. The authors interpreted their results in light of evidence from other studies that indicated that AMP inhibited the incorporation of ethanolamine and dimethylethanolamine into rat hepatic phospholipids, and that because AMP was incorporated into the phospholipids, the amount of ethanolamine in the phospholipids available for conversion into choline was decreased. The authors also cited research that indicated that the *N*-methyl derivatives of ethanolamine could reduce the "antilipotropic effects" of AMP, with betaine, methionine, and ethanol having a similar, but weaker, effect.

Yue et al.[21] reported that the effect of aminoalcohols on choline uptake by mitochondria was relatively small compared to the effect on phosphate uptake. In

addition, the aminoalcohols had only a small effect on O_2 consumption, suggesting that mitochondrial membrane permeability changes were not the principal mechanism of inhibition by the aminoalcohols.

Bridges and Ricketts[22] stated that the degree to which aminoalcohols were incorporated into the phospholipids corresponded to the degree of similarity between the aminoalcohol and ethanolamine. For the most part, the aminoalcohols were incorporated into the phospholipids unchanged. The mechanism of incorporation was not clear; the authors postulated that either calcium-mediated direct exchange (which is known to occur in vertebrates) or a magnesium-dependent pathway described by Kennedy and Weiss,[23] or a balance between the two, may be responsible for the incorporation and final distribution of unnatural aminoalcohols in phospholipids.

DiPrisco and Strecker[24] found that AMPD hydrochloride, like phosphate, could change the inhibitory effects of thyroxine and other compounds from competitive to noncompetitive with respect to crystalline beef liver glutamate dehydrogenase.

In an *in vitro* study of the incorporation of [^{32}P]phosphate into the phospholipids of swine coronary and pulmonary arteries, Morin[25] found that AMP at a concentration of 0.1 mmol/ml caused an almost complete inhibition of the incorporation of [^{32}P] into all phospholipids studied. Inhibition was dose dependent. The inhibition by AMP of phosphatidylcholine was greater than for the other phospholipids studied, and inhibition of the incorporation of [^{32}P] into the phospholipids was more pronounced in the coronary arteries than in the pulmonary arteries at all AMP concentrations studied. The addition of choline in excess of AMP caused partial to complete reversal of the inhibition. In addition to inhibiting the net synthesis of phosphatidylcholine, AMP also inhibited, though to a lesser extent, the synthesis of sphingomyelin, phosphatidylserine, and phosphatidylethanolamine.

AMP also inhibited the incorporation of [^{32}P]phosphate into the phospholipids of rabbit and human endometrial tissues *in vitro*.[26] The results obtained in this study were similar to those obtained with the coronary and pulmonary arteries of swine.

In a study of plasma membranes of murine fibroblasts, Schroeder[27] found that ethanolamine analogues, including AMP, caused alterations in the morphology of the plasma membrane, as well as alterations in thymidine transport and hormone-stimulated adenylate cyclase activity. The analogs did not simply replace the phosphatidylethanolamine; either certain types of phosphatidylethanolamine were replaced or their asymmetric distribution was changed. The conclusion was that the ethanolamine analogs created "a more symmetric distribution of acyl chains in aminophospholipids across the surface membrane bilayer" than did choline analogs. The ethanolamine analogs increased the percent aminophospholipids found in the outer monolayer without increasing their total amount; the number of negatively charged phospholipids in the outer monolayer was also increased. The conclusion reached by the author was that "choline and ethanolamine analogs may alter or regulate the aminophospholipid asymmetry of LM [choline-requiring mouse fibroblast] cell plasma membranes."[27]

D-Serine-induced renal tubular necrosis in rats was studied by Kaltenbach et al.[28] Compounds which were structurally related to D-serine were reviewed to analyze a possible mechanism of action of D-serine on the rat kidney. Among the compounds tested were AMP and AMPD. Neither were nephrotoxic; in fact, AMP reversed the toxic effects induced by 2-amino-1-propanol (this compound's toxic effects were inconsistent).

Kaltenbach et al.[29] while reviewing the protective effects of various chemicals against D-serine- and D-2,3-diaminopropionic acid-induced renal tubular necrosis in rats, found that AMP did not have a protective effect against either of these compounds.

In a study on the effects of lysosomotropic amines on protein degradation and synthesis in rat hepatocytes,[30] it was found that both AMP and AMPD inhibited degradation and synthesis, although inhibition of synthesis could be somewhat reversed with the addition of amino acids and pyruvate. This latter observation suggested that the apparent inhibition of protein synthesis by these compounds was a result of their inhibitory effects on protein degradation.

Distribution and Excretion

Yue et al.[31] studied the fate of [^{3}H]AMP when 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 h before the injection of [^{3}H]AMP, and continued on this diet until they were sacrificed at 30 min, 1, 2, 3, 6, 24, or 96 h postinjection. The rats fed the choline-adequate diet (*ad libitum*) followed the same protocol. Thirty minutes after the i.p. injection, tritium 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 the exception of the 6-h 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 which were chromatographed concurrently.

From 0.5–6 h, 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 h, 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 h, 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 h, 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 tritium in all subcellular fractions. The cytosol of both the liver and kidneys contained the most tritium. In the choline-adequate diet rats, the radioactivity in the kidneys and liver decreased with time while 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 especially striking in the liver microsomal fraction. The authors also noted that the radioactivity found in the cytosol was not free AMP since no free AMP was identified after 30 min, 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 than just with the phosphatidyl derivative.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

A reported approximate LD_{50} for AMPD in the deer mouse was 0.140 g/kg,[32] and in albino mice all animals survived a dose of 5.0 g/kg.[13] For fasted young adult male rats, the LD_{50} of AMP was 2.90 ± 0.14 g/kg.[33] The oral LD_{50} values in Cox strain albino mice for both AMP and AMP-95 were estimated at 2.15 ± 0.2 g/kg and 2.4 ± 0.089 g/kg, respectively.[34]

The acute toxicity of AMP in both rats and monkeys was studied.[35] Four groups of ten Long-Evans rats, with equal numbers of each sex, were fed a diet of lab chow and water *ad libitum*. The rats received AMP by gavage daily for 5 days at the following doses: 0, 0.5, 1.0, and 2.5 g/kg. All rats were observed for 15 days, at which time all survivors were necropsied. At the 1.0 g/kg dose, two of the five female test animals died, one on day 6 and one on day 11. At the 2.5 g/kg dose, none of the rats survived beyond the third day of feeding. In a more detailed report on this same study, it was noted that the liver and kidneys of the test animals were examined both grossly and microscopically, while the lungs were examined only for gross changes.[36] None of the changes noted were attributed to the treatment with AMP; all changes were indicative of spontaneous diseases of rats, and these changes occurred equally among control and test animals.

Two rhesus monkeys were allowed to acclimate to the laboratory for 1 week, during which time baseline values for clinical chemistry, hematology, and urinalysis were established.[35] One monkey received an AMP dose of 0.5 g/kg in distilled water and the second monkey received an AMP dose of 1.0 g/kg. Dosing continued daily for 5 days or until the high-dose monkey died. The surviving monkey was observed for a total of 14 days and was sacrificed and necropsied on the 15th day. The high-dose monkey died 2 h after the third dose of AMP. The cause of death was gastrointestinal hemorrhage. The liver appeared normal. Both monkeys lost weight during the study. The low-dose monkey had no significant hematologic changes, except for a slight increase in the while blood cell count. The low-dose monkey had significant changes in some of the clinical chemistry values: calcium decreased from 9.8 to 3.0 mg/dl; blood urea nitrogen (BUN) and creatinine were increased, and the activities of serum glutamate pyruvate transaminase (SGPT), creatine phosphokinase (CPK), and ornithine carbamyl transferase (OCT) were all increased. The toxic effects of AMP were attributed to its effects on the gastrointestinal tract, and this could be due to the alkalinity of the AMP solutions (pH > 11).

An acute toxicity study of a hair spray containing 0.25% AMP was performed using ten albino rats, five of each sex.[37] After fasting overnight, the animals received a dose

by gavage of 5.0 ml/kg of the undiluted hair spray, and then were observed for 14 days thereafter, during which they were allowed feed and water *ad libitum*. Most of the rats had either slightly decreased activity or decreased activity up to 3 h after administration of the test material, and all appeared normal from the 6 h 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 which died during the study.

Another study following the same protocol was performed with a hair spray containing 0.58% AMP.[38] All rats survived the 14-day observation period. The rats had severely decreased activity an hour after administration of the test material. Their activity remained decreased at a lessened intensity through the 6-h 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.

In another study following the same protocol, a hair spray containing 0.59% AMP was tested for oral toxicity in albino rats.[39] All of the rats died before the end of the study, seven of the ten rats on or before day 2. All rats had some degree of decreased activity for the first 24 h. Three rats which survived through day 2 appeared normal on the second day, but had recurring slightly decreased activity on day 3. These three rats all died within the first week. The following observations were noted at necropsy: the three rats which died within 1 h had severely reddened pyloric mucosae, the two rats which died at 24 h had moderately reddened pyloric and duodenal mucosae, the two rats which died on day 2 had severely reddened pyloric and duodenal mucosae, the rat which died on day 5 had necrosis of the pyloric mucosa, the rat which died on day 6 had consolidation of the superior and inferior lobes of the right lung, and the rat which died at 1 week had moderately reddened pyloric and duodenal mucosa and gas-filled stomach and intestines. The hair spray containing 0.59% AMP was toxic to rats by the oral route under the conditions of the test.

A fourth test following the same protocol was performed with three cosmetic formulations containing 0.58, 0.59, and 0.58% AMP, respectively.[40] No animals in the three 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 h. No gross abnormalities were observed at necropsy, and the three formulations containing 0.58, 0.59, and 0.58% AMP were not toxic to rats by the oral route under the conditions of the study.

An aerosol spray containing 0.40% AMPD was tested for acute oral toxicity using Charles River albino rats.[41] The rats were divided into groups of four, equally divided by sex; there were four dosage groups. 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 the administration of the test material, at which time all surviving animals were sacrificed and necropsied (animals that died during the study were also necropsied). None of the rats of the low-dose group, and one rat of the 15.4 g/kg group, died during the study. All rats in the two high-dose groups died, those in the 23.1 g/kg group within the first week, and those in the high-dose group from 45 min to 3 h after administration of the test material. The 7- and 14-day LD_{50} doses were both 17.0 ± 1.7 g/kg.

Inhalation

A group of ten Wistar rats, equally divided by sex, was exposed for 1 h to an atmosphere containing 200 mg/L of a hair spray containing AMP at a concentration of

0.59%.[42] The test animals were observed for 2 weeks following the exposure. All but one rat survived the duration of the study, all survivors gained weight during the study, and all, including the rat which died, appeared normal during the observation period. At necropsy, the left lung of the rat which 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, three cosmetic formulations containing 0.58, 0.59, and 0.58% AMP, respectively (groups 1, 2, and 3), were tested.[43] All rats survived the 2-week observation period, and all but one gained weight (one rat maintained a steady weight). The rats of the first two groups appeared normal throughout the observation period, while those of the third group had slightly decreased activity at hour 1 and were normal thereafter. The only abnormality noted upon necropsy was in one 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, ten of each sex, were exposed for 1 h to an atmosphere containing 168.2 mg/L of a spray containing AMP at a concentration of 0.26%.[44] 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 sponged off, dried, and placed in clean cages. The rats were observed during the exposure, and half of the rats of each sex were sacrificed 24 h later, and the remainder of the test animals were observed for 14 days.

During exposure to the test material all rats had decreased activity, and had labored respiration, squinting, and ataxia. The decreased activity, labored/slow respiration, and squinting continued after the exposure, and in addition, the rats had depressed righting and placement reflexes. One female rat had tremors and prostration upon removal from the test chamber, and another female also had intermittent tremors. All rats, with the exception of one male rat with a slight nasal discharge, appeared normal at 24 h. One male rat was wheezing on days 2, 3, and 14, and a second male rat appeared depressed on days 4 and 5. 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 weight and kidney/body weight ratio 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.

No deaths occurred when rats were exposed for 1 h to atmospheres containing 200 mg/L of an aerosol containing AMP at concentrations of 0.25% or 2.5% in alcohol and propellant.[34]

An acute inhalation toxicity study of a hair spray containing 0.50% AMPD was performed using ten male Sprague-Dawley rats.[45] The rats were exposed for 1 h to an aerosol atmosphere containing approximately 200 mg/L of the hair spray formulation. 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; the trachea, lungs, liver, and kidneys were examined microscopically. All rats survived the duration of the study; 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 study was unavailable.

Short-Term Toxicity

Oral

Eight beagle dogs were used in a study of the toxic effects of AMP over a 28-day period.[46] AMP was administered in the diet at concentrations of 600, 1800, 5400, and 16,200 ppm to two dogs, one of each sex for each dose. Once weekly the dogs were weighed and feed consumption was recorded. Hematologic studies and urinalyses were performed once before the administration of AMP and at week 4 during the study. Both of the dogs of the 1800 and 16,200 ppm groups, as well as the female dog of the 5400 ppm group, had frequent soft stools or diarrhea. Both dogs of the highest dose group 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 feeding.

Results of the urinalyses were normal throughout the study. The hematologic changes 4 weeks into the study 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, SGPT and alkaline phosphatase activities were moderately to markedly increased; and 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 due to the AMP were found at necropsy. Microscopic lesions in the liver included hepatocytic vacuolation, necrosis of hepatocytes, pigment deposits, centrolobular inflammatory infiltrate, and fibrosis and atrophy of centrolobular parenchymal tissue; this was 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.

In another study, AMP was fed in the diet to Charles River CD-1 mice for 8 weeks.[47] Concentrations were 200, 400, 800, 1600, and 3200 ppm; 10 mice of each sex were in each diet group. A control group was also included. The mice were observed daily, and weights and feed consumption were recorded weekly. At the end of the study, all mice appeared normal. No gross or microscopic lesions were found in the liver of the test animals (all of the 3200 ppm mice and 4 mice from each other dosage group were examined).

A similar study was undertaken with Charles River CD rats.[48] The test protocol was the same as in the mouse study[47] except that the dietary concentrations were 1000, 2000, 4000, 8000, and 16,000 ppm. 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 of 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 rats of all dose groups (all rats of 16,000 and 8000 ppm groups and 4 from each other dose group were examined), and this change was considered compound-induced.

Inhalation

An inhalation study was performed with a hair spray containing AMP at a concentration of 0.58%.[49] A group of 16 Wistar rats, eight of each sex, was exposed to an atmosphere containing 200 mg/L of the hair spray for 1 h/day, 5 days per week for 2 weeks. Four rats were sacrificed at the end of the first week, another four at the end of the second week, and the remainder after a one-week recovery period. All rats were examined for gross pathological changes, 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 h after exposure, had returned to normal by 3 h, and once again had slightly decreased activity at 24 h. The rats continued to have slightly decreased activity until day 14, at which time the rats which were to undergo a 1 week recovery period all appeared normal. No gross changes were noted at necropsy, and weight gains were comparable between the test animals and the control group.

Subchronic Toxicity

Oral

In a 90-day study, AMP solutions, at pH's of 11+ or 7, were administered to rats by stomach tube.[50] At each pH, the AMP solution was administered at doses of 0.5, 0.75, 1.1, or 1.7 g/kg/day; 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 sacrificed and necropsied after samples were taken for hematologic, urologic, and clinical chemistry measurements. Results of the study indicated that mortality caused by AMP was due to the AMP solutions with a pH of 11 or greater. The noted behavior changes were hyperventilation, hyperirritability, and hyperactivity; these were most often noted in the pH 11+ group. All surviving rats gained weight and consumed feed in a normal manner, though the test rats did appear to drink more water. In the pH 11+ group rats, packed cell volumes, hemoglobin values, and erythrocyte counts were markedly decreased for the males of the 1.1 g/kg dose group; this was due to blood loss by these rats. The pH 11+ group rats receiving doses of 0.5 and 0.75 g/kg also had slight, though significant, decreases in erythrocyte counts. In the pH 7 group rats, 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.

Tissues were taken from the rats of the 90-day study and from control rats of both pH groups and from nine male and eight female rats of the pH 7, 1.7 g/kg group and from one female of the pH 11+, 1.7 g/kg group.[51] The 1.7 g/kg oral dose of an AMP solution at a pH of 7 did not cause any significant changes in male or female rats "under the conditions of the experiment." In the tissues of the pH 11+, 1.7 g/kg group female rat, the only abnormality noted was a few papillary protrusions of epithelium at the junction between the squamous and glandular portions of the stomach.

For three months, groups of four male and four female beagle dogs were fed diets containing 0.63, 15.0, or 62.5 mg AMP/kg.[52] 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 (not indicated in this limited report). 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 months 1 and 3. The liver weights and liver/body weight ratios were slightly higher in the dogs of the high- and mid-dose groups at necropsy. In addition, two females and one male of the high-dose group had tan and mottled livers. At microscopic examination, vacuoliza-

tion, lipid deposits, and bile duct hyperplasia were found in the livers of all of the high-dose dogs and in one of the mid-dose dogs. No other organs appeared to be affected. Results of the clinical chemistry of the dogs in the mid-dose groups did not correlate with the histopathological findings for those groups. No other comments were made about the effects in dogs of 90 days of dietary consumption of AMP.

Inhalation

In a 13-week inhalation study, a group of CD-Crl: CS(SD)BR Charles River albino rats, 11 of each sex, was exposed to an aerosolized form of a pump hair spray containing 0.44% AMP for 4 h/day, 5 days/week for a total of 67 exposures.[53] The exposure concentration was 0.23 mg/m^3, an amount which was calculated to be a 100-fold increase over normal human exposure. The animals were observed daily, weighed weekly, and blood and urine samples were obtained on weeks 7 and 13. The animals were sacrificed 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, and none had an intolerance for the aerosol atmosphere. There was a significant decrease in body weight gains for female rats during weeks 1–3, but this was 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. Though 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 at week 7, and females had a significant decrease in BUN at week 13. These differences were not considered toxicologically significant when included with the other study criteria.

No abnormalities were noted in the results of the 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 evaluated tissues; frequency and severity of noted changes were equivalent for both the treated and control rats. The microscopic changes observed in the lungs and upper respiratory tract of both the treated and control rats were attributed to chronic murine pneumonia, and were unrelated to treatment. The pump hair spray formulation containing 0.44% AMP was safe under the exaggerated inhalation conditions of the test.

A 90-day inhalation toxicity study of two pump sprays, each containing 0.40% AMP, was performed using cynomolgus monkeys.[54] The test animals were divided into groups consisting of three males and six females each. One group (group 2) was exposed to the test material under static conditions by automatic dispensation of one pump sprayer every 7.5 s/10 min period/day, for a total of 800 sprays/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 two 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 had negative reactions to a tuberculosis test 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 the 89 days of the study, 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 necropsied; organ weights were obtained and various organs were preserved for microscopic examination.

The monkeys of group 2 were exposed to a mean gravimetric concentration of 6.63 ± 1.50 μg/L, and the monkeys of group 3 were exposed to a mean gravimetric concentration of 6.06 ± 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 higher number of breaths and cumulative tidal volume to washout to 2% nitrogen and had a significantly higher pulmonary flow resistance. These data "did not indicate any increase in these parameters in Group 3, merely lesser decreases between pre- and postexposure as compared to Group1 [controls]." There were no significant hematological differences noted. The test animals had lower BUN values and higher SGPT activities than the controls at both week 4 and week 13. These differences were not considered significant, since 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 since there was no evidence of hyperventilation, the cause was believed to be due to ingestion of the acidic resin, causing a nonrespiratory acidosis. Group 3 monkeys had an increased liver/body weight ratio which resulted from a higher mean liver weight coupled with lower average body weights. No compound-related alterations were found upon histopathological evaluation of the tissues in the monkeys of groups 2 and 3. Though the monkeys in group 3 did not gain weight during the study and though both groups 2 and 3 had lower serum CO_2 levels, no other compound-related adverse effects were evident 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 eight cynomolgus monkeys, divided equally by sex, were exposed for 1 h per day to a hair spray formulation containing 0.21% AMP.[55] Groups were exposed to high and low concentrations of the hair spray, as well as of the vehicle control. In addition, 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, organ/body weight ratios, organ/brain weight ratios, 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. No signs of inflammation or interstitial fibrosis were evident. In addition, 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.

A 13-week inhalation toxicity study in female Chr/CD Charles River albino rats and in female outbred Syrian golden hamsters was performed with two hair spray formulations containing 0.1350% AMPD.[56] One hair spray formulation also contained 3.00% ethylene maleic anhydride copolymer, 50%; this formulation was referred to as the hair spray, while the second formulation, without the resin, was labelled 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 h/day, 5 days/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, five animals of each species of each group were sacrificed. The remaining test animals were sacrificed starting 3 days after the last day of exposure. Blood analyses was performed on all of the test animals. Gross and microscopic examinations were also performed.

During the study, five animals either died or were sacrificed when moribund (one rat and one hamster of the low-dose hair spray group, one hamster of the high-dose hair spray group, and one animal of each species of the vehicle group). None of the deaths were the result of the aerosol treatment.

Exposure of the test animals to the aerosols was well tolerated; other than the reactions listed below, no adverse reactions were observed. 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, but not statistically significant, body weights at the end of the study.

There were scattered incidences of statistically significant differences in various parameters of the hematology and clinical chemistry, but no dose- or exposure-dependent trends were noted and, thus, 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. Exposure of 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 0.1350% was not harmful.

Dermal Irritation and Sensitization

Irritation

A group of six rabbits was tested for primary skin irritation to AMP at a concentration of 0.25% in ethanol.[57] The test was a single insult, occlusive patch test modified to include abraded and nonabraded skin. The rabbits' skin was graded for erythema and edema 24 and 72 h 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.

In a limited summary, it was noted 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.[34]

The primary irritation indices (PII) for two formulations containing 0.26% AMP were 1.13 and 1.31 (maximum possible score = 8), respectively.[58] The test formulation, 0.5 ml, was applied under an occlusive patch to the intact and abraded skin of two rabbits of each sex. The patch was removed 24 h later. The sites were graded at 25 h (1 h after patch removal) and 72 h. Each group of rabbits was tested with one formulation. With the first formulation, all of the rabbits had erythema at both sites at both gradings, with slight desquamation at the 72 h grading. One rabbit also had edema at the abraded site; this reaction had subsided by 72 h. The reactions of the rabbits tested with the second formulation were essentially the same. All rabbits had erythema at both gradings, with slight desquamation at 72 h. One rabbit had edema at the abraded site at 25 h, but was negative at 72 h. The reactions to the second formulation were slightly more severe than those to the first formulation, accounting for the differences in the PII's. The formulations containing 0.26% AMP were considered mildly irritating to intact and abraded rabbit skin.

The following four tests were each performed on cosmetic formulations containing AMP.[59–62] In each test the formulation, 0.5 ml, was applied under an occlusive patch to the abraded and nonabraded skin of six rabbits of mixed sex. After 24 h, the patch was removed. The test sites were graded upon patch removal and at 72 h. The results of these tests follow. A hair spray containing 0.25% AMP caused no irritation to either the intact or abraded skin of rabbits; the PII was 0.0.[60] The PII of a hair spray containing 0.58% AMP was 0.38.[59] At the 24-h grading, three of the rabbits had erythema at both the intact and abraded sites, while the other three rabbits had erythema at the abraded sites only. All of the reactions had cleared by 72 h. The PII for a hair spray containing 0.59% AMP was 0.35.[61] Four of the six rabbits had erythema at both the intact and abraded skin sites at the 24-h grading. All reactions at 72 h were negative. The hair spray containing 0.59% AMP was not a primary dermal irritant.

Three products containing 0.58, 0.59, and 0.58% AMP had PII's of 0.75, 1.40, and 0.35, respectively.[62] With the first formulation, five of the six rabbits had erythema at both the abraded and intact sites at 24 h; the irritation persisted through the 72-h grading period, with one rabbit having edema in addition to the erythema at both sites. With the second formulation (0.59% AMP), four rabbits had both erythema and edema at 24 h. A fifth rabbit had erythema alone, which had subsided by 72 h. Of the other four rabbits with reactions, one had no reaction at 72 h, one had erythema only, one 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), one rabbit had erythema at the abraded site, and two rabbits had erythema and edema at both sites at the 24-h grading. All of the reactions had subsided by 72 h. None of the formulations were primary dermal irritants under the conditions of the test.

In another study, an unspecified cosmetic formulation containing AMP-95 (95% AMP solution) at a concentration of 0.22% was tested for primary skin irritation potential in a group of nine rabbits using the single insult, occlusive patch test procedure.[63] The skin reactions were graded 2 and 24 h after patch removal. Three rabbits had erythema 2 h after patch removal; of these three, one had undiminished erythema 24 h after patch removal. In addition, a fourth rabbit had erythema at the 24-h grading. The group PII for the formulation containing AMP-95 at a concentration of 0.22% was 0.56 (maximum 8.00), indicating that the formulation was minimally irritating.

A "foam hair groom" containing 0.715% AMPD was tested in four New Zealand albino rabbits for primary dermal irritancy.[64] 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 h. The sites were graded 1 h after patch removal and at 72 h. No adverse reactions were noted; the hair groom containing 0.715% AMPD was nonirritating when applied to intact and abraded rabbit skin.

A hair spray formulation containing 0.50% AMPD was tested following the protocol outlined in the previous paragraph.[65] Two rabbits had erythema and edema at the intact skin site; the reaction had cleared by 72 h. One rabbit had erythema persisting through 72 h at the intact site. The fourth rabbit had no reaction at the intact skin site. At the abraded skin sites, three rabbits had erythema and edema, with the erythema persisting through 72 h while the edema subsided in all but one of the rabbits. The fourth had continuing erythema and no edema. The PII for the hair spray was 1.38.

Sensitization

The intradermal sensitization potential of AMP was studied in guinea pigs.[66] Three groups of ten male guinea pigs each were used in the study: negative control (saline), positive control (0.3% dinitrochlorobenzene), and test group (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 h later. At 48 h, 0.1 ml of the appropriate solution was injected, and the injections were repeated two to three times a week for ten 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 h after the injection; grading of the sites was performed 3 h later, and again at 48 h.

The first two injections of the induction phase, using 0.5% and 1% AMP solutions, respectively, caused necrotic lesions, and so the remainder of the induction injections were made with a 0.1% solution. One guinea pig of the test group had a slight reaction at the 24-h grading of the 0.05% AMP challenge site. This reaction had cleared by 48 h. No reactions were noted in the test group at the second challenge. At the second challenge with AMP solutions, four guinea pigs of the saline control group had reactions to the 0.05% AMP and one had a reaction to the 0.01% AMP. All of these reactions had cleared by 48 h. The positive control animals had the expected reactions. AMP was not an intradermal sensitizer in guinea pigs.

Ocular Irritation

In a limited summary, it was 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.[34] The irritation had cleared by days 2 and 4, respectively.

Five New Zealand White rabbits received in the left eye a single spray of a formulation (pH 8.3) containing 0.26% AMP.[67] The spray was directed from a distance of 6 inches from the eye; the right eye served as a control. Observations of the eyes were made at 1 and 24 h, and at 3, 4, and 7 days postinstillation. At 1 h, two rabbits had slight conjuntivitis and dull corneas, both clearing by 24 h. A third rabbit had slight conjunctivitis at 1 h, also clearing by 24 h. The fourth rabbit had slight conjunctivitis

persisting through 24 h and clearing by day 3. The fifth rabbit had no reaction. All rabbits had negative fluorescein stains 7 days after instillation of the test material. The spray containing 0.26% AMP was minimally irritating when not rinsed from sprayed rabbit eyes.

Twelve New Zealand White rabbits received a single 1-s spray, from a distance of 4 inches, of a hair spray containing 0.25% AMP.[68] The eyes of six of the rabbits were rinsed 30 s after the spraying. The animals were observed for 3 days. Two of the six 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.[69] Of the rabbits that did not have their eyes rinsed, three had slight conjunctivitis on day 1; the conjunctivitis had cleared by day 2 in two of the rabbits, and by day 3 in the third. The remaining three rabbits of the group had no reactions. Of the rabbits receiving a rinse, one had slight corneal opacity and conjunctivitis on day 1; the opacity had cleared by day 2, and the conjunctivitis by day 3. None of the other rabbits of the rinsed group had adverse reactions.

A hair spray contining 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 for the first 24 h, while the eyes of the other six were rinsed 30 s after instillation of the test material. The rabbits were observed for 3 days after the instillation. Of the rabbits that received no eye rinses, one 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 remainder of the rabbits in the test group had no ocular reaction. Of the rabbits which received eye rinses, one 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.

A cosmetic formulation containing 0.22% AMP-95 was tested in six 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 1–4, and on day 7 after instillation. Three different rabbits had conjunctivitis, one each on days 1–3. 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 hair spray containing 0.40% AMPD was sprayed into the left eye of each of five New Zealand White rabbits for a duration of 1 s.[72] The right eyes served as controls. The eyes were observed for signs of irritation at 1 and 24 h, and on days 2, 3, 4, and 7. All of the rabbits had severe iritis and slight conjunctivitis at 1 h, and in four of the rabbits this was reduced at 24 h, and cleared by day 2. In the fifth rabbit, the severe iritis continued, along with the slight conjunctivitis, through day 2, and was cleared by day 3.

A foam hair groom, 0.1 ml, containing 0.715% AMPD was instilled into the left eye of each of ten New Zealand White rabbits.[73] Half of the rabbits had their eyes rinsed 4

s after instillation of the test material. Ocular reactions were graded at 1 and 24 h, 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 h, clearing by 24 h. Two rabbits had moderate conjunctivitis which diminished steadily and was cleared by day 3. One rabbit had moderate iritis and conjunctivitis at 1 h; the iritis had cleared by 24 h, and the conjunctivitis by day 2. The fifth rabbit had moderate iritis at 1 h, clearing by 24 h. In addition, this rabbit had moderate conjunctivitis at 1 h; 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 h and the conjunctivitis diminishing at 24 h and clearing by day 2. Two rabbits had moderate conjunctivitis at 1 h, clearing by 24 h. The fifth rabbit had moderate conjunctivitis, which had diminished at 24 h and cleared by day 2. The rabbits of both test groups had negative fluorescein dye examinations on day 7.

MUTAGENICITY

A plate assay mutagenicity test, with and without metabolic activation, was performed using AMP and *Saccharomyces cerevisiae* strain D4 and *Salmonella typhimurium* strains TA1535, 1537, 1538, 98, and 100.[74] Positive activation and nonactivation controls were used; the controls were positive for either frame-shift or base-pair substitution mutations. The AMP was tested over a range of concentrations from 0.01 μl 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.

AMPD was tested for mutagenic potential using *Salmonella typhimurium* strains TA1535, 1537, 98, and 100.[75] Testing in these strains represents frame-shift and base-pair substitution type mutations. AMPD was tested at concentrations of 100, 333, 1000, 3330, and 5000 μg/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.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Irritation

The skin irritation potential of a cosmetic formulation containing 0.22% AMP-95 was examined using a single insult occlusive patch test on 15 panelists.[76] One panelist had an equivocal reaction (±), resulting in a group PII of 0.03. The cosmetic formulation containing 0.22% AMP-95 had a negligible primary skin irritation potential.

A hair spray containing 0.40% AMPD was tested for primary irritancy in 15 human subjects.[77] 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 nine panelists, with seven having one questionable response and the remainder having two questionable responses. In addition, one panelist had slight redness on day 4, and one panelist had slight redness on days 2–4.

Sensitization

A conditioning hair mousse containing 0.22% AMP-95 was tested for allergic contact sensitization potential in 97 panelists.[78] 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; five 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 patched were applied every Monday, Wednesday, and Friday for 3 weeks. The patches were removed by the panelists 24 h 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. The challenge sites were graded 24 and 48 h after patch removal.

Thirteen panelists had reactions during the induction phase of the test. Of these 13, nine had single reactions, two had two reactions each (insults 4 and 7, 1 and 8), one had three reactions (insults 1, 6, and 7), and one had four reactions (insults 2, 3, 8, and 9). All of the reactions that occurred during the induction phase were recorded as barely perceptible. In addition, another panelist had a barely perceptible reaction at the 24-h grading of the challenge phase; the results of the 72-h grading were not available. The conditioning hair mousse containing 0.22% AMP-95 did not have allergic contact sensitization potential.

A cosmetic formulation containing 0.073% AMPD was tested for sensitization potential in a group of 30 human test subjects using a repeated insult open patch test.[79] The test material was applied to the arm daily 4 days/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 received 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 h. No reactions were observed in any of the test subjects. The formulation containing 0.073% AMPD was neither a primary irritant, nor a fatiguing agent, nor a sensitizer, and the formulation was safe under the conditions of the study.

A modified repeated insult patch test of a cosmetic formulation containing 0.50% AMPD was performed on a panel of 39 women and 20 men.[80] 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 two weeks. The patch sites were graded approximately 24 h 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 one 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.

SUMMARY

AMP and AMPD are substituted aliphatic alcohols. Both occur in solid and liquid forms. AMP is miscible with water and soluble in alcohols, while AMPD is soluble in both water and alcohols.

Both AMP and AMPD are used as emulsifying agents for cosmetic creams and lotions, and as neutralizing agents in hair sprays. AMP is used in concentrations up to 10% and AMPD is used in concentrations up to 5%. All uses at concentrations above 1% involve neutralization of AMP or AMPD with fatty acids.

In industry, AMP and AMPD are used in the synthesis of surface-active agents, vulcanization accelerators, and pharmaceuticals, and as emulsifying agents for a variety of products. AMP is also listed as an indirect food additive as a component of adhesives.

AMP appears to interfere with lipid catabolism and with choline utilization and synthesis in rats fed a choline-deficient diet. AMP also increased the incidence of hemorrhagic kidneys and the amount of hepatic lipid (except at higher doses of AMP, in which the latter was reversed) in choline-deficient rats.

Aminoalcohols are incorporated into the phospholipids of rats; the degree of incorporation was related to the aminoalcohol's similarity to ethanolamine.

AMP caused a dose-dependent inhibition *in vitro* of the incorporation of [^{32}P] into the phospholipids of swine pulmonary and coronary arteries, and of rabbit and human endometrial tissues.

In vitro, AMP altered the morphology of murine fibroblast plasma membranes, either by replacing certain types of phosphatidylethanolamine or by altering the asymmetric distribution.

Intraperitoneal injection of AMP resulted in urinary excretion of tritiated AMP in rats fed either choline-adequate or choline-deficient diets, with the rats fed the choline-adequate diet accumulating more of the unchanged AMP in the urine. Radioactivity also appeared in the serum within 30 minutes of i.p. injection, and then disappeared shortly thereafter. Rats fed the choline-adequate diet accumulated a greater amount of radioactivity in the serum. Uptake of radioactivity by various organs was greater for the rats fed the choline-adequate diet during the first 6 h postinjection, after which time the trend was reversed. In the liver, the uptake of radioactivity was greater at all times for the choline-deficient rats.

According to the classification system of Hodge and Sterner,[1] AMP is nontoxic to rats and albino mice, and slightly toxic to deer mice.

In an acute oral toxicity study, AMP produced lesions in the liver, kidneys, spleen, and lungs at the LD_{50} dose. In another acute oral toxicity study in rats, AMP did not cause lesions in the kidneys and lungs of the test animals. In rhesus monkeys, the toxic effects of AMP were probably due to the alkalinity of the compound and irritation of gastrointestinal tract.

In three acute oral toxicity studies of hair sprays or cosmetic formulations containing varying concentrations of AMP, the test material was nontoxic to rats. Results of

another acute oral toxicity study of a hair spray containing AMP at a concentration which was also tested in the previous studies found the hair spray containing AMP to be toxic to albino rats.

According to the classification of Hodge and Sterner,[1] a hair spray containing AMPD was practically nontoxic to albino rats.

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 AMPD was also nontoxic to rats.

In dogs fed AMP, no gross lesions were found at necropsy. Microscopic lesions were found in the livers of all but one of the test animals, and the damage was dose dependent.

Neither gross nor microscopic lesions were found in the livers of mice fed AMP in the diet for 8 weeks. Rats of another study had vacuolization of hepatocytes in all dose groups.

When rats were exposed to atmospheres of a hair spray containing AMP over a period of 2 weeks, no toxic effects resulted from the treatment.

When AMP solutions with pH's 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 dogs of the high-dose group 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/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 vacuolization, lipid deposits, and bile duct hyperplasia in the livers of the dogs in the high-dose group, as well as in one dog of the low-dose group.

In a chronic inhalation study, rats were exposed to an aerosolized form of a pump hair spray containing AMP. The hair spray was not toxic under the exaggerated inhalation conditions of the test.

Cynomolgus monkeys were exposed to hair sprays containing AMP under static and dynamic conditions in a 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 study, cynomolgus monkeys exposed to a hair spray containing 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.

When both albino rats and Syrian Golden hamsters were exposed in a subchronic inhalation toxicity study to hair spray formulations containing AMPD, no significant compound-related adverse effects were observed.

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

AMP was not an intradermal sensitizer in guinea pigs.

In eight studies, 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. Cosmetic formulations containing AMPD were moderate ocular irritants.

AMP was not mutagenic, with and without metabolic activation, in *S. cerevisiae* strain D4, and in *S. typhimurium* strains TA1535, 1537, 1538, 98, and 100. AMPD was not mutagenic, with and without metabolic activation, in *S. typhimurium* strains TA1535, 1537, 98, and 100.

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 AMP-95 was not an allergic contact sensitizer when tested using a panel of 97 subjects. A cosmetic formulation containing AMPD was not a primary irritant, and it was neither a fatiguing agent nor a sensitizer. In another study, a cosmetic formulation containing AMPD was not a sensitizer.

DISCUSSION

Though AMP and AMPD are highly alkaline in pure form, the Panel notes that these chemicals are buffered in cosmetic formulations, and, therefore, the adverse reactions seen with the undiluted chemical would not be expected with the cosmetic product. Of greater concern is the possible presence of impurities in AMP and AMPD, especially oxazolidine or other secondary amines, which are vulnerable to *N*-nitrosation. If there is a possibility of these chemicals being present in the cosmetic-grade AMP and AMPD, then the Panel recommends that AMP and AMPD not be included in cosmetic formulations containing nitrosating agents.

AMP and AMPD were not mutagenic in the Ames assay using five and four tester strains, respectively.

The Panel is aware that AMP and AMPD are used at concentrations greater than 1%, but because available test data do not exceed 1%, the Panel recommends that AMP and AMPD are safe as cosmetic ingredients at concentrations not exceeding 1%.

CONCLUSION

On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that at concentrations not exceeding 1%, Aminomethylpropanol and Aminomethylpropanediol are safe for use in cosmetics.

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