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Final Report on the Safety Assessment of Diisopropylamine[1]

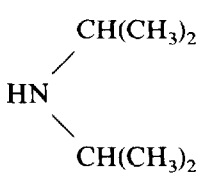
Abstract: Diisopropylamine is a strongly alkaline, aliphatic amine used to adjust the pH of cosmetic formulations. In 1993, it was reported to be used in only one formulation. In acute and short-term inhalation studies, toxic effects were observed in the respiratory system and eyes of rats and guinea pigs. Dermal application of diluted and undiluted Diisopropylamine in rats and guinea pigs showed irritation but not sensitization. This ingredient is considered an ocular irritant. Mixed results were obtained in evaluating the mutagenicity of this ingredient by the Ames test, but there were negative results in the rat hepatocyte primary culture/DNA repair assay. Occupational exposure to Diisopropylamine vapor (5–10 min, two or three times per day, mean concentration 0.1–0.2 mg/l) was associated with dimness of vision, nausea, and headaches. Because the skin irritation results were interpreted as attributable to the alkaline pH of this ingredient, and it is recognized that it is likely neutralized in cosmetic formulations, the irritation potential in actual use was not a concern. In the presence of *N*-nitrosating agents, Diisopropylamine has the potential to form nitrosamines. Based on the data presented in this report, it is concluded that Diisopropylamine is safe as a cosmetic ingredient in the present practices of use, except it should not be used in products containing *N*-nitrosating agents. **Key Words:** Diisopropylamine—Aliphatic amine—pH.

Diisopropylamine is a strongly alkaline, aliphatic amine that has the effect of adjusting the pH of cosmetic formulations. This report reviews the safety data on this ingredient.

CHEMISTRY

Definition and Structure

Diisopropylamine (CAS No. 108-18-9) is the aliphatic amine that conforms to the following formula:



[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

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Other names for this ingredient are *N*-(1-Methylethyl)-2-Propanamine and 2-Propaneamine, *N*-(1-Methylethyl)- (Nikitakis et al., 1991).

Chemical and Physical Properties

Diisopropylamine is a colorless liquid with a molecular weight of 101.19. It has a characteristic odor and is strongly alkaline (Windholz et al., 1983). The boiling point of Diisopropylamine is 83 to 84°C, and its flash point is 30°F (OC) (Sax, 1979). Diisopropylamine has a density of 0.722 at 220.0°C and is soluble in water and alcohol (Windholz et al., 1983; Sax, 1979).

Analytical Methods

Diisopropylamine has been analyzed by the following methods: liquid chromatography (Hanai and Hubert, 1985), high-performance liquid chromatography (Simon and Lemacon, 1987), thin-layer chromatography using silica gel plates (Petronio and Russo, 1980), glass capillary gas chromatography with flame photometric detection (Hamano et al., 1981), and ion mobility spectrometry (Karpas, 1989).

Impurities

Spiegelhalder et al. (1978) analyzed two samples of Diisopropylamine from different sources for traces of nitrosamines. The samples were contaminated with 0.25 to 0.39 mg/kg of its corresponding dialkyl-*N*-nitrosamine.

The potential for Diisopropylamine to form *N*-nitroso compounds in human gastric juice was investigated by Ziebarth (1975). Diisopropylamine (100 μM) was mixed with 40 to 400 μM nitrite in 10 ml of gastric juice for 1 h at 37°C. The formation of nitrosodiisopropylamine could not be reliably demonstrated. The authors noted that, in general, nitrosation is dependent on the basicity of the amine and that it is inversely related to the amine's dissociation constant (pK_a). Diisopropylamine, which is strongly basic and has a pK_a of 11.13, appears to be weakly nitrosated in human gastric juice.

COSMETIC USE

Diisopropylamine is an aliphatic amine that has been used in colognes and toilet waters, reportedly as a pH adjuster (Food and Drug Administration [FDA], 1984; Nikitakis, 1988). The product formulation data submitted to the FDA in 1993 reported that Diisopropylamine was used in one cosmetic formulation classified under the category of "Other Skin Care Preparations" (Table 1) (FDA, 1993). Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, product formulation data submitted to the FDA in 1984 stated that Diisopropylamine was used at concentrations up to 1% in colognes and toilet waters, but there was no listing for Diisopropylamine in skin care preparations (FDA, 1984).

TABLE 1. *Product formulation data on Diisopropylamine (FDA, 1993)*

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Other skin care preparations	745	1
1993 Total		1

BIOLOGY

Hypoglycemic Activity

Polacek and Breuer (1978) reported that Diisopropylamine decreased the blood glucose concentrations of fasted, glucose-loaded, or streptozotocin-diabetic rats and of fasted mice.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The oral LD_{50} for an aqueous solution of Diisopropylamine was 420 mg/kg for rats (Monsanto Company, 1985). In another study, the LD_{50} for Diisopropylamine was 0.77 g/kg for five Carworth-Wistar rats over a 14-day observation period (Smyth et al., 1954).

Dermal

The dermal LD_{50} for undiluted Diisopropylamine was calculated at 2900 mg/kg for albino rabbits exposed continuously for 24 h on intact skin (Monsanto Company, 1985).

Inhalation

In an acute inhalation study, groups of five male and five female Sprague-Dawley rats were exposed to 5.0 and 5.3 mg/L of Diisopropylamine for 4 h. The animals were observed regularly for mortality and signs of toxicity, and necropsy was performed at death or after the 14-day observation period. One male rat exposed to 5.3 mg/L Diisopropylamine died during the study. The LC_{50} was greater than 5.3 mg/L. Clinical signs of toxicity observed during the study included labored breathing, tremors, high-pitched respiratory sounds, partially or completely closed eyelids, nasal and ocular discharges and encrustation, ocular opacity, and pitted/raised corneal surface. The only lesion considered treatment related at necropsy was corneal opacity (Monsanto Company, 1985).

Groups of 10 rats (five of each sex) and 10 guinea pigs (five of each sex) were exposed to 961, 1760, and 5,120 ppm of Diisopropylamine vapor for 30 min. Three separate control groups were used. The rats were observed for 14 days. Necropsy was performed on the animals either at time of death or when they were killed at

the end of the study. No deaths occurred in the groups exposed to 961 ppm Diisopropylamine. Signs of toxicity included nasal/lacrymal irritation, which progressed to dyspnea, generalized depressed activity, and eyelid closure by 15 min; these symptoms persisted for 4 h. Other significant changes were reduced body weights in the female rats and increased weight of the lungs of both the rats and guinea pigs. No significant histopathological changes were found.

Animals exposed to 1,760 ppm of Diisopropylamine had the same signs of toxicity as those exposed to 961 ppm. The body weights of the rats and the female guinea pigs were significantly lower than those of controls, and the lung weights of the female guinea pigs and heart weights of the male rats were also significantly lower. Two guinea pigs and one rat died either during or a few minutes after exposure. One of the guinea pigs had congestion and exposure-related corneal erosion and edema, but the other guinea pig had no lesions. The rat had pulmonary congestion, inflammation, hemorrhage, and edema. Of the animals surviving the study, one guinea pig had corneal opacity 14 days after exposure. No other lesions were observed in the other animals.

All rats exposed to 5,120 ppm of Diisopropylamine died during exposure with apparent respiratory distress. At histopathological evaluation, the rats had degeneration of the renal proximal tubular epithelium and bronchial epithelium, and the guinea pigs had vacuolar degeneration of the hepatocytes (Price et al., 1979).

The nasal irritation produced by Diisopropylamine was studied using male Swiss OF_1 mice. Groups of six mice each were exposed to concentrations of Diisopropylamine ranging from 88 to 351 ppm in air for 15 min to determine the concentration at which the respiratory rate was decreased by 50% (RD_{50}). The head of each mouse was isolated in an inhalation chamber, and the breathing frequency was measured with a pressure transducer before and during the exposure period. The RD_{50} for Diisopropylamine was 161 ppm, and maximal effects were observed within 0.5 to 1 min.

The authors also exposed groups of mice to 29 to 207 ppm of Diisopropylamine via tracheal cannulation for 120 min. The concentration that caused a 50% decrease in respiratory rate via this route ($RD_{50}TC$) was compared with the RD_{50} (161 ppm). The $LD_{50}TC$ was 102 ppm, and maximal effects were observed after 120 min of exposure. The authors noted that the $RD_{50}TC/RD_{50}$ ratio was less than 1 (0.6), which indicated that Diisopropylamine primarily caused lower airway effects (Gagnaire et al., 1989).

In another study, a group of six male albino rats were exposed to a flowing stream of air saturated with Diisopropylamine. All of the rats died after 5 min (Smyth et al., 1954).

The same authors exposed groups of six rats to known concentrations of Diisopropylamine for 4 h and determined the concentration producing fractional mortality within 14 days. A concentration of 1,000 ppm caused two deaths (Smyth et al., 1954).

Diisopropylamine caused severe irritation to the respiratory mucosa of rabbits, guinea pigs, rats, and cats. Groups of two animals per species were exposed to 2,207 ppm of Diisopropylamine for 3 h. All the rats died during exposure. Toxicologic responses included sneezing, coughing, retraction of the head, rubbing of

the nose, discharge from the nostrils, lacrymation, salivation, and respiratory distress. The rabbits, cats, and guinea pigs also had cloudy corneas (Treon et al., 1949).

Short-term Toxicity

Dermal

In a range-finding study, 50, 150, 450, 1,350, and 2,000 mg/kg of undiluted Diisopropylamine were tested for dermal toxicity using groups of three male and three female Charles River CD(SD)BR rats. The rats were exposed for 5 consecutive days, and a plastic collar was placed around the neck of each animal to minimize ingestion of the test material. An untreated control group was similarly handled. All rats exposed to 2,000 mg/kg of Diisopropylamine were killed after 3 days because of severe dermal irritation. Those exposed to 450 and 1,350 mg/kg of Diisopropylamine had moderate to severe skin irritation. Mean body weights decreased slightly in the male rats treated with concentrations of 150 mg/kg of Diisopropylamine and greater; and in female rats exposed to 1,350 mg/kg (Monsanto Company, 1985).

In the follow-up study, groups of 10 male and 10 female Charles River CD(SD)BR rats were dermally exposed to 15, 50, and 150 mg/kg of undiluted Diisopropylamine five times a week for 1 month. The animals were monitored for signs of toxicity and changes in hematology and clinical chemistry parameters. Necropsy was performed on all the rats. A concurrent untreated control group of animals was also monitored.

Body weight gain and feed consumption in the test groups were comparable to those of the control group. Mild skin dryness was observed at the sites of application. Because this manifestation did not appear to be dose related, the authors attributed it to the repeated applications and evaporation rather than a compound related effect. No treatment-related changes were found among the hematology and clinical chemistry parameters investigated. Decreases were found in the absolute and relative heart weights of the male rats from the high-dose group, and increases in the absolute and relative testes weights of the males from the mid- and high-dose groups. However, the authors noted that no microscopic changes were found in these organs and that mild splenic congestion was present in all groups. No dose-response relationship or concomitant changes in splenic weights and hematology parameters were seen; thus, the splenic congestion was not considered related to the treatment. The authors concluded that there was no evidence of dermal toxicity in rats treated with doses up to 150 mg/kg/day Diisopropylamine for 1 month (Monsanto Company, 1985).

Inhalation

Groups of 15 male and 15 female Sprague-Dawley rats were exposed to 0.10, 0.60, and 2.00 mg/L Diisopropylamine for 6 h per day, 5 days a week, for 1 month. A control group of animals was handled similarly, except that Diisopropylamine was not administered. The animals were observed for mortality and clinical signs

of toxicity throughout the study, and ophthalmic examinations were performed during the last week of the study. Blood samples were taken from 10 male and 10 female rats from each group at the end of the study for clinical chemistry analyses. Necropsy was performed on the animals either at the time of death or when they were killed at the end of the study.

Three animals from the high-dose group died during the study. Signs of toxicity in the rats of this dose group included respiratory difficulties, mucous membrane irritation, and nonresponsiveness. The mean body weights of the rats exposed to the mid- and high-dose Diisopropylamine were significantly lower than those of the control group. Corneal lesions were observed in 13, 75, and 100% of the animals in the low, mid, and high-dose groups, respectively.

Erythrocyte, hemoglobin, and hematocrit values were increased in the male and female rats of the high-dose group and in the females of the mid-dose group. All treated male rats had reduced leukocyte counts. There were also changes in the values measured for albumin, total protein, alkaline phosphatase, and/or serum glutamic pyruvic transaminase, and cholesterol. The authors noted that changes in enzyme and cholesterol values were not clearly dose-related.

At necropsy, several changes in organ weights were found. The only treatment-related changes were increased absolute and relative weights of the adrenal glands and reduced absolute and relative splenic weights of the high-dose animals. Other changes were attributed to reduced body weight. All of the mid- and high-dose rats and most of the low-dose rats had hyperplasia and metaplasia in the nasal turbinates. Inflammation, mucosal erosion/ulceration, and necrosis/dissolution of turbinate septal cartilage/bone were also observed. Some rats from the high-dose group also had lesions in the trachea (hyperplasia, metaplasia, and mucosal/submucosal mineralization) and in the lungs (bronchiolitis/peribronchiolitis, bronchiolar hyperplasia/metaplasia, pneumonia, and granuloma/microgranuloma). The following lesions were found only in the high-dose animals and were observed less frequently: corneal and uveal inflammation, corneal hyperplasia, acute iridic necrosis, gaseous distention, atrophy of the thymus, thymocyte depletion, atrophy of the spleen, and atrophy and depletion of the secretory product of the seminal vesicles (Monsanto Company, 1987).

Groups of two rabbits, guinea pigs, and rats, and one cat were exposed to 777 ppm of Diisopropylamine in their air for 7 h. On the following day, they were exposed to the same concentration for 6.33 h. All the rabbits and guinea pigs died, but the rats and cat survived. Signs of toxicity included irritation of the mucous membranes, coughing, chest rales, labored respiration, lethargy, and prostration. Cloudy swelling of the corneal epithelium was observed in all except the rats (Treon et al., 1949).

These authors also exposed groups of two rabbits, guinea pigs, rats, and cats to 597 ppm of Diisopropylamine in their air for 7 h per day for 9 weeks. The rabbits died during the second exposure, the guinea pigs during the fourth exposure, and one of the rats after the fifth exposure. The animals had the same signs of toxicity as the animals exposed to 777 ppm of Diisopropylamine (Treon et al., 1949).

In another study, groups of five rabbits and groups of two guinea pigs, rats, and cats were exposed to 261 ppm of Diisopropylamine for 7 h per day for 40 days.

Four rabbits and one guinea pig died during the study. These two species sneezed, rubbed their noses, developed nasal discharge, and had labored respiration. The guinea pigs had lacrymation and accumulated mucous in their eyes and developed corneal clouding. The animals surviving the study also had corneal clouding, but this manifestation disappeared a few days after the last exposure. Evidence of irritation of the respiratory mucosa was also observed in the cats. The rats suffered the least irritation from the Diisopropylamine vapors. The rabbits did not appear to excrete Diisopropylamine or its metabolites as conjugates with glucuronic acid or sulfuric acid. Also, there was no increase in the number of Heinz bodies in the erythrocytes of the cats, and no change was noted in the number of cellular elements of the peripheral blood of the rabbits, guinea pigs, or cats (Treon et al., 1949).

Dermal Irritation

Monsanto Company (1985) reported that undiluted Diisopropylamine (0.5 ml) was corrosive to the skin of rabbits after 4 or 24 h of continuous exposure. No details were given about the testing procedures or the number of animals used.

In the range-finding study described earlier in this report (see Short-Term Toxicity section, Dermal Studies), the authors reported that rats dermally exposed to 450 to 2,000 mg/kg of undiluted Diisopropylamine for 5 consecutive days developed moderate to severe skin irritation. No irritation was observed at concentrations of 150 mg/kg and lower (Monsanto Company, 1985).

Undiluted Diisopropylamine (0.01 ml) was applied to the clipped skin of five albino rabbits for 24 h. The primary dermal irritation score was 1 (maximum possible score: 10) (Smyth et al., 1954).

Dermal Sensitization

Diisopropylamine was tested in a dermal sensitization test using Hartley guinea pigs. During the induction phase of the study, 0.3 ml of 10% Diisopropylamine was applied under occlusive patches to the shaved backs of five male and five female guinea pigs for 6 h a day, 3 days a week, for 3 weeks. After a 2-week nontreatment period, the animals were challenged with 0.3 ml of Diisopropylamine at a previously untreated site. A group of three male and three female guinea pigs were also treated with Diisopropylamine at this time to be used as an irritation control group. Two other groups of animals were treated with the vehicle (ethanol/acetone) alone or with 1-chloro-2,4-dinitrobenzene to serve as the negative and positive controls, respectively.

Severe dermal irritation appeared after the first or second induction patches with 10% Diisopropylamine, and the concentration of Diisopropylamine was reduced to 5% for the remainder of the applications. Irritation persisted throughout the induction phase, and some animals had severe irritation. However, none responded to the challenge patch. The authors concluded that Diisopropylamine was not a sensitizer, but it has the potential to cause moderate to severe dermal irritation after repeated exposures (Monsanto Company, 1985).

Ocular Irritation

Undiluted Diisopropylamine (0.1 ml) was corrosive to the eyes of rabbits. No details were given about the testing methods or the number of animals used (Monsanto Company, 1985).

Smyth et al. (1954) gave Diisopropylamine an ocular irritation grade of 8 (maximum possible grade: 10). This grade indicates that an excess of 5% Diisopropylamine causes irritation of up to 5 points (maximum possible points: 20) to the eyes of rabbits. Also, a 15% solution of Diisopropylamine causes severe ocular irritation, with scores higher than 5 points (Smyth et al., 1954).

Treon et al. (1949) conducted a study to determine whether corneal opacity associated with occupational exposure to Diisopropylamine vapors (discussed in the Clinical Toxicity section) was induced by some hematogenous or other indirect mechanism. Two guinea pigs were injected subcutaneously with either 0.42 or 1.40 g/kg of undiluted Diisopropylamine, and two other guinea pigs were injected with the same dosages of 31% aqueous neutralized Diisopropylamine hydrochloride. In both groups, the guinea pigs administered the high dose died within 9 to 19 h, whereas those administered the low dose survived. None of the guinea pigs had corneal opacity or other ocular lesions. The authors concluded that corneal opacity associated with Diisopropylamine vapors was probably due to superficial injury to the conjunctiva and cornea.

MUTAGENICITY

Diisopropylamine was evaluated at concentrations ranging from 33 to 10,000 μg/plate with the *Salmonella*/microsome test using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. Tests were conducted in triplicate both with and without activation with liver S9 from Aroclor-induced Sprague-Dawley rats and Syrian hamsters. Solvent and positive controls were also prepared with each trial. The positive controls used for tests without metabolic activation were sodium azide for strains TA1535 and TA100, 9-aminoacridine for TA1537, and 4-nitro-*o*-phenylenediamine for TA98. In tests with S9 activation, 2-aminoanthracene was used for all strains. Diisopropylamine was negative in tests both with and without metabolic activation (Mortelmans et al., 1986).

In another Ames test, Diisopropylamine was evaluated at concentrations between 0.1 and 10.0 μg/plate using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, both with and without metabolic activation (S9 from Aroclor 1254-induced rats). No significant change in the number of revertants was found with strains TA1535 and TA1537. However, with strains TA98 and TA100, as the concentration of Diisopropylamine increased, the number of revertants significantly increased both with and without metabolic activation. A dose response also occurred in tests with TA1538 without S9 activation only. The authors noted that Diisopropylamine is a simple aliphatic amine and would not be expected to be a mutagen and that Diisopropylamine did not produce equal effects when tested as diisopropylamine dichloroacetate. Therefore, it was suggested that an impurity in the Diisopropylamine may have been responsible for part of the results (Gelernt and Herbert, 1982).

Diisopropylamine was also tested in the rat hepatocyte primary culture/DNA repair assay. Primary liver cell cultures derived from male Fischer-344 rats were exposed to 10 concentrations of Diisopropylamine, ranging from 0.1 to 5,000 μg/ml in the preliminary assay and six concentrations ranging from 10 to 2,500 μg/ml in the replicate assay for 18 to 21 h. Each test was conducted in triplicate. A positive control (2-AFF), a solvent control (acetone), and an untreated control were also tested. Quantitative autoradiographic grain counting was performed on 90 cells for each concentration. Diisopropylamine was cytotoxic at a concentration of 5,000 μg/ml, and it was noted that a change in the pH of the media occurred at concentrations of 500 μg/ml and above. However, no attempt was made to adjust the pH. There was a negative grain count for all concentrations tested for Diisopropylamine and the solvent control. The authors concluded that Diisopropylamine was not genotoxic in the rat hepatocyte primary culture/DNA repair assay (Monsanto Company, 1985).

CLINICAL ASSESSMENT OF SAFETY

Occupational Exposure

Temporary dimness of vision was reported in men engaged in the distillation of Diisopropylamine in a pilot plant operation. Some workers also complained of nausea and headaches. The mean concentration of Diisopropylamine vapor was 0.1 to 0.2 mg/L and reached concentrations up to 0.74 mg/L near a drum into which pure Diisopropylamine was being drained. These concentrations occurred for 5 to 10 min two or three times per day (Treon et al., 1949).

SUMMARY

Diisopropylamine is a strongly alkaline, aliphatic amine that has the effect of adjusting the pH of cosmetic formulations. The oral LD_{50} for Diisopropylamine was 420 mg/kg or 0.77 g/kg for rats. The dermal LD_{50} for rabbits was 2,900 mg/kg of Diisopropylamine.

In an acute inhalation study, toxic effects were observed in the respiratory system and eyes of rats and guinea pigs after 30 min of exposure to 961 and 1,760 ppm Diisopropylamine; exposure to 5,120 ppm Diisopropylamine caused respiratory distress and death. In another study, the LD_{50} for rats was greater than 5.3 mg/L Diisopropylamine.

After 1 month of inhalation exposure, 0.10 mg/L of Diisopropylamine caused lesions in the cornea and nasal passages and reduced the lymphocyte counts of rats. At greater concentrations of exposure, Diisopropylamine caused death, substantial body weight reduction, and lesions.

Diisopropylamine was not dermally toxic after repeated applications to the skin of rats. However, undiluted Diisopropylamine caused moderate to severe skin irritation in rats at doses of 450 and 1,350 mg/kg. In a sensitization study with guinea pigs, 5% Diisopropylamine caused dermal irritation, but it was not a sensitizer. Diisopropylamine is an ocular irritant.

In one Ames test, a dose response was observed with Diisopropylamine both

with and without metabolic activation in *S. typhimurium* strains TA98 and TA100, and without activation only in strain TA1538. However, in another Ames test, Diisopropylamine was negative both with and without metabolic activation when tested in strains TA98, TA100, TA1535, and TA1537. Diisopropylamine was also nongenotoxic in the rat hepatocyte primary culture/DNA repair assay.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel was concerned about the dermal irritation observed in animal studies with Diisopropylamine. It was agreed that such irritation was probably due to the alkaline pH of this ingredient. Although no clinical studies on dermal reactions were available, the Panel felt that the irritation potential of this ingredient was not a concern because it is likely that Diisopropylamine is neutralized in cosmetic formulations and would therefore not pose a risk. Animal studies also indicate that Diisopropylamine is not a sensitizer.

In the presence of *N*-nitrosating agents, Diisopropylamine has the potential to form nitrosamines, which are known animal carcinogens. Therefore, Diisopropylamine should not be used in products containing such compounds.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that Diisopropylamine is safe as a cosmetic ingredient as presently used. Diisopropylamine should not be used in products containing *N*-nitrosating agents.

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