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Final Report on the Safety Assessment of Acetamide MEA

ABSTRACT

Acetamide MEA is used in cosmetics as a skin conditioning agent-humectant and hair conditioning agent. Oral LD_{50}'s of 27 g/kg were reported for Acetamide MEA in rats. No rabbits died following an acute dermal exposure of 20 ml/kg Acetamide MEA. In ocular irritation studies, 70% Acetamide MEA and cosmetic formulations containing 1.3% Acetamide MEA were classified as nonocular irritants in rabbits. Only mild skin irritation occurred following a 24-h skin exposure to undiluted Acetamide MEA. In the maximization test, Acetamide MEA was classified as a nonsensitizer in guinea pigs when tested at a concentration of 5.0%. Neither primary irritation nor sensitization reactions to 7.5% Acetamide MEA were observed in a human repeated insult patch test. Acetamide MEA was not nonmutagenic in the Ames assay. In the presence of nitrosating agents, Acetamide MEA may form N-nitroso compounds; acetamide may be a minor impurity in Acetamide MEA. On the basis of the data presented in this report, it is concluded that Acetamide MEA is safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products and is safe in the present practice of use in rinse-off products. Cosmetic formulations containing Acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide.

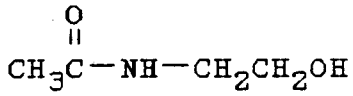
INTRODUCTION

ACETAMIDE MEA IS AN aliphatic amide used in cosmetic formulations as a skin conditioning agent-humectant and hair conditioning agent. It may be produced by the acetylation of ethanolamine, followed by vacuum distillation.

CHEMISTRY

Chemical and Physical Properties

Acetamide MEA (CAS no. 142-26-7) is the aliphatic amide that conforms to the formula (Estrin et al., 1982a):



Other names for this chemical are Acetamide, N-(2-Hydroxyethyl)-; N-beta-Hydroxyethylacetamide; N-(2-Hydroxyethyl)Acetamide; beta-Hydroxyethylacetamide; 2-Acetamidoethanol; 2-Acetylaminoethanol; Acetylcolamine, N-Ethanolacetamide; N-Acetyl Ethanolamine; and Hydroxyethyl Acetamide (RTECS, 1988). Acetamide MEA is usually marketed as a 70–75% aqueous solution (Hunting, 1983). It is said to be compatible with all types of surfactants (Hunting, 1983) and is soluble in alcohol, ether, acetone, and water (Hawley, 1971; Weast and Astle, 1982). Additional properties of Acetamide MEA are listed in Table 1.

The formation of carcinogenic N-nitrosamines (e.g., N-nitrosopiperidine) from dissolved NOCl gas in aqueous 0.1 M NaOH solution was evaluated in the presence of the following alkanolamines: triethanolamine, diethanolamine, N-methylethanolamine, N,N-diethylethanolamine, N-nitrosodiethanolamine, N-methyl-N-nitrosoethanolamine, choline chloride, and N-acetylethanolamine (Acetamide MEA). An appropriate secondary amine was added after all of the nitrosyl gas had reacted with either the alkanolamine or the solvent. In the absence of alkanolamines, along with an approximately 6-fold excess of NOCl, close to 35% of the amine was converted to N-nitrosamine in less than 3 min. However, in the presence of alkanolamines, the reactions were slower and often more extensive. It has been suggested that alkanolamines increase the extent of the reaction by initial formation of an alkyl nitrite derivative, which then reacts with the secondary amine to yield an N-nitroso product (Challis and Shuker, 1980).

METHODS OF PRODUCTION

Acetamide MEA is prepared by the reaction of acetic acid with monoethanolamine (CTFA, no date). Additional methods of production that have been reported involve

Table 1. Properties of Acetamide MEA

Form	Clear liquid	Scher Chemicals, Inc., 1977
Molecular weight	103.12	Weast and Astle, 1982
Activity	70% minimum	Scher Chemicals, Inc., 1977
Diluent (water)	30.0% maximum	Scher Chemicals, Inc., 1977
Ionic nature	Nonionic	Scher Chemicals, Inc., 1977
Shelf life	1 year minimum in closed container	Scher Chemicals, Inc., 1977
Density	1.1079 (25/4°C)	Weast and Astle, 1982
Specific gravity	1.12 ± 0.05 (25°C)	Scher Chemicals, Inc., 1977
	1.122 (20/20°C)	Hawley, 1971
Refractive index	1.4674 (20°C)	Weast and Astle, 1982
	1.4380 ± 0.001 (25°C)	Scher Chemicals, Inc., 1977
Solubility	Soluble in most alcohols, glycols, diols, triols, polyols glycol ethers, water, and acetone	Scher Chemicals, Inc., 1977; Weast and Astle, 1982
Boiling point	151°C	Sax, 1979
Melting point	63.5°C	Weast and Astle, 1982
Freezing point	15.8°C	Sax, 1979
Flash point (Anhydrous)		
Open cup	over 180°C	Scher Chemicals, Inc., 1977
Closed cup	over 100°C	
Autoignition temperature (°F)	860°F	Sax, 1979

acetamide and ethylene oxide, monoethanolamine and acetyl chloride (CTFA, no date), and the acetylation of ethanolamine using acetic anhydride, followed by vacuum distillation (Heyns and Bebenburg, 1955).

ANALYTICAL METHODS

Acetamide MEA has been identified via the following methods: thin layer chromatography (Chrystal et al., 1980), high performance liquid chromatography (Scher Chemicals, Inc., 1979; Clairol, Inc., 1991), and gas chromatography (GC) (CTFA, no date).

IMPURITIES

An analysis of four typical production lots of Acetamide MEA by gas chromatography (with flame ionization detection [FID] detection) indicated the presence of MEA and acetamide. The results were as follows: Lot 7707 (0.43% w/w MEA), Lot 7579 (0.79% w/w MEA and 0.030% w/w acetamide), Lot 7618 (0.48% w/w MEA and 0.065% w/w acetamide), and Lot 7617 (0.55% w/w MEA) (CTFA, no date). Different concentrations of MEA and acetamide impurities were reported in a second analysis in which the same four lots of acetamide MEA were analyzed by GC-mass spectrometry (MS): Lot 7707 (0.0027% w/w MEA and 0.0028% w/w acetamide), Lot 7579 (0.0006% w/w MEA and 0.0006% w/w acetamide), Lot 7618 (0.0029% w/w MEA and 0.0030% w/w acetamide) and Lot 7617 (0.0017% w/w MEA and 0.0020% w/w acetamide) (Clairol, 1992). The investigators stated that the results of the GC-MS analysis invalidate the GC-FID analysis, because, with the former method, an unknown coeluting peak was detected. Thus, concentrations of impurities reported in the second analysis are much lower than those in the first analysis.

Acetamide, one of the impurities mentioned in the preceding paragraph, induced hepatocellular carcinomas when administered orally to male and female rats (Fleischman et al., 1980; Flaks et al., 1983) and malignant lymphomas when administered orally to male and female mice (Flaks et al., 1980).

A commercial preparation of Acetamide MEA, representing an aqueous solution of active material, was analyzed by high-performance liquid chromatography. In this analysis, Acetamide MEA represented 80.55% of the total peak area and 3 other components represented 8.72%, 8.57%, and 1.76% of the peak area, respectively. The authors stated that none of these components represented free acetamide or monoethanolamine, and that there was no further determination of their identity (Clairol, Inc., 1991).

Acetamide MEA was analyzed for N-nitrosodiethanolamine content via high performance liquid chromatography (detector = TEATH Model 502 Analyzer). N-nitrosodiethanolamine was not detected (limit of detection = 0.05 ppm) (Scher Chemicals, Inc., 1979).

USE

Cosmetic

Acetamide MEA is used as a skin conditioning agent-humectant and hair conditioning agent in cosmetic products (Nikitakis, 1988).

The product formulation data submitted to the Food and Drug Administration (FDA) for Acetamide MEA indicated that it was contained a total of 102 cosmetic product formulations (FDA, 1992). Acetamide MEA was used in the following products: bubble baths; other bath preparations; hair conditioners; hair shampoos (noncoloring); tonics, dressings, and other hair grooming aids; wave sets, other hair preparations (noncoloring); and moisturizing skin care preparations. The greatest reported use of Acetamide MEA was in hair conditioners.

Concentration of use values are no longer reported to the FDA by the cosmetics industry (Federal Register, 1992). However, 1989 product formulation data submitted to FDA indicated that Acetamide MEA was used at concentrations up to 25% (FDA, 1989).

Product formulation data on Acetamide MEA are included in Table 2.

Cosmetic products containing Acetamide MEA are applied to the hair and skin and may come in contact with ocular and nasal mucosae.

Product formulations containing Acetamide MEA may be used daily or on a monthly basis. Many of the products may be expected to remain in contact with body surfaces for as briefly as a few minutes to as long as a month. Each product has the potential for being applied many times over a period of several years.

International

Acetamide MEA appears in the list of cosmetic ingredients approved for use in cosmetic formulations marketed in Japan (Nikko Chemicals Co., Ltd., 1992). This ingredient does not appear in the list of ingredients prohibited from use in products marketed in the European Economic Community (EEC Cosmetics Directive, 1990).

Noncosmetic

Acetamide MEA has the following noncosmetic uses: detoxifier (Hunting, 1983); plasticizer for polyvinyl alcohol and for cellulosic and proteinaceous materials; humectant for paper products, glues, cork, and inks; high boiling solvent for fountain-

Table 2. Product Formulation Data on Acetamide MEA (FDA, 1992)[a]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*Maximum concentration of use (%) (FDA, 1989)*
Other bath preparations	132	3	Category not reported in 1989
Hair conditioners	478	60	25
Hair shampoos (noncoloring)	909	14	5
Tonics, dressings, and other hair grooming aids	290	12	10
Wave sets	180	7	5
Other hair preparations (noncoloring)	177	3	Category not reported in 1989
Moisturizing skin care preparations	747	3	Category not reported in 1989
1992 totals		**102**	

[a] CIR requests that the cosmetics industry provide current formulation data on each product category.

pen inks; and textile conditioner (Hawley, 1971). Adhesives containing Acetamide MEA may be used safely as components of articles intended for use in packaging, transporting, or holding food (21CFR:175.105).

TOXICOLOGY

Acute Oral Toxicity

An LD_{50} of 27.66 g/kg was reported for Acetamide MEA in a study involving rats (Deichmann, 1969).

In another study, the acute oral toxicity of Acetamide MEA (activity = 70% minimum; specific gravity = 1.12) was evaluated using 6 groups of 6 albino rats (three males, three females per group; weights = 206–298 g). The following oral dosages (one per group) were administered: 5.0, 25.0, 26.5, 27.3, 28.0, and 31.5 g/kg. The animals were observed for pharmacologic activity and drug toxicity at 1, 3, 6, and 24 h postadministration and, subsequently, daily for a total of 14 days. Necropsy was performed on surviving animals as well as those killed at the end of the observation period. The LD_{50} was 26.95 (25.55–28.43) g/kg (Consumer Product Testing Company, Inc., 1981a).

The acute oral toxicity of a liquid hair product (bulk density = 1.01 g/ml) and a foam hair product, both containing 1.3% Acetamide MEA, was evaluated using young adult male and female Sprague-Dawley strain rats (weights = 193–271 g). All animals were fasted 18–20 h prior to dosing. Three dosages (10.0, 13.0, and 16.9 g/kg) of the liquid product were administered via gavage to 3 pairs of rats (1 male, 1 female), respectively. The foam product was administered to 3 male rats and 3 female rats at a dosage of 25 ml/kg. All animals were observed at 0.5, 2, and 4 h postadministration and, subsequently, daily for 7 days. At the conclusion of the study, the animals were killed and necropsy was performed. None of the rats dosed with either the liquid or foam product died. No visible lesions were found in any of the three pairs of rats dosed with the liquid product. The necropsy results for animals dosed with the foam product were not included (Hazleton Laboratories America, Inc., 1985).

Acute Dermal Toxicity

The acute dermal toxicity of Acetamide MEA was evaluated using six rabbits (weights and strain not stated). None of the animals dosed with 20 ml/kg of the test substance died (Deichmann, 1969).

Subchronic Dermal Toxicity

The subchronic percutaneous toxicity of a hair product (foam) containing 1.3% Acetamide MEA was evaluated using 10 male (weights = 2112–2971 g) and 10 female (weights = 2133–3010 g) New Zealand White albino rabbits approximately 4 months old. Half of the animals, five of each gender, were treated with deionized water (negative control). The product was diluted with deionized water to a concentration of 50.0% w/v (effective concentration of Acetamide MEA = 0.65%) and administered at a constant dosage of 2.0 ml/kg. A glass rod was used to distribute the test solution evenly over the application site, defined as an area between the shoulders and rump (12–15 cm

wide) that had been clipped free of hair. Each animal wore a plastic restraint collar during the 7 h exposure period, after which the collar was removed and the test site washed with tap water and dried. This procedure was repeated once daily (5 days per week) for 13 weeks (91 days). At the conclusion of the study, necropsy was performed on each animal. None of the animals died during the study, and there was no evidence of test substance-related systemic toxicity. Irritation reactions observed at application sites were limited to slight to moderate erythema. These reactions were initially observed on days 44–45, and continued sporadically in 1–4 animals through day 84. No signs of irritation were observed at the application sites of rabbits in the negative control group. There were no test-substance related gross lesions in organs or tissues other than skin at the application site (International Research and Development Corporation, 1987).

Ocular Irritation

The ocular irritation potential of Acetamide MEA (activity = 70% minimum; pH 7.1) was evaluated using six New Zealand White rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of each animal; eyes were not rinsed. The contralateral eye served as the control. Each animal was observed for signs of corneal opacity, iritis, and conjunctivitis at 24, 48, and 72 h postinstillation. If irritation reactions persisted, observations were also made at 4 and 7 days postinstillation. Reactions were scored according to the Draize scale: 0–110. At 24 h postinstillation, a Draize score of 0.7 was reported. Reactions were not observed after 24 h. Acetamide MEA was practically nonirritating to the eyes of rabbits (Consumer Product Testing Company, Inc., 1981b).

The ocular irritation potential of two hair products (liquid and foam) containing 1.3% Acetamide MEA was evaluated using two groups (one product per group) of six young adult, New Zealand white rabbits. The test substance (10 μl, undiluted) was placed on the cornea of one eye of each rabbit via a 100 μl glass syringe; eyes were not rinsed. The contralateral eye served as the control. Ocular reactions were scored on day 1 according to the Draize (1959) scale. Scoring was discontinued after day 1 because no ocular irritation reactions had been observed. Neither the liquid product nor the foam product was classified as an ocular irritant (Hazleton Laboratories America, Inc., 1986).

Skin Irritation

The skin irritation potential of Acetamide MEA was evaluated according to a modification of the procedure by Draize et al. (1944) using 12 albino rabbits. The test substance (500 mg) was applied to the trunk of each animal; patches (open) remained in place for 24 h. The application sites of six rabbits were abraded, whereas those of the remaining rabbits remained intact. The animals were immobilized during the exposure period. At 24 h postapplication, reactions were scored according to the scale of 1 (very slight erythema) to 4 (severe erythema to slight eschar formation); 1 (very slight edema) to 4 (severe edema, raised more than 1 mm and extending beyond the area of exposure). Reactions were also scored at 72 h postapplication. Scores determined at 24 and 72 h were averaged. Well-defined erythema and slight edema were observed. Acetamide MEA was classified as a mild skin irritant (Union Carbide Data Sheet, 1967).

In another study, the skin irritation potential of Acetamide MEA (activity = 70% minimum; pH 7.1) was evaluated using six New Zealand White rabbits. The test

substance (0.5 ml) was applied to two sites, one abraded and one intact. Each site was covered with an occlusive patch for 24 h and then scored for erythema and edema at 24 and 72 h postapplication. The mean irritation scores determined at 24 and 72 h were averaged, and a primary irritation index (PII) was calculated. Acetamide MEA was not a primary skin irritant (PII = 0.43) (Consumer Product Testing Company, Inc., 1981c).

Skin Sensitization

The sensitization potential of Acetamide MEA was evaluated in the modified Magnusson-Kligman maximization test (Magnusson and Kligman, 1969) using 10 female Dunkin-Hartley guinea pigs. During induction, the animals were injected intradermally with 5.0% Acetamide MEA in propylene glycol and 5.0% Acetamide MEA in Freund's adjuvant, and also received a topical application of 100.0% Acetamide MEA (topical induction booster). Prior to induction, the induction sites were pretreated with 5.0% w/w sodium lauryl sulfate in petrolatum. Each animal in the experimental group was challenged with topical wrappings containing Acetamide MEA at concentrations of 50.0% (applied to anterior site) and 100.0% (applied to posterior site) in propylene glycol, respectively. Similarly, the 5 guinea pigs in the control group were each challenged with 50.0% and 100.0% propylene glycol. Challenge reactions were evaluated at 48 and 72 h according to the scale of 0 (no evidence of any effect) to 4 (severe = deep red erythema with or without edema). No positive reactions were observed in the experimental or control group, and the test substance was classified as a nonsensitizer (CTFA, 1988).

MUTAGENICITY

The mutagenicity of Acetamide MEA was evaluated in the Ames test (Maron and Ames, 1983) using strains TA98, TA100, TA1535, TA1537, and TA1538 of *Salmonella typhimurium*. Each strain was incubated for approximately 46–72 h, with Acetamide MEA concentrations ranging from 100 to 5,000 μg/plate both with and without metabolic activation. Negative control cultures (all strains, with and without metabolic activation) were incubated with sterile deionized water (100 μl/plate). Positive control cultures were treated as follows: sodium azide (1 μg/plate: TA100 and TA1535 without activation); 2-aminoanthracene (0.5 μg/plate; all strains with activation); and 4-nitro-o-phenylenediamine (5 μg/plate: TA98, TA1537, and TA1538 without activation). Within the range of concentrations tested, Acetamide MEA was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. These results indicate that Acetamide MEA did not induce base-pair substitution or frameshift mutations in this bacterial test system. The increase in the mean number of revertants in positive control cultures over that noted for the concurrent negative control value for each respective strain was greater than threefold (Clairol Inc., 1991).

The genotoxicity of Acetamide MEA in primary rat hepatocytes was evaluated using the unscheduled DNA synthesis (UDS) assay (Williams 1977, 1980; Butterworth et al., 1987). Rat hepatocyte cultures were exposed to Acetamide MEA concentrations ranging from 5000 to 0.500 μg/ml (solvent = sterile deionized water) in the presence of 10 μCi/ml ^{3}HTdR (47 Ci/mM) for 18.8 h. Positive control cultures were exposed to 4.48×10^{-7} M 2-acetylaminofluorene (0.10 μg/ml) in dimethyl sulfoxide (DMSO) and, negative control cultures, to 10% sterile deionized water. The cells were

examined microscopically and UDS was measured by counting nuclear grains and subtracting the average number of grains in three nuclear-sized areas adjacent to each nucleus (referred to as net nuclear grain count). The net nuclear grain count was determined for at least 50 randomly selected cells per coverslip; nuclei with normal morphology were scored. The criteria for activity in the UDS assay were an increase in the mean net nuclear grain count to at least five grains per nucleus above the concurrent solvent control value and/or an increase in the percentage of nuclei having five or more net grains, such that the percentage of these nuclei in test cultures is at least 10% above the percentage observed in the solvent control cultures. At a concentration of 5,000 μg/ml Acetamide MEA, a slight increase in nuclear labeling was suspected. However, this observation was not confirmed. Acetamide MEA did not induce unscheduled DNA synthesis within the range of concentrations tested, and, therefore, did not induce DNA damage. The positive control, 2-acetyl-aminofluorene was active in the UDS assay (Hazleton Washington, Inc., 1991).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

A facial use test involving 19 female subjects, selected at random, was used to evaluate the skin irritation potential of a product containing 0.5% Acetamide MEA. Each subject was instructed not to wear facial makeup or a moisturizer, and also was examined for any pre-existing condition (erythema, swelling, or dryness) prior to application. The product being tested (0.1 cc) and a control product (0.1 cc) of unknown composition were rubbed onto one side of the face twice daily (6 h interval) for 5 consecutive days. After application, subjects were allowed to apply facial makeup. The following reactions to the test product were observed in a total of three subjects. On the second day of the test, one subject withdrew after observing a reaction, blotchy erythematous plaques in the cheek area, on both sides of the face. Reactions were not observed on the following morning. Another subject withdrew because of reactions classified as moderate erythema and a patchy vesicular response. These reactions were thought to have resulted from contact with poison ivy during the weekend prior to the test. Subsequent follow-up testing in which test and control products were applied to the flex area three times per day for one week revealed no reactions. Minimal erythema and dryness were observed in the third subject. These reactions were collectively referred to as a slight increase over the initial test condition and, more than likely, represented normal fluctuations. The product containing 0.5% Acetamide MEA did not evoke unacceptable clinical irritation, and was comparable to the control product (CTFA, 1987).

Skin Irritation and Sensitization

The skin irritation and sensitization potentials of Acetamide MEA (7.5% w/v in distilled water) were evaluated using 50 subjects. The test substance was applied via an occlusive patch (same site) on Monday, Tuesday, Wednesday, and Thursday for 3 consecutive weeks. Each patch remained in place for 24 h. After patch removal, sites were scored according to the following scale: 0 (no visible erythema) to 4 (severe irritation, consisting of erythema, swelling, papules, and necrosis and extension

beyond the boundaries of contact). The test site was to have been changed only if substantial irritation resulted. Substantial irritation was defined as a score of greater than 1 (erythema). After a nontreatment period of approximately 2 weeks, an occlusive challenge patch was applied for 24 h to a new test site. Reactions were scored immediately after patch removal and 24, 48, and 72 h later. Irritation reactions were not observed during the first week of induction. During the second week, erythema was observed in one subject. During the third week of induction, skin irritation was observed in two subjects. Erythema and swelling were observed in one of the subjects, necessitating a change in the application site; erythema was observed in the other subject. Reactions were not observed during the challenge phase. The authors concluded that the irritation reactions observed were indicative of skin fatigue, and that the test substance did not cause primary irritation or sensitization (Habitant Trading Corporation, 1977).

Skin Sensitization

The skin sensitization potential of a hair product (liquid) containing 1.3% Acetamide MEA was evaluated using 124 subjects (67 males, 57 females; 20–81 years old). The product was diluted with water to a concentration of 50.0% w/v (effective concentration of Acetamide MEA = 0.65%). A total of 111 subjects completed the study; 45 subjects had allergies. The 13 subjects who withdrew did so for reasons unrelated to the conduct of the study. Prior to application of the first induction patch, the test site was wiped with a gauze pad saturated with 95% ethanol or isopropanol. The test substance (0.5 ml) was then applied to the lateral surface of the upper arm, between the shoulder and elbow, via an occlusive patch secured with surgical tape. Patches were applied on Mondays, Wednesdays, and Fridays for a total of nine 24 h induction applications, and the subjects were instructed to clean the test site after each patch removal. Reactions on Monday and Wednesday were scroed at 48 h postapplication according to the scale: 0 (no visible reaction) to 5 (bullous reaction); reactions on Friday were scored at 72 h. After a 17-day nontreatment period, 2 challenge patches (1 at original site and 1 at similar site on opposite arm) were applied for 24 h. Each challenge site was wiped with a gauze pad saturated with 95% ethanol or isopropanol prior to patch application. Reactions were scored at 48 and 96 h postapplication. Twelve subjects had reactions only during the induction phase (mild erythema in 11 subjects, mild erythema with papules and/or edema in 1 subject). Reactions during induction and challenge phases were observed in two subjects. One of these subjects had mild erythema during induction and the first challenge (original and alternate sites), and the other had mild erythema during induction, the first challenge (original and alternate sites), and the second challenge (adjacent site). The authors concluded that there was no evidence of sensitization in any of the subjects tested (Harris Laboratories, Inc., 1986).

SUMMARY

Acetamide MEA (CAS No. 142-26-7) is an aliphatic amide that may be produced via acetylation of ethanolamine using acetic anhydride; the reaction is followed by vacuum distillation. It is usually marketed as a 70.0–75.0% aqueous solution.

N-nitrosodiethanolamine was not detected when Acetamide MEA was analyzed via high-performance liquid chromatography. Both acetamide (up to 0.0030%) and monoethanolamine (up to 0.0029%) were detected when Acetamide MEA was analyzed via gas chromatography–mass spectrometry.

Acetamide MEA is used as a skin conditioning agent-humectant and hair conditioning agent in cosmetic products. Product formulation data reported to FDA in 1989 indicated that this ingredient was used at concentrations up to 25%; concentration of use data are no longer reported to FDA. Current FDA data indicate that Acetamide MEA is used in 102 cosmetic products.

Noncosmetic uses of Acetamide MEA are as follows: detoxifier, plasticizer, humectant for paper products, solvent for fountain-pen inks, and textile conditioner. Adhesives containing Acetamide MEA may be used safely as components of articles intended for use in packaging, transporting, or holding food.

Oral LD50's of 27.66 g/kg and 26.95 g/kg (relatively harmless) were reported for Acetamide MEA in 2 studies involving rats. In another study involving rats, 2 hair products containing 1.3% Acetamide MEA did not cause death at a dosage of 16.9 g/kg, the highest dose tested.

The acute dermal toxicity of Acetamide MEA was evaluated using six rabbits. None of the animals dosed with 20 ml/kg of the test substance died.

The subchronic percutaneous toxicity of a hair product diluted to a concentration of 0.65% Acetamide MEA was evaluated using rabbits. None of the animals died during the study, and no evidence of systemic toxicity was observed.

In ocular irritation studies, Acetamide MEA (activity = 70% minimum) and two hair products containing 1.3% Acetamide were not classified as ocular irritants when instilled (0.1 ml) into the conjunctival sac of the eyes of New Zealand white rabbits.

Mild skin irritation reactions were observed in albino rabbits after Acetamide MEA (500 mg, open patch) was applied to the skin for 24 h. In another study, Acetamide MEA (activity = 70% minimum) was not a skin irritant when applied (0.5 ml, occlusive patch) for 24 h to abraded and intact skin of New Zealand white rabbits.

In the maximization test, Acetamide MEA was classified as a nonsensitizer in guinea pigs when tested at a concentration of 5.0% during induction and at concentrations of 50.0% and 100.0% during the challenge phase.

Acetamide MEA did not induce base-pair substitution or frameshift mutations in the Ames test. Results were also negative in the unscheduled DNA synthesis assay involving rat hepatocytes.

In a 5-day facial use test involving female subjects, a product containing 0.5% Acetamide MEA did not evoke unacceptable clinical skin irritation.

Neither primary irritation nor sensitization reactions to Acetamide MEA (7.5% w/v in distilled water) were observed in a repeated insult patch test (occlusive patches) involving male and female subjects. In another repeated insult patch test (occlusive patches) involving male and female subjects, there were no sensitization reactions to a hair product diluted to 0.65% Acetamide MEA.

DISCUSSION

Concentration of use data are no longer submitted to FDA by the cosmetics industry. Due to this fact, the Expert Panel can no longer make the conclusion "Safe as used," as was previously done, but must now make a conclusion based on the product

and test concentrations used in the report. The results of a human skin sensitization study cited in this report indicate that Acetamide MEA was not a sensitizer at a concentration of 7.5%. This maximum test concentration is the basis for the Panel's conclusion relative to use concentrations of Acetamide MEA in leave-on cosmetic products.

The Expert Panel recognizes that Acetamide MEA may form N-nitroso compounds in the presence of nitrosating agents, and that acetamide may be a minor impurity in Acetamide MEA. In commercial lots of Acetamide MEA, acetamide has been detected at concentrations up to 0.0030%. For formulated cosmetics, the expected breakdown products of Acetamide MEA are acetic acid and monoethanolamine. This means that acetamide in the formulation results from contamination of the starting material and is not a degradation product of Acetamide MEA. Therefore, when used as a cosmetic ingredient, Acetamide MEA should be free of nitrosamines and acetamide, and the finished cosmetic product should not contain nitrosating agents.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that Acetamide MEA is safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products and is safe in the present practices of use in rinse-off products. Cosmetic formulations containing Acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide.

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