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Final Report on the Safety Assessment of Ethyl Hexanediol[1]

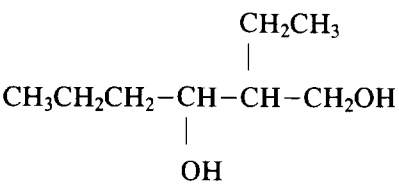
Abstract: Ethyl Hexanediol is an aliphatic alcohol used as a solvent in a small number of cosmetic formulations applied to the skin and hair. Animal data indicate that Ethyl Hexanediol is absorbed through the skin and is metabolized and eliminated in the urine. Reported oral LD_{50} values in rats are generally above 5 g/kg. In subchronic oral studies, slight toxicity was manifested as reduced growth and increased liver weight. Oral delivery of Ethyl Hexanediol in female rats did show evidence of teratogenicity, but only at levels at which significant maternal toxicity was seen. Dermal exposure also resulted in developmental changes, again at levels that also caused maternal effects. Chromosome damage was reported in vitro, but several other genotoxicity assays were negative. Dermal exposure resulted in no dose-related increases in tumor incidence in rabbits and mice. In clinical studies, undiluted Ethyl Hexanediol was a weak irritant and a weak sensitizer. The concentration at which this ingredient is expected to be used is no greater than 5%. On the basis of the animal, clinical, and use data presented in this report, it is concluded that Ethyl Hexanediol is safe as a cosmetic ingredient. **Key Words:** Ethyl Hexanediol—Cosmetics.

Ethyl Hexanediol is an aliphatic alcohol used as a solvent in cosmetic formulations. The safety data on this ingredient are presented in this report.

CHEMISTRY

Definition and Structure

Ethyl Hexanediol (CAS No. 94-96-2) is the aliphatic alcohol that conforms to the following formula (Nikitakis et al., 1991):



Other names for Ethyl Hexanediol are ethohexadiol; 2-ethyl-1,3-hexanediol; 1,3-hexanediol, 2-ethyl-; octylene glycol; ethyl hexyleneglycol; 2-ethyl-3-propyl-1,3-

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

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propanediol; and 3-hydroxymethyl-*n*-heptan-4-ol (Nikitakis et al., 1991; Sax, 1979; Syracuse Research Corp., 1982). Materials containing Ethyl Hexanediol are Lanoquat 1756, Lanoquat 1757, and Unirep U-18 (Nikitakis et al., 1991). The commercial names for this ingredient include Carbide 6-12, Compound 6-12 Insect Repellent, Repellent 612, and Rutgers 612 (Syracuse Research Corp., 1982).

Chemical and Physical Properties

Ethyl Hexanediol is a colorless, slightly viscous liquid (Hawley, 1971). Its chemical and physical properties are summarized in Table 1.

Method of Manufacture

Ethyl Hexanediol can be manufactured by hydrogenating butyraldol (Sherman, 1978). It may also be prepared by condensing butyraldehyde with magnesium aluminum ethoxide and hydrolyzing the resulting ester (Martin and Worthing, 1977).

Ethyl Hexanediol has the following specifications (Union Carbide Corp., 1978):

Purity % by wt., min.	97.0
Acidity % by wt., max., as acetic	0.02
Water % by wt., max.	0.05
Color, Pt-Co units, max.	20
Suspended matter	Substantially free

Analytical Methods

An analytical method for determining Ethyl Hexanediol in aqueous or alcoholic solution was developed for studies on the evaporation and absorption of insect repellents. This method involves reacting Ethyl Hexanediol with concentrated sulfuric acid and *p*-dimethylaminobenzaldehyde to obtain a colored compound that is estimated colorimetrically. Ethyl Hexanediol may be determined on glass, cloth, and human skin (Bowman et al., 1959).

TABLE 1. *Chemical and physical properties of Ethyl Hexanediol*

Property	Description	Reference
Molecular weight	146.26	RTECS (1992)
Appearance	Colorless, slightly viscous liquid	Hawley (1971); Sax (1979)
Odor	Odorless	Hawley (1971); Sax (1979)
Solubility	Soluble in alcohol, ether, and chloroform; partially soluble in water	Hawley (1971); Syracuse Research Corp. (1982); Hunting (1983)
Specific gravity	0.9422 (20/20°C)	Hawley (1971)
Boiling point	244°C	Hawley (1971)
Melting point	−40°C (sets to glass below this temperature)	Syracuse Research Corp. (1982)
Freezing point	< −40°C	Hawley (1971)
Flash point	260°F	Hawley (1971); Sax (1979)
Refractive index	1.4465–1.4515	Hawley (1971)
Vapor pressure	<0.01 mm (20°C)	Hawley (1971)
Viscosity	323 cp (20°C)	Hawley (1971)

USE

Cosmetic Use

United States

Ethyl Hexanediol is used as a solvent in cosmetic formulations (Nikitakis, 1988). The product formulation data submitted to the Food and Drug Administration (FDA) in 1993 reported that Ethyl Hexanediol was used in a total of three cosmetic product formulations (Table 2) (FDA, 1993*a*). Ethyl Hexanediol is also a component of quaternium-33 (and) Ethyl Hexanediol, which has the trade name Lanoquat 1756 (Nikitakis et al., 1991). Lanoquat 1756 was reported to be used in five cosmetic formulations in 1993 (FDA, 1993*b*). 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 Ethyl Hexanediol was used at concentrations up to 5% (FDA, 1984).

Ethyl Hexanediol is used as a solvent for shampoos containing quaternium-33 and quaternium-60. These quaternaries must be sold as proprietary blends with this solvent because the quaternization process occurs in this medium (Hunting, 1983).

The FDA's final rule for the use of Ethyl Hexanediol in shampoos to treat dandruff is Category III status: The available data were insufficient to permit a classification of this ingredient's safety and efficacy (Federal Register, 1990).

International

In 1991 the Canadian government moved to cancel the registration of all insect repellents containing Ethyl Hexanediol because of data suggesting that Ethyl Hexanediol is teratogenic. The Health Protection Branch is presently investigating the use of Ethyl Hexanediol in cosmetic products [Cosmetic, Toiletry, and Fragrance Association (CTFA), 1991].

Ethyl Hexanediol is approved for use in cosmetics in Japan (Nikko Chemicals Co., Ltd., 1992).

Noncosmetic Use

Ethyl Hexanediol is used in medicines, as a vehicle and solvent in printing inks, and as a chelating agent for boric acid (Hawley, 1971; Wilkinson and Moore,

TABLE 2. *Cosmetic product formulation data on Ethyl Hexanediol*

Product category	Total no. formulations in category	Total no. of formulations containing ingredient
Tonics, dressings, and other hair-grooming aids	494	1
Cleansing products	702	1
Other sun tan preparations	57	1
1993 totals		3

1982). It is used as a viscosity reducer and as a reactive diol in the manufacture of two-package urethanes. At room temperature Ethyl Hexanediol is a conventional solvent, but at elevated temperatures it reacts to eliminate or minimize solvent emissions. Ethyl Hexanediol may also be used as a conditioning agent for cork products, as a film-coalescing aid for latexes, and as an intermediate for producing antioxidants and corrosion inhibitors (Union Carbide Corp., 1978).

In the past, Ethyl Hexanediol was used in insect repellents intended for direct application to human skin and clothing. However, in 1991 Union Carbide Corp. submitted data to the Environmental Protection Agency (EPA) that indicated possible adverse developmental effects associated with Ethyl Hexanediol. After conducting a risk assessment using these data, the EPA concluded that "the use of [Ethyl Hexanediol] as a repellent by pregnant women represents an unacceptable developmental risk." Registrations for all the products containing this ingredient were voluntarily canceled by the companies making these products (Federal Register, September 4, 1991; December 2, 1991).

GENERAL BIOLOGY

Absorption, Distribution, and Metabolism

Oral

In a peroral study, groups of four CDF Fischer 344 rats were administered 1.5 and 150 mg/kg of [1,3-^{14}C]Ethyl Hexanediol (5–10 μCi) by gavage. Approximately 87 and 90% of the administered radioactivity were recovered from the high- and low-dose groups, respectively. Most of the radioactivity (70–73% of the administered dose) was found in the urine. Radioactivity was also found in the feces (7%) and as expired $^{14}CO_2$ (1–2%). Very little radioactivity was found in the organs and tissues. The most measurable radioactivity was found in the kidneys, liver, and skin. The concentration of radioactivity in the plasma had a linear dose response, and elimination via the urine followed first-order processes. Ethyl Hexanediol appeared to be completely metabolized in the rat and eliminated as at least two major metabolites (Frantz et al., 1992).

Intravenous

Frantz et al. (1991) investigated the systemic disposition of Ethyl Hexanediol in rats following intravenous injection. Groups of six male Fischer 344 rats were slowly injected with 1.5 and 150 mg/kg of [1,3-^{14}C]Ethyl Hexanediol (5 μCi) over a 2-min period via the indwelling jugular cannula. Blood, urine, and feces were collected at regular intervals, and expired $^{14}CO_2$ was monitored in four animals from each group. The rats were killed with an overdose of methoxyflurane after 48 h.

During the injection of the test material, the animals of the high-dose group experienced temporary narcosis, which diminished within the first 5 min after dosing. This effect was not observed in the low-dose group. The concentration of radioactivity in the plasma samples from both groups decreased rapidly between

2.5 min and 24 h in a biphasic manner following first-order transfer and elimination processes. Radioactivity concentrations in the 36- and 48-h samples could not be quantified. The authors stated that there was a linear dose response for the 1.5- to 150-mg/kg dose range of Ethyl Hexanediol.

The major route of excretion for Ethyl Hexanediol was via the urine. The percentages of radioactivity recovered from the urine of the high- and low-dose groups were 64.3 and 72.4%, respectively. Most of the radioactivity was excreted within the first 12 h following administration, and elimination followed first-order behavior similar to that characterized for total radioactivity in the plasma. Approximately 10.27% of the radioactivity was found in the feces of the high-dose group, and 4.99% was found in samples from the low-dose group. Expired $^{14}CO_2$ was <1% of the injected dose for the high-dose group, so $^{14}CO_2$ was not measured for the low-dose group.

The authors also measured the concentration of unchanged Ethyl Hexanediol in the plasma and urine samples collected from the rats. In the high-dose group, plasma concentrations of unchanged Ethyl Hexanediol could be quantified only up to the 18-h sample. In most cases, these concentrations closely paralleled the curve for radioactivity, but were lower than the radioactivity levels. No unmetabolized Ethyl Hexanediol was found in the urine by high performance liquid chromatography (HPLC) analysis, which indicated that Ethyl Hexanediol was probably completely metabolized by the rats. The authors did not attempt to identify the metabolites. However, in tests to demonstrate the existence of Ethyl Hexanediol in conjugated form, the authors concluded that it was probably not directly conjugated with glucuronic acid or sulfate during metabolism.

In another study, three hairless dogs were injected intravenously with 79.5 μg of [1,3-^{14}C]Ethyl Hexanediol (2 μCi). The dogs were monitored in metabolism cages for 4 days, and blood samples, urine, and feces were collected regularly. Approximately 86% of the administered radioactivity was recovered from the urine, most of which was eliminated within the first 24 h. Negligible amounts of radioactivity were found in the feces. Radioactivity in the blood decreased to near background levels 4–8 h after administration (Reifenrath et al., 1980).

Percutaneous—In Vitro

Tallant et al. (1991) compared the skin penetration of Ethyl Hexanediol in in vitro studies using excised skin from Fischer 344 rats, New Zealand white rabbits, and humans (mammoplasty patients). The penetration of 150 mg/kg of [1,3-^{14}C]Ethyl Hexanediol was analyzed over a 6-h period using a flow-through skin penetration chamber design. Under occlusive patches, ~2–3% of the applied dose penetrated the skin of rats, 3–5% penetrated the skin of rabbits, and 0.9% penetrated human skin. Less radioactivity was recovered from the effluents when tested using nonocclusive patches on human skin. This was attributed to the evaporation of Ethyl Hexanediol from the skin.

In another study, the penetration of 0.046 and 0.3 mg/cm^2 [1,3-^{14}C]Ethyl Hexanediol through excised human skin was analyzed over 1- and 12-h periods, respectively. Approximately 1% of the radioactivity from the low dose penetrated

the human skin 1 h after application, and 12.0% of the radioactivity from the high dose penetrated the skin after 12 h. Ethyl Hexanediol was fairly volatile: Approximately 47.2% of the radioactivity was recovered from the vapor trap during the 12-h study and 16.2% during the 1-h study (Reifenrath and Robinson, 1982).

Percutaneous–In Vivo

Frantz et al. (1992) investigated the penetration and nonsystemic disposition of Ethyl Hexanediol in vivo. Groups of four CDF Fischer 344 rats had 150 mg/kg of undiluted [1,3-^{14}C]Ethyl Hexanediol applied under occlusive patches to a 1-cm^2 clipped area on their backs for 48 h. Blood samples, urine, and feces were collected at regular intervals. The animals were killed with an overdose of methoxyflurane 48 h after dosing, and the major organs and tissues were examined.

The average total of the applied radioactivity recovered from the rats was 107.0% for the male rats and 94.6% for the female rats. Most of the radioactivity (55–74%) was recovered from the patch materials. The major route of excretion was in the urine; 20–25% of the radioactivity was eliminated in a first-order manner. Approximately 2–3% of the applied radioactivity was found in the feces, and ~1% was recovered as expired $^{14}CO_2$. Very little radioactivity was detected in the organs and tissues. The concentration of radioactivity in the plasma peaked between 12 and 24 h and then steadily declined. While the concentration of unchanged Ethyl Hexanediol at the high dose paralleled the radioactivity found in the plasma, Ethyl Hexanediol represented only 17–53% of the corresponding ^{14}C concentrations. Unchanged Ethyl Hexanediol could not be quantified for the low-dose group. No unmetabolized Ethyl Hexanediol was found in the urine. Using HPLC, the authors determined that Ethyl Hexanediol was excreted as at least two major, water-soluble urinary metabolites. These metabolites were not identified.

Percutaneous absorption was also tested using dogs. Three hairless dogs had 0.32 mg/cm^2 of [1,3-^{14}C]Ethyl Hexanediol applied to a 5 × 5 cm^2 site on their backs. The treated area was covered with a foam pad, which had an opening around the treated area and a nylon screen over the opening to prevent contamination of the metabolism cage with radioactivity from the skin's surface. This device protected the treated site and allowed evaporation. A new device was placed over the site after 24 h, and the device was removed and the site was swabbed after 48 h. Radioactivity was measured for the two devices and the swabbing materials, and blood samples, urine, and feces were collected regularly for 5 days.

Approximately 62.7% of the applied radioactivity was recovered after 5 days: 51.8% from the foam patches, 10.3% from the urine, and 0.7% from the application site residue. The radioactivity in the feces was at a background level, and the radioactivity in the blood was too low to be measured (Reifenrath et al., 1980).

Similar procedures were used to study the penetration of 4 μg/cm^2 of [1,3-^{14}C]Ethyl Hexanediol through the skin of three dogs. The results from this study were compared with the study previously cited to determine the effect of dose on the percentage penetration. As in the previous study, most of the radio-

activity was recovered from the patching materials (56.0%). Radioactivity was also detected in the urine (7.6%) and the residue from the application site (7.1%). The mean percentage penetration increased slightly with the greater chemical dose (8.8 and 10.3% for the low and high dose, respectively), but this change was not significant at the 95% confidence level (Reifenrath et al., 1981).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Groups of five male and five female Sprague–Dawley rats were administered undiluted Ethyl Hexanediol intragastrically. Doses of 4, 8, and 16 ml/kg were administered to the male rats and 2, 4, and 8 ml/kg to the female rats. The animals were observed for signs of toxicity over a 14-day observation period. No deaths occurred in the low-dose groups of either sex. One rat in each of the mid-dose groups died, and all rats in the high-dose groups died. The deaths occurred between 2 h and 2 days following administration. The calculated LD_{50} values were 9.85 ml/kg for male rats and 4.92 ml/kg for female rats. Signs of toxicity during the study included sluggishness, unsteady gait, prostration, and lacrimation. At necropsy, the rats that died had mottled lungs. No gross lesions were observed in the animals that survived to the end of the study (Ballantyne et al., 1985).

Other reported oral LD_{50} values for Ethyl Hexanediol using rats were >5,000 mg/kg (Eastman Kodak Co., 1988), 6.12 g/kg (Union Carbide Corp., 1978), 2.71 g/kg (Smyth et al., 1951), and 2.6 ml/kg (Draize et al., 1944).

Intravenous

The intravenous LD_{50} values for male and female Fischer 344 rats were 131 and 176 mg/kg of Ethyl Hexanediol, respectively (Frantz et al., 1991).

Dermal

Groups of five male and five female New Zealand White rabbits had undiluted Ethyl Hexanediol applied under occlusive patches to the clipped skin of their trunks for 24 h. The male rats received doses of 8.0, 11.3, and 16.0 ml/kg, and the females received 4.0, 8.0, and 16.0 ml/kg. All of the rats from the low-dose groups survived the 14-day observation period. Three male and two female rats from the mid-dose groups died, and all of the males and four of the females from the high-dose groups died. The calculated LD_{50} values for male and female rats were 10.88 and 9.51 ml/kg, respectively. All the deaths occurred between days 2 and 5 postadministration. Signs of toxicity included sluggishness, unsteady gait, and prostration. The animals from both the low-dose and the mid-dose groups had transient weight loss. At necropsy, the animals that died had mottled lungs and some of the animals had black foci on the mucosal surface of their stomach. Two

rats had a brown liquid in their pleural cavity. These lesions were not found in the animals that survived the 14-day test period (Ballantyne et al., 1985).

Other reported dermal LD_{50} values of Ethyl Hexanediol for rabbits were >20 ml/kg (Eastman Kodak Co., 1988), 14.3 g/kg (Union Carbide Corp., 1978), and 10.0 ml/kg (Draize et al., 1944).

Inhalation

Groups of five male and five female Wistar albino rats were exposed to atmospheres saturated with a vapor of Ethyl Hexanediol for 6 h. The vapor was generated either statically or dynamically in vapor chambers. None of the animals died during exposure or during the 14-day observation period. The animals exposed to the dynamically generated vapor were hypoactive during exposure, but this did not occur in the animals exposed to statically generated vapor. No lesions were observed at necropsy (Ballantyne et al., 1985).

In another study, five male and five female Sprague–Dawley rats were exposed for 4 h to an aerosol of Ethyl Hexanediol. The atmospheric concentration of Ethyl Hexanediol was 3.8 ml/L, and the particle size distribution had a mass median aerodynamic diameter of 2.0 μm (with a geometric SD of 4.3 μm). No deaths occurred either during exposure or during the 14-day observation period. Perioral and perinasal wetness with encrustation were observed on day 1 and were the only signs of toxicity during the study. No gross lesions were observed in any of the animals at necropsy (Ballantyne et al., 1985).

Short-Term Toxicity

Oral

Groups of five male and five female rats [CD(SD)BR] were administered 0, 100, 300, and 1,000 mg/kg/day of Ethyl Hexanediol in corn oil by gavage five times a week for 29 days (21 total doses). A control group of rats was administered corn oil alone. The behavior, feed consumption, and weights of the animals were monitored throughout the study. Necropsy was performed on all of the rats, and hematology and clinical chemistry examinations were conducted. None of the rats died before termination of the study, and no adverse clinical signs were observed in any of the dosage groups. The only reduction in body weight occurred in the male rats of the 300- and 1,000-mg/kg/day treatment groups on days 21 and 28; body weight gains were 9 and 6% lower than in the control group, respectively. However, these differences were not statistically significant. The body weight gain of the males from the 100-mg/kg/day treatment group was 8% greater than in the controls. The mean body weights of the female rats were comparable with those of the controls in all dose groups.

All of the treated rats had increased mean leukocyte counts regardless of administered dose. This change appeared to be dose dependent in the female rats; statistically significant increases were observed in the 300- and 1,000-mg/kg/day dose groups. In male rats, the mean leukocyte count was not significantly differ-

ent from that of the controls. The female rats also had a statistically significant lower platelet count in the 1,000-mg/kg/day dose group. All other hematological parameters for both sexes were comparable with those of the controls, and no changes in the clinical chemistry parameters were found in any of the treated rats.

Changes in organ weights occurred only in the 1,000-mg/kg/day treatment group. Male rats had statistically significantly increased mean relative liver and spleen weights. Increases were also measured in the mean absolute liver and spleen weights, but these were not statistically significant. In female rats, the mean absolute and relative liver weights were significantly increased. No treatment-related lesions were found in any of the treated animals at necropsy or microscopic examination of the tissues (Eastman Kodak Co., 1989*a*).

Dermal

Eight rabbits had 0.9 ml/kg/day of Ethyl Hexanediol applied to the clipped skin of their abdomens five times a week for 18 weeks. Each application was rubbed gently into the skin until it was substantially absorbed (10–60 min). The rabbits were weighed weekly and blood counts and blood chemistry were analyzed. Necropsy was performed on all of the animals at the end of the study, and the liver, kidneys, and skin were microscopically examined. No evidence of toxicity was observed during the study (Mellon Institute of Industrial Research, 1946).

Subchronic Oral Toxicity

Ethyl Hexanediol was administered in the feed to 10 rats for 90 days at concentrations ranging from 0.20 to 0.70 g/kg. The only sign of toxicity was reduced growth in the rats from the high-dose group. The maximum dose that had no toxic effects was 0.48 g/kg. No lesions were found during microscopic examination (Smyth et al., 1951).

Dermal Irritation

Ethyl Hexanediol [0.01 ml (0.009 g)] was mildly irritating to the skin of rabbits (number unspecified) after a single application (Union Carbide Corp., 1978).

Five guinea pigs had 0.5 ml of undiluted Ethyl Hexanediol applied to the clipped skin of their backs. A total of nine applications were made over an 11-day period. Slight erythema was first observed after the third application, and by the end of the study, the animals had slight to moderate erythema. There was no evidence of percutaneous absorption (Eastman Kodak Co., 1988).

In another study, 0.5 ml of undiluted Ethyl Hexanediol was applied under occlusive patches for 24 h to the depilated abdomens of five guinea pigs. No signs of irritation were observed 24 or 48 h following application or after 2 weeks (Eastman Kodak Co., 1988).

The primary irritation potential of Ethyl Hexanediol was also investigated by Ballantyne et al. (1985). Three male and three female New Zealand White rabbits had 0.5 ml of undiluted Ethyl Hexanediol applied under occlusive patches to the

clipped skin of their backs, and the application sites were evaluated after 1 h and after 1, 2, 3, and 7 days. Slight erythema was observed in five rabbits after the first hour and one rabbit had well defined edema. All signs of irritation subsided by 24 h.

In the acute dermal toxicity study (described earlier in this report), signs of inflammation, erythema, and edema were observed at the application sites of rabbits treated with undiluted Ethyl Hexanediol (doses ranging from 4.0 to 16.0 ml/kg). Erythema and edema disappeared by day 7, but desquamation was present until the end of the study (Ballantyne et al., 1985).

A minor degree of erythema with desquamation was also present during the short-term dermal toxicity study (described earlier in the report), in which eight rabbits were treated with 0.9 ml/kg/day of Ethyl Hexanediol for 18 weeks (Mellon Institute of Industrial Research, 1946).

Sensitization

Eastman Kodak Co. (1988) conducted a sensitization test following the Kodak Footpad Method. Ten Hartley guinea pigs were inducted with 0.05 ml of 1.0% Ethyl Hexanediol in Freund's Complete Adjuvant and were challenged with 1.0 ml of Ethyl Hexanediol in 10.0 ml of a solution of acetone, dioxane, and guinea pig fat. No sensitization was observed.

Ocular Irritation

The primary ocular irritation potential of Ethyl Hexanediol was investigated using groups of New Zealand White rabbits (six rabbits per group) whose corneas did not stain with 2% fluorescein. One group of rabbits had 0.1 ml Ethyl Hexanediol instilled into the inferior conjunctival sac of one eye and two other groups of rabbits had 0.01 or 0.005 ml of Ethyl Hexanediol placed directly onto the cornea of one eye. The eyes were examined after 1 and 24 h and after 2, 3, and 7–14 days. The animals treated with 0.1 ml Ethyl Hexanediol developed mild to severe conjunctivitis, seen as marked injection, mild to severe chemosis, and mild to marked discharge. Moderate iritis and moderate corneal injury were also observed. Only one case of conjunctivitis resolved within 24 h. The remainder of the cases resolved very slowly, the eyes becoming clinically normal after 7 days. Similar effects were observed at the lower doses (0.01 and 0.005 ml). Moderate to severe conjunctivitis persisted for 24 h, and conjunctival injection, chemosis, and discharge persisted for 2–7 days. Moderate iritis and corneal injury were present for 3–7 days (Ballantyne et al., 1985).

Six New Zealand white rabbits had 0.1 ml of undiluted Ethyl Hexanediol instilled into the conjunctival sac of one eye. Three of the treated eyes were immediately rinsed after instillation. The eyes were observed for signs of irritation immediately after instillation, after 1, 24, 48, and 72 h, and after 7 and 14 days. Fluorescein staining was conducted 24 h after dosing. At the 24-h grading period, Ethyl Hexanediol caused moderate to severe erythema and severe edema of the conjunctivae and nictitating membranes in the unrinsed eyes. The eyelids had

slight erythema and edema, there was slight corneal opacity, and moderate discharge was observed. Adnexal and corneal staining were also observed after treatment with fluorescein dye. Erythema developed in the irises after 48 or 72 h. Signs of irritation subsided by day 7 and the eyes appeared normal at day 14.

Irritation was less severe in the rinsed eyes. The conjunctivae and nictitating membranes of the eyes had only slight to moderate erythema, and discharge occurred only during the 1-h grading period. When the eyes were stained with fluorescein dye, only adnexal staining occurred. The eyes of two rabbits appeared normal after 72 h, and the eye of the third rabbit was normal by day 7 (Eastman Kodak Co., 1988).

Carpenter and Smyth (1946) gave Ethyl Hexanediol an overall ocular irritation grade of 5 (on a scale of 1–10, 10 being the greatest injury grade). By definition, grade 5 means that 0.02 ml of undiluted Ethyl Hexanediol caused an ocular irritation score over 5 (maximum score: 20) after a 24-h exposure period and that 0.005 ml Ethyl Hexanediol did not cause a reaction >5.

Maternal Toxicity and Teratogenicity

In a developmental toxicity probe study, groups of eight timed pregnant rats were administered 500, 1,000, 2,000, or 4,000 mg/kg Ethyl Hexanediol in corn oil by gavage on days 6–15 of gestation. A control group of rats was administered corn oil alone. The animals were observed throughout the study, and necropsy was performed at the time of death or on day 20 of gestation.

Seven rats from the 4,000-mg/kg group and one from the 2,000-mg/kg group died before the end of the study. These dams had signs of weakness, respiratory difficulty, dehydration, sialorrhea, gait disturbances, nasal discharge, porphyrin tears, diarrhea, decreased volume of feces, and unkempt haircoats. The rats from the high-dose group also had hypothermia, partially closed eyes, and excessive tearing. No clinical abnormalities were observed in the rats of the 500- or 1,000-mg/kg dose groups.

In all of the treatment groups, feed consumption was reduced during the first 3 days of treatment. The only statistically significant reduction occurred with the one surviving rat from the 4,000-mg/kg group. Mean body weight gains were reduced for all the treatment groups, but the reductions were not statistically significant. The only significant change in organ weight was a greater mean relative liver weight in the 2,000-mg/kg group. The relative liver weights at the lower doses were comparable with those of the control group.

At necropsy, lesions were found only in the dams that died before the end of the study. The dams from the 4,000-mg/kg group had Ethyl Hexanediol in their stomachs and duodenum, necrosis of the glandular gastric mucosa, excessive mucus in the cecum, and atrophy of the thymus and adipose tissue. The one dam from the 2,000-mg/kg group that died had hemorrhage in the glandular gastric mucosa and atrophy of the thymus and adipose tissue.

Pregnancy rates were low for the control and 1,000-mg/kg groups. However, the pregnancy rates of the other treatment groups were normal when compared with historical controls. The numbers of resorptions and postimplantation losses were

significantly increased in the rats of the 2,000-mg/kg group. The mean fetal body weights from this group were significantly decreased. None of these changes were observed in the lower-dose groups, and no changes in the mean number of corpora lutea, implantation sites, viable fetuses per litter, or preimplantation loss were observed in any of the treatment groups.

There was a statistically significant increase in the incidence of the following malformations in the fetuses from the dams in the 2,000-mg/kg group: rudimentary tails, missing tails, one case each of small tail and curly tail, edematous and/or hemorrhagic tails, a tail with a cyst, curvature of the hindlimbs, arthrogryposis, shortened trunk, umbilical hernia, and hematomas. Two fetuses from the dams of the 1,000-mg/kg group and one fetus from the dams of the 500-mg/kg group had rudimentary tails, and one fetus from a dam of the 1,000-mg/kg group had a hematoma on the face.

The authors concluded that doses of 2,000 and 4,000 mg/kg Ethyl Hexanediol were maternally toxic and lethal and that significant evidence of teratogenicity was observed only at maternally toxic doses. They noted that the number of control fetuses was very low, which might have obscured the effects seen in the lower-dosage groups (Eastman Kodak Co., 1989*b*).

In another study, 1.0, 2.0, and 4.0 ml/kg of undiluted Ethyl Hexanediol was applied under occlusive patches to the skin of groups of 25 timed pregnant Sprague–Dawley rats for 6 h on days 6–15 of gestation. The volume of the test material was based upon the weight of the dam on day 6. A control group of rats was treated with deionized water. Feed consumption and gestational body weight were measured daily and the rats were killed on day 21 of gestation.

Signs of maternal toxicity observed in the 4.0-ml/kg/day group included skin irritation, decreased gestational body weight gain, and increased liver weight. Relative liver weights were also increased in dams from the 1.0- and 2.0-ml/kg/day groups, and mild skin irritation was observed in some of the dams in the 2.0-ml/kg/day group. Significant changes in the other gestational parameters measured were not observed.

There were no significant changes in the incidence of individual external or skeletal malformations, malformations by category, or total malformations. One visceral malformation, hydroureter, was increased in the fetuses from the dams of the 4.0-ml/kg/day treatment group. There were also statistically significant increases in the incidence of the following visceral variations in this group: fetal atelectasis, partial fetal atelectasis, dilated lateral ventricle with no tissue depression, and bilateral dilated ureter. Additionally, a total of 13 of the 91 individual skeletal variations were statistically increased, which the authors attributed to reduced ossification. In the fetuses from the 2.0-ml/kg/day group, the following aberrations were observed: dilated lateral ventricle with no tissue depression, bilateral dilated ureters, and a reduced number of caudal segments. No significant developmental or teratogenic effects were observed in the fetuses from the 1.0-ml/kg/day group. The authors concluded that at topical doses of 1.0, 2.0, and 4.0 ml/kg/day, Ethyl Hexanediol caused maternal effects in Sprague–Dawley rats, and that at doses of 2.0 and 4.0 ml/kg/day, Ethyl Hexanediol appeared to be a mild developmental toxicant (Bushy Run Research Center, 1992).

MUTAGENICITY

In Vitro Studies

The mutagenic potential of Ethyl Hexanediol was evaluated in the Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100. Ethyl Hexanediol was tested in triplicate at concentrations ranging from 0.3 to 28.0 mg/plate both with and without metabolic activation with rat liver S9 mix. The positive control used for all the strains of the activated protocol was 2-aminoanthracene. For the protocol without S9 activation, 4-nitro-*O*-phenylenediamine was the positive control for strains TA1538 and TA98, sodium azide was used for TA1535 and TA100, and 9-aminoacridine was used for TA1537. Ethyl Hexanediol was negative in both test systems for each of the strains tested (Slesinski et al., 1988).

Ethyl Hexanediol was also tested in the quantitative assay of mutation induction at the hypoxanthine–guanine phosphoribosyl transferase locus in Chinese hamster ovary cells (CHO/HGPRT System). CHO cells were incubated with Ethyl Hexanediol at concentrations ranging from 1.0 to 4.5 mg/ml both with and without rat liver S9 activation. The cells were rinsed after 5 h, and cell viability was determined after a 18-h recovery period. Periodic replating was done at 2 to 3-day intervals, and the percentage of clonable cells and the incidence of mutants resistant to 6-thioguanine were determined after 9 days. The positive controls for the tests conducted with and without S9 activation were dimethylnitrosamine (DMN) and ethylmethanesulfonate (EMS), respectively.

Cytotoxic effects were observed even though a 18-h recovery period was allotted before evaluating colony forming ability. The mean percentage of clonable cells from the treatment groups was not significantly different from solvent controls. In tests without metabolic activation, doses of 1.0 and 4.0 mg/ml of Ethyl Hexanediol produced statistically significant increases in the number of mutant colonies formed. However, this was not a dose-related trend, as concentrations between the two doses did not increase the mutation index above that of the solvent controls. Additionally, there was a lack of agreement in duplicate cultures, and the values were within the historical control range for the laboratory (Slesinski et al., 1988).

In a sister chromatid exchange (SCE) assay, CHO cells were treated with Ethyl Hexanediol at concentrations of 1.0–3.0 mg/ml for 2 h with S9 activation and for 5 h without S9 activation in medium with bromodeoxyuridine. After 24–28 h, the chromosomes were harvested for SCE staining. EMS and DMN were used as positive controls. The 3.0-mg/ml dose of Ethyl Hexanediol alone was cytotoxic to the CHO cells and could not be evaluated due to a low mitotic index. However, during the shorter exposure time when Ethyl Hexanediol was tested with S9 activation, such excessive cytotoxicity was not observed. Overall, Ethyl Hexanediol, both with and without metabolic activation, did not increase SCEs above that of the negative control, and no dose-related trend relative to the concentration of Ethyl Hexanediol was found (Slesinski et al., 1988).

Ethyl Hexanediol was also tested for clastogenic activity. CHO cells were

exposed to Ethyl Hexanediol alone for 6–12 h or to Ethyl Hexanediol with S9 activation for 2 h. Two concentrations of S9 homogenate were used: 50 μl/5 ml and 100 μl/5 ml. The chromosomes were harvested following exposure and chromosome damage was evaluated. Triethylenemelamine (TEM) was used as the positive control for the nonactivated test and cyclophosphamide was used in the tests with S9 activation. In tests without metabolic activation, Ethyl Hexanediol was tested at concentrations ranging from 1.3 to 2.0 mg/ml. None of these concentrations increased the incidence of chromosome aberrations. Under activation conditions, 3.0–4.5 mg/ml Ethyl Hexanediol caused statistically significant increases in chromosome aberrations at isolated time periods only. When activation was induced with 50 μl S9/5 ml, positive results were reported at 8 h but not at 12 h. Similarly, when activation was induced with 100 μl S9/5 ml, a significant increase in aberrations was reported at 10 h, but at 12 h there was only a marginally positive increase. Most of the chromosome damage was simple chromatid and chromosome breakage. The authors stated that such damage would probably be lethal to the cell and thus concluded that Ethyl Hexanediol did not have the potential to cause any inheritable damage (Slesinski et al., 1988).

In Vivo Studies

Swiss–Webster mice were used to investigate the effects of Ethyl Hexanediol upon the incidence of micronucleated polychromatic erythrocytes (mPCEs) in peripheral blood. Groups of 5–10 mice were given intraperitoneal injections of Ethyl Hexanediol at concentrations of 18.75, 37.5, 60, 75, and 120 mg/kg. Blood samples were taken after 24, 48, and 72 h. A total of 2,500 PCEs were examined for each animal. Bone marrow cytotoxicity was assessed by determining the PCE to normochromatic (mature) erythrocyte (NCE) ratio for 1,000 cells/animal. TEM was used as the positive control. The two highest doses caused sedation, lethargy, and periocular encrustation in the mice, and a few of the mice died. However, no significant or dose-related increases in mPCEs were found in the blood from any of the dosage groups. Also, no remarkable bone marrow cytotoxicity was evident, as the PCE/NCE ratios of the treated animals were similar to those of controls (Slesinski et al., 1988).

Two bone marrow cytogenetic tests were conducted using Sprague–Dawley rats. In one study, groups of 10 rats were given a single intraperitoneal injection of 60, 200, or 600 mg/kg of Ethyl Hexanediol. In the other study, rats were injected with the same concentrations of Ethyl Hexanediol daily for 5 days. The chromosomes were sampled 12, 24, and 48 h after dosing in the acute study and 6 h after the last injection in the repeated dose study. The bone marrow was flushed from the femurs, and the chromosomes were prepared by fixation; 100 cells/animal were evaluated. The high dose caused sedation and weight loss in the animals treated with the high dose in both protocols, and no cumulative toxicity was apparent as the clinical signs of toxicity were essentially the same following both single and multiple injections. The authors noted that three animals in the 600-mg/kg treatment group in the repeated dose study died and were replaced by extra high dose animals to keep the group size consistent. Ethyl Hexanediol did

not significantly increase chromosome damage at any time during either protocol (Slesinski et al., 1988).

The authors also investigated the penetration of bone marrow by Ethyl Hexanediol. Sprague–Dawley rats were injected intraperitoneally with 600 mg/kg of [1,3-^{14}C]Ethyl Hexanediol (10 μCi/kg) in corn oil. Two animals were killed 0.5, 1, 2, 4, and 8 h following injection, and radioactivity values in the bone and blood were quantified. Ethyl Hexanediol was rapidly taken up by the bone marrow, being detectable after 0.5 h and up to 8 h. The bone marrow/plasma ratios were not significantly different between the 2- and 8-h samples, which indicated that radioactivity uptake and elimination were at a steady state. The authors concluded that Ethyl Hexanediol penetrated the bone marrow cells, and the results supported the conclusion of the bone marrow cytogenetic test that Ethyl Hexanediol was not clastogenic (Slesinski et al., 1988).

CARCINOGENICITY

Groups of five New Zealand White rabbits had 0.02 ml of 10, 50, and 100% Ethyl Hexanediol applied to their interior left ear twice a week for their lifetime. A positive control group of 15 rabbits was treated with 9,10-dimethylbenz(a)anthracene (DMBA), and the study was terminated after 50 weeks for morphological analysis. An untreated control group of five rabbits was allowed to die spontaneously. The lifespan of the animals treated with Ethyl Hexanediol was not significantly different from the survival of the untreated control rabbits. The DMBA-treated animals developed several cutaneous ear tumors including papillomas, keratoacanthomas, and squamous cell carcinomas. However, no cutaneous tumors were found in the ears of the rabbits treated with Ethyl Hexanediol (Stenback, 1977).

The carcinogenic potential of Ethyl Hexanediol was also investigated using Swiss mice. Groups of 50 female mice had 0.02 ml of 10, 50, and 100% Ethyl Hexanediol applied to a shaved 1-in^2 area on their back twice a week for their lifetime. A positive control group of mice were treated with DMBA and a negative control group of 150 mice received no treatment. Necropsy was performed on all of the mice. During the study, the authors noted a slight inflammation and atrophy of the skin. The lifespan of the treated animals did not differ significantly from that of untreated controls. However, the tumor incidence for animals treated with Ethyl Hexanediol (46–64%) was greater than for untreated controls (42%). Tumor incidence did not appear to be specifically related to tumor type. The more commonly found neoplasms were lymphomas, lung adenomas, liver hemangiomas, and skin tumors. These types of tumors were also found in untreated control mice. The authors concluded that Ethyl Hexanediol did not produce a statistically significant increase in skin tumor incidence when compared with both untreated and positive control animals (Stenback and Shubik, 1974).

However, the EPA reviewed this study in the toxicology profile of its Pesticide Registration Standard for Ethyl Hexanediol and found it to be inadequate. They noted discrepancies between the number of animals tested and the number of total tumors. Additionally, a linear trend analysis and a site-specific χ^2-test conducted

by the EPA on the data indicated a possible oncogenic potential. The EPA concluded that the data were insufficient to assess the chronic effects of Ethyl Hexanediol (EPA, 1981).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

A prophetic patch test was conducted with 5% and undiluted Ethyl Hexanediol using 106 and 30 subjects, respectively. Each subject had two applications of 0.2 ml Ethyl Hexanediol applied to the infrascapular region of the back for 48 h. One of the sites was covered with an occlusive dressing and the other with a semiocclusive dressing. Evaluations of the treatment sites were made at the time of patch removal and 24 h later. Of the 106 subjects treated with 5% Ethyl Hexanediol, one had barely perceptible erythema after 48 h under the semiocclusive patch and one subject had a similar reaction at 48 and 72 h under the occlusive patch. With undiluted Ethyl Hexanediol, similar reactions were observed in 4 of 30 subjects tested using occlusive patches and in 2 subjects using semiocclusive patches. One case of definite erythema was observed at 72 h in a subject tested with occlusive patches (Ballantyne et al., 1989).

Ethyl Hexanediol was also tested in a 21-day cumulative irritation study. Twenty-seven subjects had 0.2 ml of undiluted Ethyl Hexanediol applied to two sites on infraclavicular skin. One site was covered with an occlusive patch, and the other with a semiocclusive patch. Applications were made daily, except for Saturdays and Sundays, when the patch applied on Friday was left in contact for 3 days. The sites were scored at each patch removal. Under semiocclusive conditions, the incidence of barely perceptible erythema increased with the number of applications. However, only one case of definite erythema was observed after 14 applications. Similar results were observed under occlusive conditions: The cases of marginal erythema increased with the number of applications, definite erythema developed in three subjects, and one subject had both erythema and edema (Ballantyne et al., 1989).

Sensitization

Ballantyne et al. (1989) conducted a repeated insult patch test with 203 subjects using undiluted Ethyl Hexanediol. Each subject had 0.2 ml of Ethyl Hexanediol applied under an occlusive patch to the infrascapular area of the back for 24 h three times a week for 3 weeks. After a 2-week nontreatment period, Ethyl Hexanediol was applied under occlusive patches for 24 h to previously untreated sites. The challenge sites were evaluated 24 and 48 h following removal of the patch. Two of the 202 subjects who completed the study had definite erythema following challenge at the 48-h reading. Three subjects had questionable reactions. When the two subjects with positive sensitization reactions were retested using occlusive and semiocclusive patches, only one subject developed definite erythema and edema when occlusive patches were used. The other subject was described as having questionable erythema.

In another human repeated insult patch test, Ethyl Hexanediol was a weak primary irritant and/or weak sensitizer. Four of 200 individuals tested had a reaction. The details of this unpublished study were not given. However, the EPA stated in its Pesticide Registration Standard: "This study is acceptable to fulfill the data requirement for primary dermal irritation and skin sensitization, although it was not conducted in accordance with the requirements of the Guidelines" (EPA, 1981).

SUMMARY

Ethyl Hexanediol is an aliphatic alcohol that is used as a solvent in cosmetic formulations. Oral and intravenous studies indicate that it is completely metabolized in the rat and rapidly eliminated in the urine as at least two major metabolites. Ethyl Hexanediol is also absorbed through the skin of rats and dogs.

Ethyl Hexanediol was slightly toxic to rats in acute oral studies. Reported LD_{50} values for rats were 4.92 ml/kg (females), 9.85 ml/kg (males), >5,000 mg/kg, 6.12 g/kg, 2.71 g/kg, and 2.6 ml/kg. Dermal LD_{50} values for rabbits were 9.51 ml/kg (females), 10.88 ml/kg (males), >20 ml/kg, 14.3 g/kg, and 10.0 ml/kg. Ethyl Hexanediol was not toxic in inhalation studies with rats.

Ethyl Hexanediol was slightly toxic in subchronic oral studies. The most significant effects were reduced growth and increased hepatic weights. It also caused mild to moderate irritation when applied to the skin of guinea pigs and rabbits. However, no evidence of sensitization was found. Ethyl Hexanediol was a moderate to severe ocular irritant in rabbits.

In a developmental toxicity study, 2,000- and 4,000-mg/kg doses of Ethyl Hexanediol given orally were maternally toxic and lethal, and significant evidence of teratogenicity was observed at maternally toxic doses only. In a dermal developmental toxicity study, 1.0, 2.0, and 4.0 ml/kg/day Ethyl Hexanediol caused maternal effects, and at doses of 2.0 and 4.0 ml/kg/day it appeared to be a mild developmental toxicant.

There was no evidence that Ethyl Hexanediol was mutagenic or had DNA damage potential when tested with the Ames test, the CHO/HGPRT gene mutation test system, and the SCE test both with and without metabolic activation. Ethyl Hexanediol was also negative in the in vivo micronucleus test and bone marrow cytogenetic tests. The only evidence of clastogenicity was reported in two in vitro chromosome damage tests with CHO cells. These effects were observed in the presence of S9 activation only and were observed for a brief time span only.

In dermal carcinogenicity studies, no dose-related increases in tumor incidence were observed.

In clinical studies, Ethyl Hexanediol was a weak primary irritant, weak cumulative irritant, and weak sensitizer.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel noted the lack of irritation when Ethyl Hexanediol was tested in humans at a concentration of 5%. This contrasts with animal dermal irritation data, suggesting that positive findings of irritation in animals exposed to undiluted Ethyl Hexanediol have limited rele-

vance. Based on the available data on use, the Panel believes that 5% is also the highest concentration at which the ingredient is actually used.

The Panel noted the absence of data on the absorbance of Ethyl Hexanediol in the ultraviolet region. However, based on the chemical structure of this ingredient, it was agreed that it was not likely that there would be significant absorption in the UVA or UVB regions. While there was likewise no information on possible impurities in Ethyl Hexanediol, the Panel considered it unlikely that toxic impurities would be present and concluded that the lack of such data did not preclude making a safety assessment of this ingredient.

The Panel did express concern about the evidence of weak teratogenicity in rats following dermal exposure to undiluted Ethyl Hexanediol. It was believed, however, that no such effect would occur in humans; the high levels shown to be weakly teratogenic in animals extrapolate to kilogram quantities of cosmetic formulation in a human exposure. Such a use pattern was considered unlikely.

CONCLUSION

On the basis of the animal, clinical, and use data presented in this report, the CIR Expert Panel concludes that Ethyl Hexanediol is safe as a cosmetic ingredient.

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