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Final Report on the Safety Assessment of Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamine

Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamine are used as water-soluble emulsifiers and neutralizers in cosmetic products at concentrations up to 1%. In animal studies these ingredients were slightly toxic to practically nontoxic to rats and guinea pigs via acute oral administration. Triisopropanolamine was relatively nontoxic to rats in the two subchronic oral studies. These ingredients were moderate skin irritants for rabbits. All four ingredients, when tested at 100% concentrations, were severe ocular irritants in rabbits. Products containing small amounts (~1%) of Diisopropanolamine or Triisopropanolamine were not ocular irritants in rabbits. The Triisopropanolamine salt was not mutagenic in *Aspergillus nidulans*. Diisopropanolamine and Isopropanolamine at concentrations of 2% did not induce allergic contact dermatitis or photoallergic dermatitis in humans. Clinical studies on cosmetic products containing no more than 1% Diisopropanolamine or 1.1% Triisopropanolamine were minimal skin irritant and contact sensitizers. It is concluded that Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamine are safe as cosmetic ingredients in the present practices of use and concentration. The Isopropanolamines should not be used in products containing N-nitrosating agents.

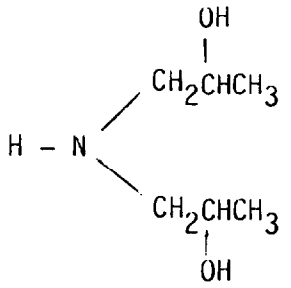
INTRODUCTION

Diisopropanolamine, Triisopropanolamine, and Isopropanolamine are aliphatic amines of isopropyl alcohol. Mixed Isopropanolamines is a mixture of Di-, Tri-, and Isopropanolamine. The Isopropanolamines are emulsifying agents and neutralizers in cosmetics.

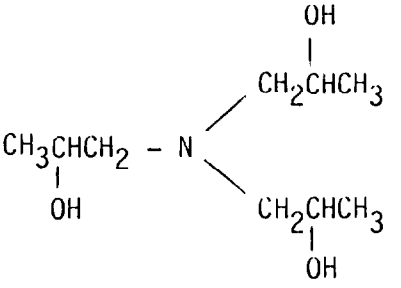
CHEMISTRY

Definition and Structure

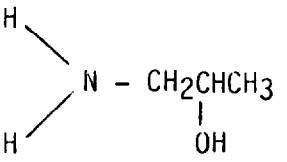
Diisopropanolamine (CAS No. 110-97-4), Triisopropanolamine (CAS No. 122-20-3), and Isopropanolamine (CAS No. 78-96-6) are hydroxylated aliphatic amines with two, three, and one isopropanol group attached to one nitrogen atom, respectively.[1]



Diisopropanolamine
(M.W. 133.22)



Triisopropanolamine
(M.W. 191.27)



Isopropanolamine
(M.W. 75.11)

Mixed Isopropanolamines (RD No. 977060-04-0) is a blend of 40–50% Diisopropanolamine, 40–50% Triisopropanolamine, and 10–15% Isopropanolamine.[2]

Synonyms for these ingredients include: **Diisopropanolamine:** DIPA, 1,1'-iminobis-2-propanol, bis(2-hydroxypropyl)amine, bis(2-propanol)amine. **Triisopropanolamine:** TIPA, 1,1',1''-nitrilotris-2-propanol tris(2-hydroxypropyl)amine, tris(2-hydroxy-1-propyl)amine. **Isopropanolamines:** MIPA, 1-amino-2-propanol, 1-aminopropan-2-ol, monoisopropanolamine, alpha-aminoisopropyl alcohol, 2-hydroxy-1-propylamine,1-methyl-2-aminoethanol.[1,3]

In this review Diisopropanolamine, Triisopropanolamine, and Isopropanolamines will be referred to as DIPA, TIPA, and MIPA, respectively. Mixed Isopropanolamines will be referred to as Mixed Isopropanolamines.

Physical Properties and Reactivity

DIPA is a white, waxy solid with a low melting range of 32–42°C. It is completely miscible with water and alcohol, slightly soluble in toluene, and insol-

uble in hydrocarbons. DIPA is stable under normal storage conditions but may darken with prolonged exposure to air or iron.[4]

TIPA is a white solid which is soluble in water, alcohol, and benzene and slightly soluble in n-heptane. It is stable under normal conditions but should be protected from exposure to carbon dioxide and water.[5]

MIPA is a clear, colorless liquid. It is completely miscible with water, benzene, and alcohol. It is stable under normal storage conditions but, like DIPA, tends to darken on prolonged exposure to air or iron.[6]

Mixed Isopropanolamines occur as a clear colorless liquid that is stable under normal storage conditions. The liquid is miscible with water, alcohol, benzene, glycerin, and acetone and insoluble in hydrocarbons.[2]

All of these propanolamines react rapidly with acid to form the corresponding amine salt. DIPA and MIPA can react with fatty acid esters to form diisopropanolamides or monoisopropanolamides. DIPA, TIPA, MIPA, and Mixed Isopropanolamines form nitrosamines under appropriate conditions.[2,4-6] Propanolamines burn when exposed to heat, flame, sparks, and powerful oxidizers. TIPA emits toxic fumes when heated to decomposition.[7] Extensive information on the physical properties, chemical properties, and reactivity of alkanolamines in general is available.[8] Physical and chemical properties for DIPA, TIPA, MIPA, and Mixed Isopropanolamines are presented in Table 1.

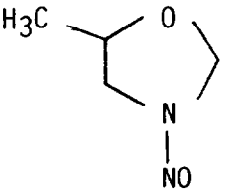
N-Nitroso-5-Methyl-1,3-Oxazolidine Formation

N-nitroso-5-methyl-1,3-oxazolidine was detected as a contaminant of cutting fluid.[10,11] A model study indicated that N-nitroso-5-methyl-1,3-oxazolidine can form slowly from aqueous formaldehyde, 1-amino-2-propanol (MIPA), and so-

TABLE 1. Physical Properties[1-6,9]

Property	*Diisopropanolamine*	*Triiso-propanolamine*	*Isopropanolamine*	*Mixed Isopro-panolamines*
Molecular weight	133.22	191.27	75.11	~140
State (room temperature)	Waxy solid	Solid	Liquid	Liquid
Melting point	32°-42°C	60°C	1.4°C	−20--30°C (pour point)
Boiling point	249°C	305°C	160°C	181°-315°C
Flash point	127°C	160°C	77°C	110°C
Specific gravity	0.9890 (45°/20°C)	1.02 (20°/20°C)	0.9619 (20°/20°C)	1.007 (20°/20°C)
Refractive index	1.4450-1.4550 (60°C)	1.4600 (40°C)	1.4462 (20/D)	1.4601 (25°C)
Vapor density	4.7	---	2.6	---
Vapor pressure	0.02 mm (42°C)	<0.01 mm (20°C)	---	---
pH of 5% aqueous solution	11.5	10.8	12.1	11.6
Percent pure ingredient	97.0	98.0	98.5	99.5 alkanolamine

dium nitrate under alkaline conditions at room temperature. This nitrosamine has been reported to be mutagenic in the Ames Salmonella Mutagenicity Assay and carcinogenic in rats.[12,13]



N-nitroso-5-methyl-1,3-oxazolidine

Analytical Methods and Impurities

The alkanolamines can be analyzed by gas–liquid chromatography after derivation of the alcohol groups. Solvent extraction coupled with infrared film spectra analysis has been used for the separation and identification of DIPA, specifically.[14]

For cosmetic use, DIPA typically contains a minimum of 97.0% Diisopropanolamine, TIPA contains 98.0% Triisopropanolamine, MIPA contains 98.5% Isopropanolamine, and Mixed Isopropanolamines contains 99.5% alkanolamine, and the four cosmetic ingredients contain 0.5% maximum moisture.[2,4–6] Commercial DIPA and TIPA were reported to contain between 20–1300 ppb and 21–270 ppb of N-nitrosobis(2-hydroxypropyl)amine, respectively.[15] The highest concentrations of the nitrosamine were found in samples that were at least 5 years old. DOW Chemical U.S.A.[16] has detected no nitrosamines in their isopropanolamine products. The analytical technique used, thermal energy analysis following liquid chromatographic separation, has a detection limit of 20 ppb. Data were not available about the possible contamination of cosmetic products that contain isopropanolamines with N-nitrosobis(2-hydroxylpropyl)amine and/or N-nitroso-5-methyl-1, 3-oxazolidine. N-nitrosobis(2-hydroxyproply)amine is a potent pancreatic carcinogen in hamsters.[17] It is absorbed rapidly through the skin of hamsters[18] and, upon topical application, induced neoplasms of the lip, cheek pouch, and vaginal epithelium.[19] In rats, it induced neoplasms of the colon, respiratory tract, esophagus, and liver,[20,21] in mice it induced neoplasms of the lung, liver, and nasal cavity, and in rabbits and guinea pigs, it induced neoplasms of the liver.[22]

Method of Manufacture

DIPA, TIPA, MIPA, and Mixed Isopropanolamines are manufactured from propylene oxide and aqueous ammonia by distillation at high temperature and pressure. The excess ammonia and water are removed from the resulting mixtures of isopropanolamines.[2,4–6]

USE

Purpose in Cosmetics

The Isopropanolamines are used in conjunction with fatty acids as emulsifying agents in bath preparations and cosmetic lotions.[9,23,24] The alkaline character of DIPA, TIPA, and MIPA is used to neutralize cosmetic preparations, such as cold wave solutions (hair perms), aerosol hair fixatives, and indoor tanning lotions[14,25] (Table 2).

Scope and Extent of Use in Cosmetics

DIPA, TIPA, and MIPA are used in a wide variety of cosmetics, including fragrance, hair, skin care, and tanning preparations. They constitute <0.1% to 10% of the product, with the majority of the products containing >0.1–1% DIPA or TIPA or ≤0.1% MIPA.[26]

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 part 720.4 of the Code of Federal Regulations (1982). Since certain cosmetic ingredients are supplied by the manufacturer at concentrations less than 100%, the concentration reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Surfaces, Frequency, and Duration of Application

Cosmetic products containing DIPA, TIPA, or MIPA can be applied to all parts of the body, including the skin, face (including eyes and lips), nails, and hair. Products can be applied occasionally or up to several times a day, and they remain in contact with the body for a short time (as with hair permanents) or continuously for several days. Many of these products have the potential for constant use spanning several years.

Noncosmetic Uses

The Isopropanolamines are used as emulsifying agents in polishes, textile specialty products, leather compounds, metal cutting oils, waterbase paints, drycleaning soaps, wax removers, plasticizers, and insecticides.[9,27,28] DIPA and Mixed Isopropanolamines are used as antimicrobial agents in cutting fluids.[29] DIPA, TIPA, and MIPA are used in adhesives, paper and paperboard, paper and paperboard coatings, and production aids and sanitizers for food packaging and, as such, are regulated as indirect food additives by the FDA in the Code of Federal Regulations (1982). DIPA has been used in prescription drug formulations of theophylline[30,31] and ophthalmic preparations of tropicamide.[32] DIPA is also on FDA's List of Inactive Ingredients in Marketed Prescription Products.[33]

TABLE 2. Product Formulation Data[26]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)				
			Unreported concentration	>5–10	>1–5	>0.1–1	≤0.1
Diisopropanolamine							
Colognes and toilet waters	1120	2	–	–	–	–	2
Other fragrance preparations	191	13	–	–	–	11	2
Hair conditioners	478	1	–	–	–	1	–
Hair sprays (aerosol fixatives)	265	1	–	–	1	–	–
Permanent waves	474	7	–	6	–	1	–
Tonics, dressings, and other hair grooming aids	290	2	–	–	–	1	1
Wave sets	180	1	–	–	–	1	–
Other hair preparations (noncoloring)	177	2	–	–	2	–	–
Makeup foundations	740	2	–	–	2	–	–
Other makeup preparations (not eye)	530	5	–	–	1	4	–
Aftershave lotions	282	4	–	–	–	3	1
Other shaving preparation products	29	2	–	–	–	1	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	10	–	–	–	10	–
Moisturizing skin care preparations	747	4	–	–	1	2	1
Night skin care preparations	219	1	–	–	–	1	–
Paste masks (mud packs)	171	2	–	–	1	1	–
Skin fresheners	260	2	–	–	–	1	1
Wrinkle smoothers (removers)	38	1	–	–	–	1	–
Other skin care preparations	349	1	–	–	–	1	–
Suntan gels, creams, and liquids	164	2	–	–	–	2	–
Indoor tanning preparations	15	1	–	–	–	1	–
1981 TOTALS		66	–	6	8	43	9

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			Unreported concentration	>1–5	>0.1–1	≤0.1
Triisopropanolamine						
Baby lotions, oils, powders, and creams	56	1	–	–	1	–
Hair conditioners	478	4	–	1	3	–
Hair sprays (aerosol fixatives)	265	9	–	–	6	3
Tonics, dressings, and other hair grooming aids	290	13	–	1	11	1
Wave sets	180	2	–	–	2	–
Other hair preparations (noncoloring)	177	2	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	1	–	1	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	1	–
Moisturizing skin care preparations	747	3	–	–	3	–
1981 TOTALS		36	–	3	29	4
Isopropanolamine						
Mascara	397	3	–	–	1	2
Tonics, dressings, and other hair grooming aids	290	1	–	–	–	1
Aftershave lotions	282	2	–	–	2	–
Depilatories	32	1	–	–	–	1
Moisturizing skin care preparations	747	3	–	–	2	1
Suntan gels, creams, and liquids	164	1	–	–	–	1
1981 TOTALS		11	–	–	5	6

BIOLOGY

Metabolism

Microbial Metabolism

MIPA (1-amino-2-propanol) is a precursor of vitamin B_{12} and/or an intermediary in the production of propionaldehyde in many microbial genera. The metabolic pathways of MIPA and aminoacetone have been studied in several microbial genera, including *Pseudomonas*.[34-43]

Mammalian Metabolism

A 19.5 mg/kg dose of ^{14}C-DIPA was dissolved in acetone and applied to an area of skin on the shoulders of four female Fischer 344 rats.[44] The solvent was allowed to evaporate, and neat DIPA remained in contact with the skin for 48 h. The treatment site was occluded. At 48 h, 25% of the DIPA had penetrated the skin. Of the absorbed amount, 12% was excreted in the urine and another 12.5% remained in the tissues of the animals. Less than 1% was eliminated in feces and expired air. DIPA did not accumulate in the fat. About 50% of the applied radioactivity was recovered from the site of application, and approximately 23% was recovered from the skin at and around the application site. A 19 mg/kg dose of aqueous ^{14}C-DIPA was administered intravenously to four female Fischer 344 rats. Greater than 70% of the radioactivity was cleared from the blood within the first 6 h. About 90% of the dose was recovered in the urine within 12 h. Metabolites of DIPA were not isolated from the urine. It was concluded that DIPA does not penetrate the skin of rats rapidly. It is anticipated that DIPA, present in cosmetic products, will be absorbed only slowly through the skin. That portion that is absorbed will be eliminated rapidly and almost entirely in the urine.

Isopropanolamine (MIPA) is a naturally occurring amino alcohol and has been isolated from human and rat urine. It arises from threonine in the rat, most likely via aminoacetone. 1-Aminopropan-2-ol dehydrogenase activity has been found in rat liver.[45,46] MIPA was readily phosphorylated by rat hepatocytes but was only slowly incorporated into phospholipids. MIPA inhibited the incorporation of choline into phosphatidylcholine but was ineffective at inhibiting ethanolamine incorporation into phospholipids. MIPA was also a competitive inhibitor of ethanolamine for the enzyme ethanolamine deaminase.[47-50] MIPA did not have any antagnostic activity against the binding of epinephrine to alpha-adrenergic receptors in isolated rat tests.[51]

ANIMAL TOXICOLOGY

Oral Toxicity

Acute

A 30% aqueous solution of DIPA was administered orally to two groups of two rats. One group received a dose of 2.0 g/kg; DIPA had no observable effects on these rats. The other group received a dose of 3.98 g/kg; both rats died within 24 h.[52]

An 85% aqueous solution of TIPA was administered orally by gavage to male CDF albino rats. Groups of six rats were given 630–10,000 mg/kg TIPA. The single dose oral LD_{50} was 5994 mg/kg. Following administration of TIPA, all the rats were lethargic. A rough hair coat was observed in rats given 5000 and 10,000 mg/kg, a dark exudate around the eyes of rats given 5000 mg/kg, and pale, watery eyes and diarrhea in rats given 10,000 mg/kg. Surviving rats gained weight during the 2 weeks after TIPA administration. No treatment-related effects were observed at pathological examination at the end of the 2 weeks.[53]

A 10% corn oil solution of MIPA was administered orally by gavage to male CDF albino rats. Groups of six rats were given 500 to 3500 mg/kg MIPA. The single dose oral LD_{50} was 2098 mg/kg. Following administration of MIPA, all the rats were lethargic and had diarrhea and rough hair coats. Rats that received 2000 mg/kg MIPA had watery eyes and/or palpebral closure. All surviving rats gained weight during the 2 weeks after MIPA administration. No treatment-related effects were observed upon pathological examination at the end of the 2 weeks.[54]

The acute oral LD_{50}s for TIPA, MIPA, and Mixed Isopropanolamines (12% MIPA, 44% DIPA, and 44% TIPA) were determined using male Wistar rats and guinea pigs of both sexes. A single dose of a 50% aqueous solution of the test material was administered by gavage to 10 animals per dosage group. The LD_{50}s for rats were: TIPA, 6.50 g/kg; MIPA, 4.26 g/kg; Mixed Isopropanolamines, 5.24 g/kg. In the guinea pig, the LD_{50}s for TIPA and Mixed Isopropanolamines were 1.58 g/kg and 1.52 g/kg, respectively.[55,56]

The acute oral toxicity of a sunscreen containing 1% DIPA was evaluated in five female and five male albino rats. The rats were fasted the night prior to a single 5 g/kg dose of the product. The product was administered by gavage, and the animals were observed for 14 days for signs of toxicity. No unusual behavior was observed and no animals died. No lesions were found at necropsy. The LD_{50} for the sunscreen lotion was >5 g/kg.[57]

A facial sunscreen containing 1% DIPA was administered to rats by gavage. A single 5 g/kg dose of undiluted product was given to five male and five female Sprague-Dawley rats following a 16–22-h fast. No animals died during the 14-day observation period, but one animal had diarrhea 2 h after administration of the test substance. Nothing abnormal was observed at necropsy[58] (Table 3).

Subchronic

Doses of 0, 100, 300, 600, 1200, and 3000 mg/kg per day DIPA were given in the drinking water to groups of five male and five female CDF Fischer 344 rats for 2 weeks. Appearance and demeanor of the rats were observed during the study, body weights, feed and water consumption, and standard clinical biochemical parameters were measured, and at necropsy, gross pathological observations were made, organ weights were recorded, and the liver, kidneys, and urinary bladder were examined histopathologically. The 3000 mg/kg per day dose of DIPA was not well tolerated by either male or female rats. Two of five male rats died during the 2 weeks. At this dose, marked reductions in body size, body fat, and organ sizes and various alterations in clinical biochemical parameters and organ weights were observed due to the emaciated state that resulted from a decrease in feed and water consumption. Acute inflammation and degen-

TABLE 3. Acute Oral Toxicity

Ingredient	LD_{50} (g/kg)		Reference
	Rat	Guinea pig	
DIPA[a]	>2	---	52
TIPA[b]	5.99	---	53
TIPA[c]	6.5	1.58	55
MIPA[c]	2.10	---	54
MIPA[c]	4.26	---	56
Mixed Isopropanolamine[a]	5.24	1.52	55
DIPA[e]	>5[f]	---	57, 58

[a]Administered as a 30% aqueous solution.
[b]Administered as an 85% aqueous solution.
[c]Administered as a 50% aqueous solution.
[d]Administered as a 10% corn oil solution.
[e]1% DIPA in sunscreen products.
[f]Product LD_{50}.

eration of the kidneys and urinary bladder were observed in the highest dose rats. The researchers postulated that this was due to decreased water intake that resulted in a concentration of DIPA or its metabolite(s) in these tissues. Generalized hepatic atrophy was also observed in these rats, but there was no other evidence of significant hepatotoxicity. Slight reductions in feed and water consumption were observed in male and female rats that received 1200 mg/kg per day DIPA. A small decrease in body weight was observed in male but not in female rats. Relative kidney weights were slightly increased. An unspecified kidney alteration, similar to that observed in rats given 3000 mg/kg per day DIPA, was seen in one male rat given 1200 mg/kg per day. This was the only histopathological treatment-related effect observed at this dose. At doses of 600 mg/kg per day DIPA or less in the drinking water, no significant toxicological effects were observed.[59]

Doses of 0, 100, 300, 600, 1200, and 2000 mg/kg per day TIPA were given in the drinking water to groups of five male and five female of CDF Fischer 344 rats for 2 weeks. Appearance and demeanor of the rats were observed during the study. Body weights, feed and water consumption, and standard clinical biochemical parameters were measured, and, at necropsy, gross pathological observations were made, organ weights were recorded, and the liver, kidneys, and urinary bladder were examined histopathologically. All the rats survived the study. Decreased body weight gain was observed in male and female rats that received the 2000 mg/kg per day TIPA dose. Water consumption may have decreased in females at this dose. Other water consumption data were variable. Food intake of the highest-dose female rats was slightly but significantly lower than that of control rats. A trend toward decreased serum glucose was noted in male rats that received 300 mg/kg per day or more TIPA and in females that received 600 mg/kg per day or more TIPA. At the 1200 and 2000 mg/kg per day TIPA doses, slight decreases in total serum protein and albumin were observed in both male and female rats. There were no other significant differences in stan-

dard clinical biochemical parameter measurements. There was a trend toward increased relative kidney weights in all rats that were given 300 mg/kg per day or more TIPA. These increases were significant in male rats given 600 mg/kg per day or more TIPA and in female rats given 2000 mg/kg per day TIPA. There were no other indications of a nephrotoxic response, either upon kidney examination or from blood urea nitrogen values. There were no TIPA-related effects on the liver or urinary bladder observed upon histopathological examination.[60]

Subchronic oral toxicity of TIPA was studied in rats. Three or four groups of five rats were given 0.14 g/kg per day to 1.35 g/kg per day TIPA in the drinking water for 30 days. The animals were evaluated for body weight gain, reduction in appetite, and histopathological changes of adrenal glands, upper intestine, kidneys, liver, spleen, and testes. No compound-related deaths were observed. The minimum daily dosage of TIPA causing reduced growth and reduced appetite was 1.35 g/kg per day. A dose of at least 0.26 g/kg per day produced unspecified histopathological changes.[61]

Intraperitoneal Toxicity

Adult mice were given single 0.5 ml intraperitoneal injections of MIPA in isotonic saline and observed for 7 days. Five mice received 0.5 ml/kg MIPA, and groups of three mice each received 0.25, 0.125, 0.0625, or 0.0313 ml/kg MIPA. Four of the five mice in the highest dosed group died within 1¾ h. One animal in the 0.25 ml/kg group died on day 3, and no other mice from any group died within the 7-day observation period.[62]

Skin Toxicity and Phototoxicity

Undiluted DIPA was applied to seven intact sites and one abraded site on the abdomens of rabbits. Moderate hyperemia and severe necrosis were observed at the intact sites, and slight hyperemia, edema, and moderate denaturation were observed at the abraded sites. A 10% aqueous solution of DIPA was applied to 10 intact sites on the ears of rabbits and 10 intact sites and 2 abraded sites on the abdomens of rabbits. DIPA had no observable effect on the ears of rabbits. Moderate hyperemia and slight blistering were observed at the intact sites, and moderate hyperemia, slight edema, and moderate denaturation were observed at the abraded sites on the abdomens of the rabbits.[52]

DIPA was noncorrosive, as described in the Federal Hazardous Substances Act, in a 4-h test.[63]

Two rabbits received 5000 mg/kg TIPA as an 85% aqueous solution in an acute percutaneous absorption test. Both rabbits survived the 2-week observation period, and no symptoms of toxicity were noted.[53]

An 85% aqueous solution of TIPA was applied to the unconfined skin of rabbits, and slight redness, very slight swelling, very slight exfoliation, and a superficial burn were observed. The same solution was applied to the confined skin of rabbits, and moderate to marked redness, slight swelling, and slight exfoliation were observed. A moderate burn and scar formation were observed after the application of TIPA to three abraded and nine intact sites on the skin of rabbits.[53]

MIPA was applied in doses of 630–5000 mg/kg to the skin of rabbits in an acute percutaneous absorption test; the LD_{50} was 1851 mg/kg. Marked redness,

moderate swelling, and marked necrosis of the skin were observed. At all doses, rabbits were lethargic. At doses of 630 and 1300 mg/kg, anorexia was observed, and at a dose of 1300 mg/kg, diarrhea was observed. At necropsy at the end of a 2-week observation period, no treatment-related changes were noted.[54]

MIPA was applied repeatedly to the skin of rabbits. Marked redness, very slight swelling, and, after seven applications, a moderate burn were observed on unconfined skin. Marked redness, moderate swelling of intact skin, marked swelling of abraded skin, slight exfoliation, and, after one application, a moderate burn that resulted in very slight scar formation were observed on confined skin. MIPA was also applied to the shaved abdomen of a rabbit; after 45 minutes, there was a superficial burn, and, after 1 h, there was a moderate burn.[54]

A 0.5 ml volume of a 1.0% aqueous solution of MIPA was applied to the clipped skin on the backs of one male and five female rabbits under a gauze patch for 4 h. Sites were graded for erythema, edema, and necrosis within 30 minutes of patch removal and then at 24, 48, and 72 h. No irritation was observed.[64]

MIPA was corrosive, as described in the Federal Hazardous Substances Act, in a 4-h test.[65]

Range-finding toxicity tests were performed with MIPA, and the cutaneous LD_{50} of MIPA for rabbits was 1.64 ml/kg. Five rabbits were evaluated for primary skin irritation with undiluted MIPA. Mild erythema ("strong capillary injection") was observed, and MIPA had a skin irritation score of 3 (maximum 6). The maximum saturated vapor inhalation time that caused no deaths in rats was 8 h.[56]

The primary skin irritation and phototoxicity of a facial sunscreen product containing 1% DIPA were evaluated using seven New Zealand rabbits (four male and three female). Two occlusive patches containing 200 mg product were applied to the clipped backs of six rabbits. The seventh rabbit served as a positive control and received 0.5 ml undiluted Oxsoralen, a known phototoxin. After 2 h, one patch per animal was removed, and the site was exposed to approximately 5×10^7 erg/cm^2 ultraviolet (UV) radiation with wavelengths of 320–450 nm. The test sites were 10 cm distant from the UV source. After UV exposure, patches were replaced for 48 h, then all patches were removed and the sites were scored for irritation 1, 24, and 48 h after patch removal. The group mean primary irritation score was 1.33 (individual animal scores—average of the three readings—were 0.33, 0, 3.33, 2.00, 1.67, and 0.67), the phototoxicity score was 1.50 (individual animal scores—average of the three readings—were 0.67, 0, 2.67, 2.00, 2.67, and 1.00) and the positive control score was 5.33 (scoring scale not given). The difference between the dermal irritation score and the dermal phototoxicity score was not significant. The facial sunscreen was a weak phototoxin and skin irritant.[66]

Six New Zealand rabbits (three male and three female) were used to evaluate the primary skin irritation and photoxicity of a facial sunscreen containing 1% DIPA. Two occlusive patches containing 0.2 ml undiluted product were applied to the shaved backs of each rabbit. Two hours later, one patch per animal was removed, and the test site was exposed for 30 minutes to UV radiation from a bank of four Sylvania F-40BLB UV bulbs (320–450 nm; peak at 360 nm). After the UV exposure, patches were replaced, then all wrappings and patches were removed 48 h after the initial application of the test material. Excess product was removed with damp gauze at this time. Test sites were graded 1, 24, and 48 h

after patch removal according to the Draize[67] scoring criteria (max PII of 8). The three scores for each animal were averaged, and group PIIs were calculated. Irradiated and nonirradiated sites had scores of 1 or 2 (max 4) at all three scorings. Slight edema was observed at 1 and 24 h after patch removal. The group PII was 1.2 (max 8) and group phototoxicity PII was 1.3. The facial sunscreen was both a mild primary irritant and phototoxin to skin.[68]

Ocular Irritation

The ocular irritation of 180 compounds was estimated by the range-finding test using rabbits. Five μl of undiluted test material was dropped onto the center of the cornea, and the lids were retracted for 1 minute, then released. Eighteen to 24 h later, the eye was examined, stained with fluorescein, and the injury was scored. TIPA, MIPA, and Mixed Isopropanolamines had scores of 6, 9, and 7 (max 10), respectively. These isopropanolamines were moderate to severe eye irritants.[56,69]

Fifty mg of DIPA, TIPA, or MIPA was instilled into the left eye of 12 rabbits, and the right eye served as an untreated control. All three compounds caused burns of the eyelid, eyeball, and corneal mucosa. Ocular damage was greatest with MIPA, intermediate with DIPA, and least with TIPA. Recovery occurred within 7 days for TIPA, 22 days for DIPA, and 32 days for MIPA. Cataracts and opaque corneas remained after recovery from ocular burns. Undiluted DIPA, TIPA, and MIPA were severe eye irritants.[70]

TIPA was instilled into the eyes of a rabbit and caused slight discomfort, severe conjunctival redness and swelling, a discharge, and moderate reddening of the iris, and moderate corneal injury. No signs of irritation were observed 21 days after treatment.[53]

MIPA was instilled into the eyes of a rabbit and caused severe discomfort, severe conjunctival redness and swelling, a discharge, moderate reddening of the iris, and opacity covering up to 100% of the cornea. Corneal damage was observed 21 days after treatment.[54]

A 0.1 ml volume of a 1.0% aqueous solution of MIPA was instilled into the conjunctival sac of one eye of each of three male and three female New Zealand white rabbits. The behavior of the rabbits was observed for indications of pain or discomfort. The eyes were examined at 1, 24, 48, and 72 h after treatment. The rabbits did experience slight discomfort upon instillation of the test material. Slight to moderate conjunctival redness was observed in three of the rabbits. All ocular redness was gone by 72 h after treatment.[71]

The ocular irritation of a sunscreen product containing 1% DIPA was evaluated in nine albino rabbits. One tenth milliliter of the product was instilled into the right eye of each animal, and the other eye served as an untreated control. In six rabbits, the eyes were not rinsed, and in the remaining three rabbits, the treated eyes were rinsed after 4 seconds with 20 ml water. Treated eyes were observed for irritation 1 h and 1, 2, 3, 5, and 7 days after instillation. No irritation was observed in animals with unrinsed eyes, and slight irritation (average ocular irritation score of 1.3; max 110) was observed at 1 h in the rabbits with rinsed eyes. No other irritation was observed in the animals with rinsed eyes. The product was not an ocular irritant.[72]

Another sunscreen containing 1% DIPA was tested for eye irritation using six

albino rabbits. The product was tested undiluted; 0.1 ml of product was instilled into the conjunctival sac of one eye of each animal. The eyes were not rinsed. Animals were observed, and the eyes were evaluated according to Draize[73] 1, 2, and 3 days after treatment. All irritation scores were 0; the product was not an eye irritant.[74]

A lotion containing 1.1% TIPA was evaluated for ocular irritation in nine albino rabbits. Undiluted product, 0.1 ml, was instilled into one eye of each animal, and the untreated contralateral eye served as control. Three of the nine rabbits had the test eye rinsed with 20 ml deionized water. Eyes were scored for irritation 1, 2, 3, 4, and 7 days after product application. One rabbit in the rinsed group had minimal swelling of the conjunctiva at the day 1 scoring (1 on a 0–4 scale), and one animal in the rinsed group had minimal conjunctival redness on day 1 (1 on a 0–3 scale). No other irritation was observed in any animal during the 7 days of observation. The product was not an ocular irritant[75] (Table 4).

Inhalation

Groups of four to six male and four to six female B6C3F$_1$ mice and Fischer 344 rats were exposed to 0, 25, 50, and 75 ppm MIPA vapors 6 h a day, 5 days a week for a total of nine exposure periods. All animals appeared to be normal and in good health throughout the study. MIPA had no effects on body and organ weights, gross and microscopic appearance of tissues, hematological parameters, serum chemistry, and rat urinalyses. An active bronchopneumonia and rhinitis was observed in many control and treated animals and MIPA did not appear to exacerbate the condition in the treated animals.[76]

Mutagenicity

No studies on the mutagenicity of DIPA, TIPA, or MIPA, specifically, were found in the published literature. However, a mutagenicity study on the pesticide, Tordon, the Triisopropanolamine salt of 4-amino-3,5,6-trichloropicolinic acid was performed using *Aspergillus nidulans* as the test organism. Point mutation was studied at the hypoxanthine phosphoribosyltransferase (HGPRT) locus by induction of 8-azaguanine resistance. Chromosome nondisjunction and mitotic crossover were studied with a diploid strain of the mold. Tordon was not mutagenic in any of the assays.[77,78]

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation, Sensitization, and Photosensitization

Diisopropanolamine

A modification of the Draize repeat insult patch test was used to test a 2% aqueous solution of DIPA for photosensitization.[67,79] A 0.2 ml volume of the DIPA solution was applied to patches, and the patches were applied to the lower backs of 25 male and female volunteers for 24 h 3 successive days a week for 3 successive weeks. At patch removal, the sites were irradiated with a combination of UV-A and UV-B in a dose of three times the minimal erythema dose. A chal-

TABLE 4. Rabbit Ocular Irritation

Ingredient	*No. of rabbits*	*Vehicle or product*	*% Ingredient in product*	*Amount instilled*	*Eye rinsed*	*Observation time*	*Results*	*Reference*
DIPA	NS[a]	None	100	50 mg	NS	NS	Eye irritant; 22 days required for recovery	70
TIPA	NS	None	100	50 mg	NS	NS	Eye irritant; 7 days required for recovery	70
TIPA	NS	None	100	5 μl	No	18–24 h	Scored 6 (10 max). Eye irritant	69
TIPA	1	None	100	NS	NS	21 days	Eye irritant. Recovery by 21 days	53
MIPA	NS	None	100	50 mg	NS	NS	Severe eye irritant; 32 days required for recovery	70
MIPA	NS	None	100	5 μl	No	18–24 h	Scored 9 (10 max). Severe eye irritant	56
MIPA	1	None	100	NS	NS	21 days	Eye irritant. Corneal damage still present at 21 days	54
MIPA	6	Water	10	0.1 ml	No	72 h	Mild eye irritant. No ocular redness remained at 72 h	71
Mixed Isopropanolamines	NS	None	100	5 μl	No	18–24 h	Scored 7 (10 max). Eye irritant	69
DIPA	6	Sunscreen	1	0.1 ml	No	7 days	No irritation in unrinsed eyes, rinsed eyes scored 1.3 (110 max) at 24 h. Not an eye irritant	72
	3	Sunscreen	1	0.1 ml	Yes	7 days		
DIPA	6	Sunscreen	1	0.1 ml	No	7 days	All scores = 0. Not an eye irritant	74
TIPA	6	Lotion	1.1	0.1 ml	No	7 days	One animal with unrinsed eye had minimal conjunctival swelling at 24 h. One animal with rinsed eye had minimal conjunctival redness at 24 h. Not an eye irritant	75
	3	Lotion	1.1		Yes			

[a]Not specified.

lenge was performed during week 6, and only UV-A in a nonerythema dose was used. Two patches were applied to the back. One patch remained in place for 24 h and the site was irradiated at patch removal. The other patch remained in place for 48 h and was used to measure contact dermatitis. DIPA did not induce allergic or photoallergic dermatitis.

A facial sunscreen containing 1% DIPA was tested for primary irritation using 10 panelists. An occlusive patch containing 0.05 ml product was applied for 48 h to the upper back of each subject. No irritation was observed 2 or 24 h after patch removal; the sunscreen was not a primary irritant.[80]

A 21-day cumulative irritation test was performed using 24 subjects. A facial sunscreen lotion containing 1% DIPA was 1 of 10 products tested. Fifteen separate applications of 0.5 ml of the test material were applied for 24 h to the back as semiocclusive patches over a period of 22 days. Patches were not applied on Saturday or Sunday, but test materials remained in contact with the skin over the weekend. The mean cumulative irritation indices ranged from 0.17 to 1.31 (max 84) for the 10 products tested, but individual product scores were not reported. The irritation produced by these products was considered minimal.[81]

Two hundred twenty-one subjects participated in a repeat insult patch test (RIPT) to determine the irritation and sensitization potential of several products, including a facial sunscreen containing 1% DIPA. Ten semiocclusive patches with patches in place 24 h on weekdays and 72 h on weekends containing 0.5 ml of product were applied to the same site on the upper back over a period of 3.5 weeks. Two weeks after the last application, a challenge patch was applied for 48 h to a previously untreated site. One subject had erythema covering the entire test site at challenge (score of 2 on a 0–5 scale). A second challenge produced the same response in this subject, and after further testing, it was concluded that this subject had been sensitized to the sunscreen. Hyperpigmentation at test sites was also observed, but the product(s) causing the hyperpigmentation was not specified.[82]

The irritation and sensitization potential of a facial sunscreen containing 1% DIPA was evaluated in an RIPT using 203 panelists. Occlusive patches containing 0.2 ml product were applied to the upper back for 24 h, then removed and scored. Twenty-four hours later, another patch was applied for 24 h, and this procedure was repeated on weekdays for a total of 10 induction patches. Subjects were not treated on Saturday and Sunday. After a 13-day nontreatment period, panelists were challenged at the same test site with an occlusive patch for 48 h, and 8 days later a second challenge patch was applied for 48 h. Six +1 reactions (0–+4 scale), five +2 reactions, and one +3 reaction were observed during induction. Treatment was discontinued until challenge on subject 4, following a +3 reaction after the fourth induction patch. Two subjects had +1 challenge reactions that were considered clinically insignificant. Subject 4 had +3 reactions to all challenge patches, including an additional challenge patch administered 1 month after termination of the test. It was concluded that this sunscreen product was not a strong irritant but may be capable of inducing contact sensitization.[83]

Triisopropanolamine

Ninety-eight panelists participated in a Schwartz-Peck Prophetic Patch test to determine the irritation, sensitization, and phototoxicity of a lotion product containing 1.1% TIPA. Open and occlusive patches were applied for 48 h, and re-

sults were scored according to the International Contact Dermatitis Research Group procedure with a 0–3+ scoring scale.[84] After a nontreatment period of approximately 14 days, a second set of open and occlusive patches was applied and scored 48 h later. After scoring the second occlusive patch reactions, these same test sites of all panelists were irradiated for 6 minutes with a Hanovia Tanette Mark I Lamp (wavelengths including 360 nm). This site was scored for phototoxicity 48 h later. No reactions were observed at the first or second open patch, the first occlusive patch, or 48 h after irradiation. Four subjects had 1+ (weak, nonvesicular) reactions to the second occlusive patch, and one subject had a 2+ (strong, edematous or vesicular) reaction to the second occlusive patch. These reactions were not considered clinically significant. The product was not an irritant, phototoxin, or sensitizer under these test conditions.[85]

The irritancy of a prototype lotion product containing 1.1% TIPA was evaluated in a 21-day cumulative irritation test using 10 panelists. Occlusive patches containing 0.3 ml lotion were applied to the upper back of each panelist, and panelists were instructed to remove the patch in 23 h, bathe or shower, then present themselves at the clinic for test site scoring and reapplication of the next patch. Patches were applied for 21 consecutive days. One panelist had no reactions throughout the study. Nine of the 10 panelists had three or more grade 1 (max 7), minimal erythematous reactions, 5/9 had one or more grade 2, definitely erythematous reactions, and 1/9 had three reactions accompanied by glazing with peeling and cracking of the skin. The group total cumulative irritation score was 89 (max 630). The prototype lotion was a slight skin irritant.[86]

A maximization test involving 25 subjects was performed to determine the contact sensitization of a prototype lotion containing 1.1% TIPA. Test sites on the volar forearm or back were pretreated for 24 h with 2.5% sodium lauryl sulfate under occlusive patches. The test material was then applied under occlusive patches to the same site for 5 alternate-day 48-h periods. Following a 10-day nontreatment period, an occlusive challenge patch was applied for 48 h to a different site. The challenge site was scored for sensitization at the time of patch removal and 24 h later. No reactions were observed in any panelist. The prototype lotion was not a contact sensitizer[87] (Table 5).

Isopropanolamine

Modifications of the Draize repeat insult patch test were used to test a 2% aqueous solution of MIPA for skin sensitization and photosensitization.[67,79] For skin sensitization, a 0.2 ml volume of the MIPA solution was applied to patches, and the patches were applied to the lower backs of 150 male and female volunteers for 48–72 h three times a week for 3 weeks. Sites were scored at patch removal. A challenge patch was applied 2 weeks later to a naive site. It was scored at 48 and 96 h on a scale of 0–4. MIPA did not induce allergic contact dermatitis. For photosensitization, a 0.2 ml volume of the MIPA solution was applied to patches, and the patches were applied to the lower backs of 25 male and 25 female volunteers for 24 h 3 successive days a week for 3 successive weeks. At patch removal, the sites were irradiated with a combination of UV-A and UV-B in a dose of three times the minimal erythema dose. A challenge patch was applied to the back. One patch remained in place for 24 h, and the site was irradiated at patch removal. The other patch remained in place for 48 h and was used to measure contact dermatitis. MIPA did not induce allergic or photoallergic dermatitis.

TABLE 5. Clinical Studies on Skin Irritation, Sensitization, and Phototoxicity—All Products

Ingredient	*Test/procedure*[a]	*No. of subjects*	*Product type*	*% ingredient in product*	*Amount of product applied*	*Results*	*Reference*
DIPA	RIPT with irradiation/9 occlusive 24-h patches; challenge patch after 2 weeks nontreatment period. Irradiation at each patch removal	25	Aqueous solution	2	0.2 ml	No photosensitization	79
DIPA	Primary irritation/single 48-h occlusive patch	10	Sunscreen	1	0.5 ml	No irritation. Not a primary irritant	80
DIPA	21-day cumulative irritation/15 semiocclusive 24-h patches over 22 days	24	Facial sunscreen	1	0.5 ml	Several products tested; cumulative irritation scores ranged from 0.17 to 1.31 (max 84). Individual product scores not reported. All products were minimal skin irritants	81
DIPA	RIPT/10 semiocclusive 24-h patches; 48-h challenge patch after 2 weeks nontreatment period	221	Facial sunscreen	1	0.5 ml	1 subject sensitized. Product was minimal sensitizer	82
DIPA	RIPT/10 occlusive 24-h patches; two 48-h patches 13 and 21 days after induction patches	203	Facial sunscreen	1	0.2 ml	12 irritant reactions during induction. Two clinically insignificant reactions at challenge; 1 subject sensitized. Mild irritant and sensitizer	83

TIPA	Schwartz-Peck prophetic patch and phototoxicity/single 48-h open and closed patches; 14 days nontreatment period; 48-h open and closed patches; 2nd closed patch site irradiated after patch removal and scored for phototoxicity 48 h later	98	Lotion	1.1	– – –	Four, weak 1+ (0–3+ scale) and one, strong, 2+ reactions to the 2nd closed patch. No reactions at open and irradiated sites. Not an irritant, sensitizer, or phototoxin	85
TIPA	21-day cumulative irritation/21 occlusive 23-h patches on 21 consecutive days	10	Lotion	1.1	0.3 ml	9/10 panelists had mild reactions; cumulative irritation score was 89 (max 630). Mild irritant	86
TIPA	Maximization test/pretreatment with sodium lauryl sulfate; 5 alternate-day 48-h occlusive patches; 10-day nontreatment period; occlusive 48-h challenge patch	25	Lotion	1.1	Not specified	No reactions. Not a contact sensitizer	87
MIPA	RIPT/9 occlusive 48–72 h patches; challenge patch after 2 weeks nontreatment period	150	Aqueous solution	2	0.2 ml	No sensitization	79
MIPA	RIPT with irradiation/9 occlusive 24-h patches; challenge patch after 2 weeks nontreatment period. Irradiation at each patch removal	25	Aqueous solution	2	0.2 ml	No photosensitization	79

[a]See text for detailed procedures and results.

SUMMARY

Diisopropanolamine (DIPA), Triisopropanolamine (TIPA), Isopropanolamine (MIPA), and Mixed Isopropanolamines are viscous liquid or waxy solid aliphatic amines. They are used as water-soluble emulsifiers and neutralizers in cosmetic creams and hair preparations. DIPA, TIPA, and MIPA are usually used in cosmetics at concentrations of 0.1–1%.

Commercial samples of DIPA and TIPA were found to contain 20–1300 ppb of N-nitrosobis(2-hydroxypropyl)amine, an agent that is absorbed through the skin of hamsters and is a strong carcinogen in hamsters, rats, mice, rabbits, and guinea pigs.

DIPA was absorbed through the skin of rats and primarily excreted in the urine. Following intravenous administration of DIPA to rats, most of the dose was also eliminated in the urine. No metabolites of DIPA were isolated from the urine.

MIPA is a naturally occurring compound and has been isolated from the urine of rats and humans.

Mutagenicity data on the pure isopropanolamines were not available. A Triisopropanolamine salt used as a pesticide was not mutagenic in *Aspergillus nidulans*. No data were available on the carcinogenic or carcinogenic enhancement activity of DIPA, TIPA, MIPA, or Mixed Isopropanolamines.

DIPA, TIPA, MIPA, and Mixed Isopropanolamines were slightly toxic to practically nontoxic to rats and guinea pigs via acute oral administration. DIPA, administered in the drinking water, was not tolerated by rats at a dose of 3.0 g/kg per day. At doses of 600 mg/kg per day DIPA or less, no significant toxicological effects were observed. TIPA was relatively nontoxic to rats in two subchronic oral studies. Reduction of growth and appetite was observed in test animals at a dose of $\geq$1.35 g/kg per day.

Undiluted DIPA and MIPA were moderate skin irritants for rabbits, and sunscreen products containing DIPA were mild skin irritants for rabbits. TIPA was also a moderate skin irritant. DIPA was noncorrosive and MIPA was corrosive in a 4-h test. Exposure to UV radiation did not increase the severity of the irritation caused by the DIPA-containing sunscreens. No information was available on the skin toxicity of Mixed Isopropanolamines.

Undiluted DIPA, TIPA, MIPA, and Mixed Isopropanolamines were severe ocular irritants in rabbits. Products containing small amounts (approx. 1%) of DIPA or TIPA were not ocular irritants in rabbits.

DIPA and MIPA at concentrations of 2% in aqueous solution did not induce allergic contact dermatitis or photoallergic dermatitis in humans. The clinical studies on the isopropanolamines were confined to cosmetic products containing no more than 1% DIPA or 1.1% TIPA. These products were minimal skin irritants and contact sensitizers. One product containing TIPA was evaluated for phototoxicity, and it was not a phototoxin.

CONCLUSION

The Panel concludes that Diisopropanolamine, Triisopropanolamine, Isopropanolamine, and Mixed Isopropanolamines are safe as cosmetic ingredients

in the present practices of use and concentration. The Isopropanolamines should not be used in products containing N-nitrosating agents.

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