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Final Report on the Safety Assessment of Methoxyisopropanol and Methoxyisopropyl Acetate as Used in Cosmetics[1]

Methoxyisopropanol and Methoxyisopropyl Acetate, commonly known as propylene glycol monomethyl ether (PGME) and propylene glycol monomethyl ether acetate (PGMEA), respectively, have fragrance, solvent, and viscosity-decreasing functions in cosmetics, although only Methoxyisopropanol is in current use at concentrations ranging from 4% to 35%. Methoxyisopropanol is easily absorbed into the bloodstream upon inhalation or ingestion. The acetate ester is readily metabolized to Methoxyisopropanol in the body, which is excreted unchanged in the expired breath or in the urine as free or conjugated Methoxyisopropanol, or as the primary metabolite propylene glycol. In acute oral toxicity studies, the LD_{50} values of Methoxyisopropanol were 4.6 to 9.2 g/kg in rats, with similar low acute toxicity in other animal species. Inhalation exposures of rats, mice, and rabbits to 3000 ppm Methoxyisopropanol for 6 h per day for 9 days to 13 weeks produced increased relative liver weights, signs of central nervous system (CNS) depression, and in some cases, elevated serum alkaline phosphatase, alanine aminotransferase, or hepatocellular hypertrophy, but the kidneys were unaffected. The no observed adverse effect level (NOAEL) for 13-week inhalation exposures to Methoxyisopropanol was 1000 ppm in rats and rabbits. In a 90-day dermal exposure study using rabbits, 10 ml/kg undiluted Methoxyisopropanol produced narcosis and increased kidney weights and the NOAEL was 7.0 ml/kg. Chronic (2-year) daily inhalation exposures of rats and mice to 3000 ppm Methoxyisopropanol produced signs of liver toxicity (rats and mice) and some evidence of renal toxicity in rats. The only observation at 1000 ppm was dark foci of the liver in male rats. For female rats and male and female mice, the NOAEL of this chronic inhalation study was 1000 ppm Methoxyisopropanol. Methoxyisopropanol and Methoxyisopropyl Acetate were found to be nonirritating to slightly irritating and non-sensitizing in rabbit and guinea pig skin. Repeated applications of undiluted Methoxyisopropanol to the eyes of rabbits produced transient slight to moderate irritation. Pregnant rats exposed to 200 or 600 ppm Methoxyisopropanol by inhalation on gestation days 6 to 17 had no effects on maternal health or normal fetal development. Adult male rats exposed to these concentrations had no effects on the reproductive organs. Pregnant rats and rabbits exposed to 500 to 3000 ppm Methoxyisopropanol by inhalation during gestation had no significant embryotoxic or fetotoxic effects, althougth CNS depression and reduced body weight gain were observed in the 3000 ppm group. In a two-generation inhalation study using rats, continuous inhalation of 3000 ppm Methoxyisopropanol produced CNS depression, prolonged estrous cycles, reduced fertility indices, reduced pup weights and pup survival, and delayed sexual development, with a NOAEL for reproductive and developmental effects of 1000 ppm. In a continuous breeding protocol using mice, 2.0% Methoxyisopropanol in drinking water produced reduced growth, reduced relative epididymis weight, reduced relative prostate weight, and increased liver weight (females only) in offspring, with a NOAEL at a 1% concentration. Exposure of mice or rats to 300 ppm to 3000 ppm Methoxyisopropanol by inhalation produced no signs of carcinogenicity. Methoxyisopropanol was negative for mutagenicity or genetic toxicity in the bacterial reverse mutation assay ($\leq$5000 μg/plate), the unscheduled DNA synthesis (UDS) assay ($\leq$0.1 M), V79 Chinese hamster lung assay (>100 mM), and in the Siberian hamster embryo assay (concentrations not reported). In other assays, 100 mM Methoxyisopropanol increased sister chromatid exchanges in V79 cells. In human inhalation exposure studies of 1 to 7 h duration, 50 to 75 ppm Methoxyisopropanol vapor had an objectionable odor; 150 ppm was slightly irritating to the eyes and throat; 250 ppm produced eye irritation, lacrimation, blinking, rhinorrhea, and headache; 300 ppm was mildly irritating to the eyes, nose, and throat; 750 ppm was extremely irritating; and 2050 ppm produced extreme discomfort with severe lacrimation, blepharospasm, and painful breathing. None of the concentrations tested impaired motor coordination or performance on neurological tests. The irritating effects subsided within 15 min to 24 h of removal from the inhalation chamber. The National Institute of Occupational Safety and Health (NIOSH) recommended an 8-h time-weighted average for occupational exposure of 100 ppm. A margin of safety of 500 was determined, based on a calculated exposure from the normal use of nail polish remover products (100% absorption) and the NOAEL for reproductive toxicity. The absorption of Methoxyisopropanol through the nail is likely to be low, suggesting this margin of safety is conservative. Because Methoxyisopropanol is volatile, exposure by inhalation is possible, but the odor becomes objectionable at 50 to 75 ppm in air. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that Methoxyisopropanol and Methoxyisopropyl Acetate are safe for use in nail care products in the practices of use and concentration as described in this safety assessment.

INTRODUCTION

Methoxyisopropanol and Methoxyisopropyl Acetate are names used in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004) for the two cosmetic ingredients considered in this safety assessment. Most of the published literature, however, refers to these two compounds as Propylene Glycol Monomethyl Ether (PGME) and Propylene Glycol Monomethyl Ether Acetate (PGMEA),

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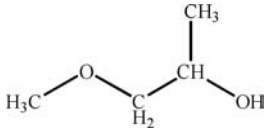

FIGURE 1
Chemical formula for Methoxyisopropanol.

respectively. Many of the available studies addressed PGME, but these data may be applied to assess the safety of PGMEA, as the Acetate is quickly metabolized to the parent compound.

CHEMISTRY

Definition and Structure

Methoxyisopropanol (CAS No. 107-98-2) is the aliphatic alcohol that conforms to the formula in Figure 1. Other names for Methoxyisopropanol include 1-Methoxy-2-hydroxypropane; 1-Methoxypropan-2-ol; 1-Methoxy-2-propanol; 2-Propanol, 1-Methoxy-; Propylene Glycol Monomethyl Ether; and PGME (Boatman 2001; Gottschalck and McEwen 2004). There are two isomeric forms of PGME: the alpha (α) or 1-methoxy-2-propanol, and the beta (β) or 2-methoxy-1-propanol. Unless otherwise stated, Methoxyisopropanol refers to the α-isomer (Miller et al. 1986).

Methoxyisopropyl Acetate (CAS Nos. 108-65-6 and 84540-57-8) is the acetate derivative of Methoxyisopropanol that conforms to the formula in Figure 2. It is also known as 2-Methoxy-1-Methylethyl Acetate and Propylene Glycol Methyl Ether Acetate (PGMEA) (Gottschalck and McEwen 2004). CAS No. 108-65-6 refers to the α-isomer only, whereas CAS No. 84540-57-8 is a mixture of the α- and β-isomers (proportions not reported) (Boatman 2001).

Physical and Chemical Properties

Availble data on the physical and chemical properties of Methoxyisopropanol and Methoxyisopropyl Acetate are given in Table 1.

Methoxyisopropanol is a colorless flammable liquid that is miscible to easily soluble in water (International Programme of Chemical Safety & Commission of the European Communities 1998).

Methoxyisopropanol has a mild ether-like odor, which is detectable to human olfaction at 10 ppm and becomes objectionable at 50 to 75 ppm, but human volunteers rapidly developed tolerance for the odor (Boatman 2001; Stewart et al. 1970). According to the Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS), Methoxyisopropanol vapors degrade quickly to produce hydroxyl radicals when exposed to sunlight, with a photochemical degradation half-life of 3.1 h (OECD/SIDS 2001a).

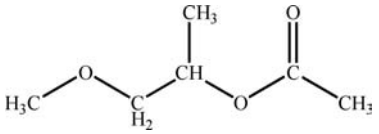

FIGURE 2
Methoxyisopropyl Acetate.

Method of Manufacture

Methoxyisopropanol is produced by reacting propylene oxide with methanol. U.S. production of Methoxyisopropanol was 145 million pounds in 1995 (Boatman 2001). In 1999, U.S. manufacturers produced 176 million pounds of Methoxyisopropanol, and in 2004, the projected US production is 209 million pounds (SRI International Chemical Economics Handbook 2000).

Analytical Methods

Ferrala et al. (1994) used capillary gas chromatography (GC) and flame ionization detection to simultaneously determine Methoxyisopropanol and its metabolite propylene glycol in rat and mouse plasma. Jones et al. (1997) used a gas chromatograph and a GC-mass spectrometer (GC-MS) to measure Methoxyisopropanol in human blood, in which the detection limit was found to be 1 μmol/L.

Impurities

Miller et al. (1986) reported that the Methoxyisopropanol in commercial products could contain 5% 2-methoxy-1-propanol. Current standards call for commercial grade Methoxyisopropanol to contain less than 0.5% of the β-isomer, 2-methoxy-1-propanol (Oxygenated Solvents Producers Association 2001).

Methoxyisopropyl Acetate may contain less than 0.5% of the β-isomer, 2-methoxy-1-propyl acetate and 0.2% propanol (OECD/SIDS 2001a).

USE

Cosmetic

Methoxyisopropanol functions in cosmetics as a fragrance ingredient, a solvent, and a viscosity-decreasing agent (Gottschalck and McEwen 2004). Uses of Methoxyisopropanol reported to the Food and Drug Administration (FDA) by industry include basecoats and undercoats and nail polish and enamels (FDA 2002). In a survey of current concentrations of use, the Cosmetic, Toiletry, and Fragrance Association (CTFA) reported that Methoxyisopropanol is used in nail polishes and enamels at 4% and in nail polish and enamel removers at 4% to 35% (CTFA 2003). Product use and concentration data are given in Table 2.

Dentan et al. (2000) reported one perfume containing 30% to 50% Methoxyisopropanol, two with 10% to 30% Methoxyisopropanol, four with 1% to 10% Methoxyisopropanol, and

TABLE 1
Physical and chemical properties of Methoxyisopropanol and Methoxyisopropyl Acetate.[a]

Property	Methoxyisopropanol	Methoxyisopropyl Acetate
Chemical formula	$C_4H_{10}O_2$	$C_6H_{12}O_3$
Molecular weight	90.1	132.16
Density	0.92 g/cm^3	0.965– 0.970 g/cm^3
Boiling point	120°C	145.8°C
Melting point	−96°C	−96.7°C; < −10°C
Flash point	38°C	45°C
Vapor pressure	1.2 kPa at 20°C	1.57kPa at 25°C 3.7 kPa at 20°C
Autoignition temperature	270°C	315°C
Viscosity (20°C)	1.9 cps	—
Solubility in water (20°C)	200 g/L (miscible)	160,000 mg/L; >100 g/L
Appearance	Colorless liquid	—
Henry's law constant	0.28 Pa m^3/mol	0.43 Pa m^3/mol
Log $P_{o/w}$ (octanol/water partition coefficient)	−0.437; 0.36	0.430; 0.36
Other partition coefficients:		
Water/air	12,280	—
Blood/air	12,383	—
Oil/air	696	—
Water/blood	0.992	—
Oil/water	0.057	—
Oil/blood	0.056	—

[a]From Johansen and Dynésius 1988; International Programme of Chemical Safety and Commission of the European Communities 1998; OECD/SIDS 2001a, 2001b; Staples and Davis 2002; Diacel Chemical Industries, Inc. 2003.

two containing 1% Methoxyisopropanol. Methoxyisopropanol has reportedly been used at concentrations as high as 20% as a solvent in nail-varnish remover (OECD/SIDS 2001a).

Methoxyisopropyl Acetate functions as a solvent in cosmetic formulations (Gottschalck and McEwen 2004); however, the FDA (2002) and CTFA (2003) reported no current uses of Methoxyisopropyl Acetate.

Noncosmetic

Methoxyisopropanol is used primarily as a solvent in manufacturing processes of the chemical, agricultural, automotive, paint, lacquer, and varnish industries. Approximately 34% of Methoxyisopropanol produced in the United States is used in the manufacture of Methoxyisopropyl Acetate. The remaining United States–produced Methoxyisopropanol is used in surface coatings (30% of Methoxyisopropanol produced), cleaners (23%), inks (6%), and miscellaneous adhesives and electronics (7%) (OECD/SIDS 2001a).

According to the FDA regulations, Methoxyisopropanol may be safely used as a component of articles intended for use in packaging, transporting, or holding food (21CFR175.105).

Methoxyisopropyl Acetate is used in surface coatings, inks, and cleaners (Boatman 2001).

TABLE 2
Cosmetic product uses and concentrations for Methoxyisopropanol.

Product category (total number of products in each category) (FDA 2002)	Ingredient uses in each product category (FDA 2002)	Use concentrations (CTFA 2003) (%)
Nail care products		
Basecoats and undercoats (44)	2	—
Nail polishes and enamels (123)	2	4
Nail polish and enamel removers (36)	—	4–35
Total uses/ranges for Methoxyisopropanol	4	4–35

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Animal

Methoxyisopropanol

Miller et al. (1983) described the metabolism and disposition of Methoxyisopropanol in male rats. Male F344 rats were given a single oral dose of 8.7 mmol/kg [^{14}C]Methoxyisopropanol. Expired air, urine, and tissues were analyzed for ^{14}C, and metabolites in the urine were identified. Forty-eight hours after the oral dose, 5.7% to 6.3% of the administered dose remained in the tissues, with 1.7% in the skin, 1.40% in the liver, 0.14% in the kidneys, and 0.1% in the blood. Fifty percent to 60% of the administered ^{14}C was exhaled as $^{14}CO_2$, whereas 10% to 20% was excreted in the urine as Methoxyisopropanol, propylene glycol, and as the sulfate and glucuronide conjugates of Methoxyisopropanol.

Morgott and Nolan (1987) studied the kinetics of inhaled Methoxyisopropanol in F344 rats. Rats were exposed to 300, 750, 1500, or 3000 ppm Methoxyisopropanol from a nose cone or 300 or 3000 ppm Methoxyisopropanol in a whole-body inhalation chamber ($n = 12$ rats/treatment condition). The kinetics of repeated inhalation exposures to Methoxyisopropanol was also studied in rats. F344 rats were exposed to 300, 750, 1500, or 3000 ppm Methoxyisopropanol vapor in a whole-body inhalation chamber 6 h per day for 10 days ($n = 12$ rats/group). Blood was collected from surgically implanted indwelling jugular cannulae. Animals were killed 18 h after the last exposure, and the liver microsomes were analyzed.

The blood concentration of Methoxyisopropanol rose proportionately with the concentration of Methoxyisopropanol in the air and continued to rise without plateau during the 6-h exposures. However, the half-life of elimination was increased with increasing dose, suggesting to the authors that Methoxyisopropanol does not follow first-order elimination.

The primary metabolite detected was the demethylation product propylene glycol (PG), and production of PG was saturated at 1500 ppm. The end-exposure blood concentrations of Methoxyisopropanol were lower after the 10th whole-body 300 and 3000 ppm exposure (67 and 1002 μg/g, respectively) than after the single whole-body 300 and 3000 ppm exposure (74 and 1816 μg/g, respectively), suggesting an induction of the enzymes that metabolize Methoxyisopropanol. Likewise, the biological half-life of Methoxyisopropanol in the blood was reduced after the 10th 3000 ppm exposure (9.7 h), compared to the half-life after the single 3000 ppm exposure (15.5 h).

Liver microsome analysis showed that multiple exposure to 3000 ppm Methoxyisopropanol caused increases in microsomal P450 activity, aniline hydroxylase activity, and *p*-nitroanisole-*O*-demethylase activity. The authors associated the changes in Methoxyisopropanol elimination rate after multiple 3000 ppm exposures with higher levels of cytochrome P450 and mixed function oxidase activities. Multiple exposures to 300 ppm Methoxyisopropanol did not affect the elimination rate or enzyme activities (Morgott & Nolan 1987).

Ferrala et al. (1994) gave male B6C3F1 mice a single oral dose of 90 mg/kg Methoxyisopropanol in saline and then collected blood samples at 2, 5, 7, 10, 20, and 30 min and 1, 1.5, 2, 4, and 5 h after dosing. The number of animals dosed was not reported. Blood samples were analyzed to detect Methoxyisopropanol and propylene glycol. Methoxyisopropanol was readily absorbed from the gastrointestinal tract and rapidly metabolized to propylene glycol. Methoxyisopropanol and propylene glycol were detected in blood samples as soon as 2 min after dose administration. The blood concentration of Methoxyisopropanol peaked at 76.5 μg/ml 20 min after dosing. Propylene glycol in the blood reached a maximum concentration of 18.5 μg/ml 30 min after dosing. By 2 h after dosing, Methoxyisopropanol was not detected in the blood. Propylene glycol was detectable at 4 h but not at 5 h after dosing.

Methoxyisopropyl Acetate

Miller et al. (1984) studied the metabolism and disposition of Methoxyisopropyl Acetate in F344 rats. Male rats (number not given) were given a single oral dose of 8.7 mmol/kg [1-^{14}C]Methoxyisopropyl Acetate. Approximately 64% of the administered radioactivity was exhaled as $^{14}CO_2$ and 24% was excreted in urine within 48 h of the oral dose. Free Methoxyisopropanol and Methoxyisopropanol sulfate and glucuronide conjugates were identified in the urine.

In another experiment, male F344 rats (number not given) were exposed to 3000 ppm [1-^{14}C]Methoxyisopropyl Acetate in an inhalation chamber for 6 h. Approximately 53% of the administered radioactivity was exhaled as $^{14}CO_2$, and 26% was excreted in urine within 48 h of the end of the inhalation exposure period. Methoxyisopropanol and sulfate and glucuronide conjugates were identified in the urine.

The similarities between the metabolism and disposition of Methoxyisopropyl Acetate and those previously observed in Methoxyisopropanol indicated that Methoxyisopropyl Acetate is rapidly hydrolyzed to Methoxyisopropanol (Miller et al. 1984).

Stott and McKenna (1985) measured the rate of hydrolysis of Methoxyisopropyl Acetate by carboxylesterase in the nasal mucosa of mice, rats, rabbits, and dogs. Samples of nasal mucosal tissue from each species were incubated in vials with 1.0 to 23 mM Methoxyisopropyl Acetate for 10 min, and then centrifuged. The supernatant was removed and analyzed by gas chromatography to measure the Methoxyisopropanol content. The apparent V_{max} and K_M for the hydrolysis of Methoxyisopropyl Acetate were 0.080×10^{-3} M/min and 2.67×10^{-3} M, respectively.

Domorandzki et al. (2003) gave male F344 rats an intravenous injection of 10 or 100 mg/kg Methoxyisopropanol or 14.7 or 147 mg/kg Methoxyisopropyl Acetate into an indwelling jugular vein cannula (number of animals per treatment not reported). Blood samples from the jugular vein cannulae were collected 5, 10, 15, 30, and 45 min and 1, 2, 4, 6, 8, and 12 h after injection. The blood time courses of Methoxyisopropanol

elimination for both doses of both compounds were identical. The $t_{1/2}$ values for the low and high doses of Methoxyisopropyl Acetate were 1.6 and 2.3 min, respectively. The clearance rates of 14.7 and 147 mg/kg Methoxyisopropyl Acetate were 4 and 11.0 ml/min, respectively.

These authors also incubated rat blood and liver homogenate with 5 or 50 μg/ml Methoxyisopropyl Acetate and measured the in vitro hydrolysis rate of Methoxyisopropyl Acetate to Methoxyisopropanol in each tissue type. The hydrolysis $t_{1/2}$ values of Methoxyisopropyl Acetate in whole rat blood was 16 and 15 min with the 5 and 50 μg/ml concentrations, respectively. The $t_{1/2}$ of Methoxyisopropyl Acetate hydrolysis in rat liver homogenate was 34 min for both concentrations. The authors concluded that because this hydrolysis rate is rapid, the kinetic activity of Methoxyisopropyl Acetate would be identical to that for Methoxyisopropanol (Domorandzki et al. 2003).

Human

Methoxyisopropanol

Dugard et al. (1984) measured the absorption of Methoxyisopropanol across human abdominal skin prepared in glass diffusion cells. Methoxyisopropanol was applied to the donor site, and its appearance in the receptor fluid was measured by gas chromatography. Integrity of the skin was tested with tritiated water applied to the donor side and measured from the receptor side before and after treatment with Methoxyisopropanol. The absorption rate of Methoxyisopropanol into the receptor fluid was 1.17 mg/cm^2/h. The authors reported that the permeability constant was 12.5×10^{-4} cm/h.

Hubner et al. (1992) examined the occupational exposure of employees of a brakehose manufacturing plant to Methoxyisopropanol. Twenty men and two women were studied during their work in brakehose production, leak test, and mounting. Urine samples were collected before and after work shifts, and blood was collected after work shifts. Biological samples were analyzed for Methoxyisopropanol content.

Employees who worked in the brakehose production area where the air contained 82.2 mg/m^3 (22.3 ppm) Methoxyisopropanol had 8.5 ± 12.7 g Methoxyisopropanol/g creatinine in the urine and 13.5 ± 4.4 mg/L Methoxyisopropanol in the blood ($n = 6$). In the leak testing area, where the Methoxyisopropanol concentration in the air was 68.6 mg/m^3 (18.6 ppm), workers had 6.5 ± 6.4 g Methoxyisopropanol/g creatinine in the urine and 11.0 ± 4.4 mg/L Methoxyisopropanol in the blood ($n = 8$). Workers who spent their shift mounting brakehoses were exposed to 11.3 mg/m^3 (3.1 ppm) and had respective urine and blood concentrations of Methoxyisopropanol of 0.5 ± 0 g/g creatinine and 0.5 ± 0 mg/L ($n = 6$). The elimination half-life of Methoxyisopropanol in brakehose workers was found to be 4.4 h (Hubner et al. 1992).

Laitinen et al. (1997) collected urine samples from 23 silkscreen printers at the end of a work week. The workers had an average workplace exposure of 4.92 cm^3/m^3 Methoxyisopropanol in the air for 8 h per day. The urine samples showed that the excretion of propylene glycol (a metabolite of Methoxyisopropanol) was 2.52 mmol per mole of creatinine. There was a correlation between propylene glycol excretion and occupational Methoxyisopropanol exposure ($r = 0.67$). Urine collected from control subjects who did not have occupational exposure to Methoxyisopropanol showed an average propylene glycol level of 1.18 mmol per mole of creatinine.

Jones et al. (1997) exposed volunteers to 100 ppm Methoxyisopropanol by inhalation for two 4-h periods separated by a 30-min break. Methoxyisopropanol was measured by GC and GC-MS in urine, blood, and exhaled air. Blood and exhaled air showed time-dependent increases in Methoxyisopropanol content and rapid decreases after exposure ended. Methoxyisopropanol was rapidly excreted in the urine with a half-life of less than 2.6 h. Metabolites of Methoxyisopropanol in the urine were not measured.

Kumagai et al. (1999) exposed four healthy male volunteers to 25, 50, and 100 ppm Methoxyisopropanol for 10 min and determined the uptake of the Methoxyisopropanol by the lungs. The mean uptake of Methoxyisopropanol in the last 5 min of exposure was 81.3%.

Devanthéry et al. (2000) collected and analyzed urine samples from three male workers who were exposed to Methoxyisopropanol while cleaning vats in an ink factory. The workers were exposed to Methoxyisopropanol by inhalation. Gloves and work clothes prevented skin exposure, but filter masks were not worn. Personal air sampling for an 8-h day was obtained by pumping air from the breathing zone into activated charcoal tubes. The Methoxyisopropanol absorbed into the charcoal was analyzed by gas chromatography with flame ionization detection. Urine was collected before the work shift and ad libitum throughout the day. Methoxyisopropanol was not detected in the urine of workers in the morning before the work shift. The range of Methoxyisopropanol concentrations in urine after the work shift was about 2 to 8 mg/L. Air concentrations of Methoxyisopropanol were 20 to 40 ppm with the average at about 30 ppm. There was a statistically significant correlation between air exposure and urine concentration of Methoxyisopropanol ($R^2 = 0.423$). After exposure ended, at end of the work shift, the urine concentrations of Methoxyisopropanol declined rapidly.

Devanthéry et al. (2002) simulated occupational inhalation and dermal exposure to Methoxyisopropanol vapor in six healthy male volunteers. The subjects were nonsmokers whose occupations do not involve Methoxyisopropanol exposure, and they abstained from alcohol and medications for 1 day before, 1 day after, and during the experiment. Exposures were in a 12-m^3 exposure chamber at 15, 50, or 95 ppm Methoxyisopropanol α-isomer for 6 h with a 30-min break at the half-way point. Each subject was treated with each concentration six times. Methoxyisopropanol content in blood, urine, and expired air were measure before, during, and after exposures.

Methoxyisopropanol was not detected in blood, urine, or expired air before the exposures. Methoxyisopropanol in the urine was free or conjugated to sulfate or glucuronide. Conjugation of Methoxyisopropanol was apparently saturable, as the fraction of

conjugated Methoxyisopropanol in the urine decreased with increasing exposure concentrations, 53.5% in the low dose, 37.5% in the middle dose, and 26.7% in the high dose. Total (free + conjugated) Methoxyisopropanol in the urine reached 2.5 ± 0.8, 6.2 ± 1.6, and 10.3 ± 2.3 mg/L at the end of the 15, 50, and 95 ppm exposures, respectively. Blood levels reached 2.0 ± 0.9, 4.9 ± 2.3, and 11.8 ± 2.4 mg/L Methoxyisopropanol after 6 h of inhalation exposure to 15, 50, and 95 ppm, respectively.

The mean half-life of Methoxyisopropanol excretion in urine was 3.5 h (range 2 to 4.5 h). Levels of Methoxyisopropanol in expired air reached 0.4 ± 0.1, 1.4 ± 0.4, and 2.9 ± 0.9 ppm after the 15, 50, and 95 ppm Methoxyisopropanol treatments, respectively. The half-life of Methoxyisopropanol in expired air was 10 min.

Subjects also experienced 6-h exposures to 15, 50, and 95 ppm Methoxyisopropanol in the chamber while wearing positive-pressure respirators. This was done to measure absorption of the Methoxyisopropanol vapor through the skin without inhalation. Methoxyisopropanol vapor was apparently not absorbed through the skin, as no Methoxyisopropanol was detected in the blood, urine, or expired air after 6 h of exposure (Devanthéry et al. 2002).

Devanthéry et al. (2003) used a study design similar to the one described above (in Devanthéry et al. 2002) to determine the amount of the β-isomer metabolite 2-methoxypropionic acid in urine after 6-h exposures to 15, 50, and 95 ppm Methoxyisopropanol α-isomer. The concern was that commercially available Methoxyisopropanol α-isomer contains small amounts of the β-isomer. The β-isomer is known to have a higher toxicity than the α-isomer, attributed to the metabolite 2-methoxypropionic acid.

The concentration of 2-methoxypropionic acid in urine ranged from below the detection limit (0.10 mg/L) to 0.30 mg/L before Methoxyisopropanol exposure. The urine content of 2-methoxypropionic acid after 6 h of inhalation exposure to 15 ppm Methoxyisopropanol α-isomer was similar to background levels. 2-Methoxypropionic acid in the urine after the 50 and 95 ppm Methoxyisopropanol treatments were 1.19 to 3.29 mg/L. The surprisingly high concentrations of 2-methoxypropionic acid in urine after Methoxyisopropanol α-isomer exposure was attributed to the way the two isomers of Methoxyisopropanol are metabolized. Approximately 2% of the α-isomer is excreted unchanged in the urine, whereas 68% of the β-isomer is released as 2-methoxypropionic acid (Devanthéry et al. 2003).

Methoxyisopropyl Acetate

Domorandzki et al. (2003) incubated human whole blood and liver homogenate with 5 or 50 μg/ml Methoxyisopropyl Acetate and measured the in vitro hydrolysis rate of Methoxyisopropyl Acetate to Methoxyisopropanol in each tissue type. The hydrolysis half-lives ($t_{1/2}$) of Methoxyisopropyl Acetate in whole blood was 36 and 34 min with the 5 and 50 μg/ml concentrations, respectively. The $t_{1/2}$ of Methoxyisopropyl Acetate hydrolysis in human liver homogenate was 27 to 30 min for both concentrations. The authors concluded that because this hydrolysis rate is rapid, the kinetics of Methoxyisopropyl Acetate would be identical to that for Methoxyisopropanol.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Methoxyisopropanol

The median lethal dose (LD_{50}) of acute oral exposure to Methoxyisopropanol has been investigated in several species. The reported LD_{50} values of the α-isomer of Methoxyisopropanol in rats include 6.6, 5.20, and 7.51 g/kg (Smyth et al. 1941, 1962; Rowe et al. 1954). Two oral LD_{50} values of the β-isomer (2-methoxy-1-propanol) in rats were 5.71 and 11.9 g/kg (Smyth et al. 1941, 1969). Rowe et al. (1954) attributed the deaths of rats to severe central nervous system (CNS) depression.

The oral LD_{50} of Methoxyisopropanol in the mouse is 10.8 g/kg (Stenger et al. 1972). Stenger et al. (1972) and Shideman and Procita (1951) reported LD_{50} values for the dog and rabbit as 4.6 to 9.2 g/kg and 5.3 g/kg, respectively. Shideman and Procita (1951) attributed the Methoxyisopropanol-induced canine deaths to respiratory arrest.

Methoxyisopropyl Acetate

Carreon et al. (1980) reported oral LD_{50} values of $>10{,}000$ mg/kg in male rats and 8532 mg/kg in female rats for Methoxyisopropyl Acetate. Watery eyes, anorexia, rapid shallow breathing, and excess salivation were observed in rats given a single dose of 4000, 6300, or 10,000 mg/kg Methoxyisopropyl Acetate.

Acute Dermal Toxicity

Methoxyisopropanol

The dermal LD_{50} of occluded Methoxyisopropanol in rabbits was found to be 13 to 14 g/kg. Respiratory depression was observed at doses of 10 g/kg (Rowe et al. 1954; Smyth et al. 1962).

Methoxyisopropyl Acetate

Carreon et al. (1980) applied 5000 mg/kg undiluted Methoxyisopropyl Acetate to the clipped backs of two male and two female rabbits. The dose site was occluded for 24 h before the site was washed. Rabbits wore collars to prevent licking of the dose site for 72 h after removal of the test material. The animals were observed for signs of toxicity for 2 weeks after dosing. No signs of systemic toxicity were noted during the 2-week observation period or at necropsy. The dermal LD_{50} of Methoxyisopropyl Acetate in rabbits was considered to be >5000 mg/kg.

Acute Inhalation Toxicity

Methoxyisopropanol

Rowe et al. (1954) reported that rats and guinea pigs survived 7 h in a chamber containing 5000 ppm Methoxyisopropanol. When exposed to 10,000 ppm Methoxyisopropanol, rats died at 5 to 6 h and guinea pigs died at 7 h. At 15,000 ppm, rats died at 4 h and guinea pigs at 10 h. CNS depression was apparent in the rats before they died.

Acute Parenteral Toxicity

Methoxyisopropanol

Intravenous LD_{50} values in mice, rats, rabbits, and dogs were 4.9, 3.9, 1.1, and 1.8 to 2.3 g/kg, respectively. The intraperitoneal LD_{50} was 3.9 g/kg in rats. The subcutaneous LD_{50} was 7.2 g/kg in rats and 4.6 g/kg in rabbits (Stenger et al. 1972).

Subchronic Dermal Toxicity

Methoxyisopropanol

Rowe et al. (1954) applied 1.0, 2.0, 3.0, 4.0, 5.0, 7.0, or 10.0 ml/kg Methoxyisopropanol (apparently undiluted) to the bare abdomens of male albino rabbits. There were 65 applications in a 90-day period. Narcosis and increased kidney weights were seen in rabbits of the 10-ml/kg group. Dermal effects are described in Dermal Irritation and Sensitization later in this report.

Subchronic Inhalation Toxicity

Methoxyisopropanol

Goldberg et al. (1964) trained female rats to avoid a buzzer-signaled electric shock by climbing a pole. The rats were exposed to 0, 2500, 5000, or 10,000 ppm Methoxyisopropanol in an inhalation chamber 4 h per day for 5 days per week for 2 weeks. The rats showed transient depression of shock avoidance or pole-climbing behavior after the first or second exposure to 5000 or 10,000 ppm Methoxyisopropanol, but tolerance developed thereafter. Growth rate was decreased in the 10,000 ppm group.

Miller et al. (1981) studied the short-term inhalation toxicity of Methoxyisopropanol in rodents. Male and female F344 rats and B6C3F1 mice were exposed to 0, 300, 1000, or 3000 ppm Methoxyisopropanol in whole-body inhalation chambers, 6 h per day for 9 days (n = 5–10 animals/sex/species/exposure group). Methoxyisopropanol exposure did not affect body weights in either species. Male and female rats and female mice of the 3000 ppm group had increased relative liver weights. Male rats in the high-dose group had signs of CNS depression. There were decreases in the specific gravity of urine in male and female high-dose rats. There were no other treatment-related effects observed. The lowest observed effect level (LOEL) in this study was the high dose, 3000 ppm Methoxyisopropanol.

Landry et al. (1983) studied the toxicity of Methoxyisopropanol in rats and rabbits following inhalation exposure. F344 rats were exposed to 0, 300, 1000, or 3000 ppm Methoxyisopropanol for 6 h per day, 5 days per week, for 13 weeks (n = 10 rats/sex/group). Transient CNS depression was observed in rats of the 3000 ppm group. Rats of both sexes in the 3000 ppm group had 6% to 8% increases in mean relative liver weights. Female rats in the high-dose group had elevated ($p < 0.05$) serum alanine aminotransferase and hepatocellular hypertrophy, with no microscopic evidence of damage to hepatocytes. There were no signs of pathology of the kidneys or hematological effects of Methoxyisopropanol at any exposure level. No toxic effects were observed at the lower dose levels.

New Zealand white rabbits were exposed to 0, 300, 1000, or 3000 ppm Methoxyisopropanol for 6 h per day, 5 days per week, for 13 weeks (n = 7 rabbits/sex/group). Transient CNS depression was observed in rabbits of the 3000 ppm group. Male and female rabbits had elevated ($p < 0.05$) serum alkaline phosphatase, compared to control rabbits. There were no signs of pathology of the kidneys or hematological effects of Methoxyisopropanol at any exposure level. The LOEL of Methoxyisopropanol by inhalation in this study was 3000 ppm (Landry et al. 1983).

Methoxyisopropyl Acetate

Miller et al. (1984) exposed F344 rats and B6C3F1 mice to 0, 300, 1000, or 3000 ppm Methoxyisopropyl Acetate vapor for 6 h per day for 9 days over an 11-day period. At the end of the last exposure, blood was collected, and the rats were killed for gross necropsy and microscopic examinations. There were no unscheduled deaths or clinical signs of toxicity during the exposure period. Body weights and hematological parameters were not affected by the Methoxyisopropyl Acetate treatments. Female rats of the 3000 ppm group had higher relative liver weight, compared to controls. However, the toxicological significance of the increased liver weight is uncertain because the hepatic tissues showed no histological changes. All other organ weights were unaffected by treatment. Some slight changes were observed in the appearance of renal tissues in rats exposed to 3000 ppm Methoxyisopropyl Acetate . Slight to moderate degeneration of the olfactory epithelium in the nasal cavities was seen in rats of the 3000 ppm groups and in mice of all exposure groups.

Chronic Inhalation Toxicity

Methoxyisopropanol

Spencer et al. (2002) exposed F344 rats and B6C3F1 mice to 0, 300, 1000, or 3000 ppm Methoxyisopropanol by inhalation in whole-body exposure chambers 6 h per day, 5 days per week, for 1, 2, 13, 26, 52, 78, or 104 weeks (n = 10–20 animals/species/sex/dose/duration). Animals were killed for necropsy and microscopic examination after their respective exposure periods ended. Liver and kidney functions were also determined.

Rats and mice of the 3000 ppm Methoxyisopropanol group showed incoordination, decreased activity, and transient sedation (i.e., signs of CNS depression) during exposure for the first week. Animals usually recovered 1 to 2 h post exposure. Mortality patterns were similar between all groups. There was an increase in deaths of 3000-ppm males of both species toward the end of the 2-year dosing period, but this increase was not significantly different from deaths in control groups. In rats of the 3000 ppm group, serum creatinine was increased by 78% and urea nitrogen was increased by 100% after 2 years of exposure. Serum alkaline phosphatase activities were increased in male rats exposed to 3000 ppm Methoxyisopropanol for 6 to 24 months and in male rats exposed to 1000 ppm Methoxyisopropanol for 24 months. Although serum alanine aminotransferase and serum aspartate aminotransferase were mildly and inconsistently elevated in the 3000 ppm groups during the first year of exposure, there was no apparent treatment-related effect during the second year of exposure. Urine and hematological parameters were not affected by Methoxyisopropanol exposure.

Liver weights were increased in both species exposed to 3000 ppm Methoxyisopropanol for 2 weeks to 2 years. Male rats exposed to 1000 and 3000 ppm for 24 months had increased numbers of dark foci in the liver, which were consistently correlated with eosinophilic hepatocellular foci. Cystic degeneration of the liver was also seen in male rats of the 3000 ppm group at 24 months. No treatment-related lesions were observed in mice. Hepatic mixed function oxidase (MFO) activities in rats and mice exposed to 3000 ppm Methoxyisopropanol were increased in the first 13 weeks of exposure. MFO activity in rats returned toward control levels by week 52. In mice, however, the elevated MFO activity persisted for about 18 months.

The kidney weights of male rats increased with time of exposure to 3000 ppm Methoxyisopropanol after 6 months to 24 months. Kidney weights in female rats of the high-dose group were elevated after 13 weeks and remained high to the 24th month. Glomerulonephritis was observed in male and female rats exposed to 3000 ppm Methoxyisopropanol. Glomerulonephritis is a common spontaneous disease in F344 rats and may have been exacerbated by Methoxyisopropanol exposure. Nephropathy seen in the high-dose rats was associated with α_{2u}-globulin, an effect specific to male rats. No treatment-related effects were seen in the kidney weights of mice.

The no observed effect level of Methoxyisopropanol in rats in this study was 300 ppm, due to altered hepatocellular foci in males of the 1000 ppm group. In mice, the no observed effect level was 1000 ppm Methoxyisopropanol (Spencer et al. 2002).

Dermal Irritation and Sensitization

Methoxyisopropanol

Rowe et al. (1954) applied 1.0, 2.0, 3.0, 4.0, 5.0, 7.0, or 10.0 ml/kg Methoxyisopropanol (apparently undiluted) to the bare abdomens of male albino rabbits. There were 65 applications in a 90-day period. There was evidence of mild irritation (scaling and erythema) in some rabbits, but there was no significant difference between Methoxyisopropanol-treated animals and control animals treated with water.

Smyth et al. (1962) applied 0.01 ml undiluted Methoxyisopropanol to the shaved abdomen of each of five New Zealand white rabbits. Application sites were occluded with gauze wrap for 24 h, when the skin at the site was scored for signs of irritation. The Methoxyisopropanol treatment site was given a score of 2 out of 10, "the least visible capillary injection."

Carreon and Wall (1984) found that 10% Methoxyisopropyl in water was not a sensitizer in a guinea pig maximization test. Ten guinea pigs received four 0.1-ml applications of the test material on shaved dorsal skin in 9 days. Each application remained occluded for 2 days. Freund's complete adjuvant was injected adjacent to the treatment site when the second dose was applied. After the fourth application, the animals rested for 2 weeks, and then a challenge patch of 0.1 ml of the test material was applied to the shaved flank of each guinea pig. Sites were scored for erythema and edema. None of the animals exhibited an irritation to the induction treatments or a sensitization response to the challenge application. Methoxyisopropanol was found to be nonsensitizing in this guinea pig assay.

Zissu (1995) found that 0.5 ml of undiluted Methoxyisopropanol applied to the shaved flank of New Zealand albino rabbits under occlusive patch for 4 h was nonirritating ($n = 3$), but the same amount was slightly irritating when applied under occlusive patch for 24 h ($n = 6$; primary irritation index = 1.3).

Methoxyisopropyl Acetate

Carreon et al. (1980) applied 0.5 ml of undiluted Methoxyisopropyl Acetate to an intact and an abraded site on the shaved backs of each of six rabbits. Treatment sites were occluded for 24 h, and signs of irritation were assessed. The sites were examined again 48 h later. No irritation was observed in abraded or intact skin. Methoxyisopropyl Acetate was not an irritant in this test.

These authors also reported that 10% Methoxyisopropyl Acetate in water was not a sensitizer in a guinea pig maximization test. Ten guinea pigs received four 0.1-ml applications of the test material on shaved dorsal skin in nine days. Each application remained occluded for 2 days. Freund's complete adjuvant was injected adjacent to the treatment site when the second dose was applied. After the fourth application, the animals rested for 2 weeks, and then a challenge patch of 0.1 ml of the test material was applied to the shaved flank of each guinea pig. Sites were scored for erythema and edema. None of the animals exhibited an irritation to the induction treatments or a sensitization response to the challenge application. The authors concluded that Methoxyisopropyl Acetate was not a sensitizer in this test (Carreon et al. 1980).

Zissu (1995) found that 0.5 ml of undiluted Methoxyisopropyl Acetate applied to the shaved flank of New Zealand albino rabbits under occlusive patch for 4 h was nonirritating ($n = 3$), but the same amount was slightly irritating when

applied under occlusive patch for 24 h ($n = 6$; primary irritation index = 2.0).

Ocular Irritation

Methoxyisopropanol

Rowe et al. (1954) found that Methoxyisopropanol was found to be only slightly irritating to the eyes of rabbits. One drop of undiluted Methoxyisopropanol per day for 5 days in rabbit eyes caused only mild transitory irritation of the eyelid. Fluorescein staining showed no conjunctival injury.

Methoxyisopropyl Acetate

Carreon et al. (1980) reported the results of an eye irritation test of Methoxyisopropyl Acetate in rabbits (strain not specified). Each of nine rabbits (group A) received an instillation of 0.1 ml of undiluted test material in the right eye. The left eye remained untreated. Three additional rabbits (group B) received the same amount of test material in the right eye, and their left eyes were untreated. After 30 s, the eyes were rinsed for 1 min. Then the right eye of group B rabbits were treated with a second instillation of 0.1 ml of undiluted test material and remained unrinsed. All eyes were examined 1, 2, 3, 4, and 7 days following treatment.

Moderate to severe discomfort was experienced at instillation of Methoxyisopropyl Acetate to the eyes for all treated rabbits. Observations upon eye examinations of group A (unrinsed eyes) rabbits included slight (5/9) to moderate (3/9) conjunctival redness, slight (4/9) to moderate (2/9) conjunctival swelling, slight discharge (4/9), reddening of the iris (2/9), and 100% corneal opacity (4/9). Signs of irritation were absent by day 2 in one rabbit, day 3 in four rabbits, day 4 in three rabbits, and day 7 in one rabbit.

The rinsed eyes of the three Group B rabbits exhibited slight conjunctival redness (3/3), slight (1/3) to moderate (1/3) conjunctival swelling, slight discharge (1/3), and 40% corneal opacity (2/3). All signs of irritation were absent by day 7 (Carreon et al. 1980).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Methoxyisopropanol

Doe et al. (1983) exposed pregnant Wistar rats to 0, 200, or 600 ppm Methoxyisopropanol in inhalation chambers for 6 h per day on gestation days 6 to 17 ($n = 20$ rats/group). The rats were allowed to deliver their litters. Pups were observed for 3 days post partum. There were no treatment-related effects on the dams or offspring.

In a second study, male Wistar rats were exposed to 0, 200, or 600 ppm Methoxyisopropanol by inhalation for 6 h per day for 10 days ($n = 10$ rats/group). The rats were killed for necropsy after the last dose, with particular attention to the testis. There were no treatment-related effects observed. The no observed effect level of inhaled Methoxyisopropanol in this study was the highest dose tested, 600 ppm (Doe et al. 1983).

Hanley et al. (1984) studied the reproductive effects of inhaled Methoxyisopropanol in rats and rabbits. Pregnant F344 rats were exposed to 0, 500, 1500, or 3000 ppm Methoxyisopropanol in an inhalation chamber for 6 h per day on gestation days 6 through 15 ($n = 31$–33 rats/group). Initial exposures to 3000 ppm Methoxyisopropanol caused signs of CNS depression, but recovery was rapid. Rats in the 3000 ppm group had reduced weight gain throughout the testing period and reduced food consumption for the first 3 days of exposure. There were no embryotoxic or teratogenic effects seen in rats at any concentration, except delayed sternebral ossification in the 3000 ppm group.

Pregnant New Zealand White rabbits were exposed to 0, 500, 1500, or 3000 ppm Methoxyisopropanol in an inhalation chamber for 6 h per day on gestation days 6 through 18 ($n =$ 31–33 rabbits/group). Initial exposures to 3000 ppm Methoxyisopropanol caused signs of CNS depression, but recovery was rapid. Rabbits in the 3000 ppm group had reduced weight gain throughout the testing period and reduced food consumption for the first 3 days of exposure. There were no signs of embryotoxic, teratogenic, or fetotoxic effects in any of the Methoxyisopropanol treatment groups. The lowest observed effect level for inhaled Methoxyisopropanol in this study was 3000 ppm, based on maternal effects (Hanley et al.1984).

Chapin and Sloane (1997) used Swiss CD-1 mice in a reproductive assessment by continuous breeding (RACB) protocol. Task 1 of the RACB protocol is a dose range-finding study, and in this case the doses chosen were 0%, 0.5%, 1.0%, or 2.0% Methoxyisopropanol in drinking water. The number of animals per dose level were not reported, but the RACB protocol calls for 20 mice/sex/dose level for the F_0 generation. In task 2 of the RACB protocol, male and female mice were paired and allowed multiple matings, gestations, and deliveries while being given the Methoxyisopropanol-treated water for 15 weeks. Litters produced were examined and killed.

The low-, medium-, and high-dose groups had average Methoxyisopropanol consumption rates of 0.95, 1.9, and 3.3 g/kg/day, respectively. There were no treatment-related effects on body weight changes, water consumption, number of litters per pair, number of live pups per litter, or viability of live pups. Mean pup weight per litter size was reduced by 4% in the 2.0% (3.3 g/kg/day) Methoxyisopropanol group only.

Because fertility was not affected by Methoxyisopropanol treatments, task 3 of the RACB protocol, involving cross-mating of high-dose mice with control mice, was not performed.

For task 4, the original mating pairs produced litters that were allowed to grow to become the F_1 generation. F_1 mice of the high-dose and control groups were bred within their treatment groups, and the offspring of those unions were examined. In F_1 mice of the high-dose group (3.3 g/kg/day), both sexes had reduced growth to weaning; males had reduced adult body weight, relative epididymis weight, and relative prostate weight; and females had increased liver weight. However, fertility of the F_1 generation was not affected by Methoxyisopropanol treatment,

nor was viability of the F_2 offspring in the high-dose group, and there were no effects on the ovarian follicle counts. Thus, the lowest observed effect level for Methoxyisopropanol in this continuous breeding protocol was the highest dose tested, 2% in water or 3.3 g/kg/day. The no observed effect level for Methoxyisopropanol in this study was 1% or 1.9 g/kg/day Methoxyisopropanol (Chapin and Sloane 1997).

Carney et al. (1999) evaluated Methoxyisopropanol in a two-generation study. Sprague-Dawley rats were exposed to 0, 300, 1000, or 3000 ppm Methoxyisopropanol vapors in inhalation chambers. Exposures were for 6 h per day, 5 days per week for 10 weeks before mating, and 6 h per day, 7 days per week during mating, gestation, and lactation, for two generations. Second-generation weanlings were not exposed to Methoxyisopropanol until postnatal day 28 when treatments resumed. The calculated amounts of Methoxyisopropanol exposure for rats in the low-, medium-, and high-dose groups were 396, 1325, and 3974 mg/kg/day, respectively.

Rats exposed to 3000 ppm Methoxyisopropanol showed signs of sedation in weeks 3 to 5 in the first generation and for the first 2 weeks in the second generation. Sedation was not seen thereafter in the 3000 ppm group and was not seen at all in the 300 or 1000 ppm groups. No other treatment-related behavioral effects were noted in the adult rats. Body weights of first- and second-generation rats in the 3000 ppm group were reduced beginning in the premating dosing period and throughout mating, gestation, and lactation.

There was an increase in the number of days in the estrous cycles of females of both generations in the 3000 ppm group, resulting in fewer estrous cycles in the observation period. Sperm count and motility were not affected by Methoxyisopropanol treatment. There were no treatment-related effects on gestational survival, pup sex ratio, gestation length, or time to mating. However, fertility indices were decreased in the 3000 ppm group. The high-dose group also had decreased pup body weights, reduced pup survival during lactation, and reduced litter size. Offspring of the 3000 ppm group had delayed vaginal opening in females and preputial separation in males.

First-generation adult males of the 3000 ppm group had increased relative testes, brain, and kidney weights and decreased thymus weight. First-generation adult females had higher adrenal, liver, and lung weights than control females. Second-generation adult males of the high-dose group had increased relative liver, lung, and seminal vesicle weights. Brain (absolute) and ovary (absolute and relative) weights were decreased in second-generation adult females in the high-dose group. Ovarian atrophy was seen at 3000 ppm in females of both generations. There were no treatment-related effects on organ weights in the 300 and 1000 ppm groups.

The lowest observed effect level for reproductive/neonatal effects of Methoxyisopropanol in this two-generation inhalation study was the highest dose tested, 3000 ppm (3974 mg/kg/day), with the corresponding no observed effect level at 1000 ppm (1325 mg/kg/day) Methoxyisopropanol. The no observed effect level for parental toxicity was 300 ppm (396 mg/kg/day) (Carney et al. 1999).

Methoxyisopropyl Acetate

Tanaka et al. (1998) gave Sprague-Dawley rats daily oral gavage doses of 0, 100, 300, or 1000 mg/kg/day Methoxyisopropyl Acetate ($n = 10$ rats/sex/dose level). Males received the doses for 44 days prior to mating, whereas females received their doses from 14 days prior to mating to day 3 of lactation. Males were killed for necropsy the day after their last dose. Females and their litters were killed and examined on day 4 of lactation. Adults in the 100 and 300 mg/kg/day dose groups showed no signs of systemic toxicity. At the 1000 mg/kg/day dose, males had depressed body weight gain, reduced food consumption, decreases in blood glucose and inorganic phosphorus, and increased relative adrenal weights. Adult females of the 1000 mg/kg/day group had depressed body weight gain in the premating period but not during gestation.

Methoxyisopropyl Acetate had no adverse effect on reproductive parameters (e.g., fertility index, number of implantations or corpora lutea, gestation time, etc.) at any dose in this study. Likewise, there were no differences in the developmental parameters of the offspring between control and dosed groups. In this study, the no observed effect level (NOEL) of Methoxyisopropyl Acetate was 1000 mg/kg/day for reproductive and developmental toxicity and 300 mg/kg/day for repeated dose toxicity in adult rats (Tanaka et al. 1998).

2-Methoxypropanol and 2-Methoxypropyl Acetate (β-Isomer)

As noted earlier, 2-methoxypropanol and 2-methoxypropyl Acetate, the β-isomers of methoxyisopropanol and methoxyisopropyl Acetate found as impurities in commercial grade Methoxyisopropanol are currently limited to concentrations of less than 0.5% (Oxygenated Solvents Producers Association 2001).

Merkle et al. (1987) studied the developmental and reproductive toxicity of 2-methoxypropyl acetate in rats and rabbits. Pregnant Wistar rats were exposed to 0, 110, 550, or 2700 ppm 2-methoxypropyl acetate in inhalation chambers 6 h per day on gestation days 6 through 15 ($n = 21$–24 rats/dose level). Skeletal malformations of the thorax were observed in fetuses of the 2700 ppm group.

Himalayan rabbits were exposed to 0, 36, 145, or 550 ppm 2-methoxypropyl acetate in inhalation chambers 6 h per day on gestation days 6 to 18 ($n = 11$–15 rabbits/dose level). All fetuses of the 550 ppm group had developmental anomalies in the absence of maternal toxicity. No maternal or fetal effects were seen in the 36 or 145 ppm groups.

Dermal applications of 1000 or 2000 mg/kg 2-methoxypropyl acetate on gestation days 6 through 18 produced no evidence of maternal or fetal toxicity (Merkle et al. 1987).

Hellwig et al. (1994) tested the prenatal inhalation toxicity of 2-methoxypropanol in Himalayan rabbits. Pregnant rabbits were exposed to 0, 145, 225, 350, or 545 ppm 2-methoxypropanol

in inhalation chambers for 6 h per day from gestation days 6 through 18 (n = 12 rabbits/dose level). From gestation day 12 to the end of the study, maternal toxicity was apparent in the 545-ppm group. Dose-dependent increases in number of resorptions, fetal malformations, and skeletal variations occurred in the 225, 350, and 545 ppm groups. The rate of skeletal malformations in the 545 ppm group was 100%. Malformations observed included absent phalanges, absent or rudimentary metatarsal bones, malformed ribs, and enlarged sternebrae. No treatment-related effects were observed in the 145 ppm group.

Carney et al. (2003) studied the significance of 2-methylpropionic acid (2-MPA), a major metabolite of 2-methoxypropanol, in the developmental toxicity of methoxyisopropanol described earlier. 2-MPA produced fetal malformations in New Zealand white rabbits with a LOEL of 78 mg/kg/day, given by gavage on gestation days 7 to 19. The authors concluded that there is a negligible risk of developmental toxicity due to 2-MPA formation from the small amounts of 2-methoxypropanol in commercial grade Methoxyisopropanol.

GENOTOXICITY

Methoxyisopropanol

Methoxyisopropanol was negative in several tests for mutagenicity or genotoxicity in bacterial and mammalian systems. However, some cytotoxicity was observed at higher exposures (Elias et al. 1996; OECD/SIDS 2001a).

OECD/SIDS (2001a) reported that up to 0.1 M Methoxyisopropanol was negative in the unscheduled DNA synthesis assay using rat hepatocytes without metabolic activation. Cytotoxicity, as indicated by detachment of cells and/or granular appearance, was observed at the 0.0316 and 0.1 M concentrations.

Elias et al. (1996) reported the results of several genotoxicity assays using Methoxyisopropanol. Exposure to 14 to 55 mM Methoxyisopropanol was negative for genotoxic effects in a gene mutation assay using Chinese hamster lung (V79) cells without metabolic activation. There was no cytotoxicity, but cell growth inhibition was observed (effective concentration not reported). The test material in this study contained 1.2% of the β-isomer, 2-methoxy-1-propanol. A range of Methoxyisopropanol concentrations from $\geq$10 to $\sim$100 mM was tested in a sister-chromatid exchange (SCE) assay using V79 cells without metabolic activation. A small but statistically significant increase in SCEs was seen at the highest concentration. The test material in this study contained 1.2% of the β-isomer. The same range of concentrations ($\geq$10 to $\sim$100 mM Methoxyisopropanol) was tested in a chromosomal aberration assay using V79 cells without metabolic activation. Although the test material was negative for genotoxicity, concentration of up to 200 mM Methoxyisopropanol dose-dependently enhanced the genetic damage induced by methylmethanesulfonate. The Methoxyisopropanol tested in this study contained 1.2% of the β-isomer. A single intraperitoneal injection of 2500, 4000, 5000, or 6000 mg/kg Methoxyisopropanol did not increase the frequency of micronuclei in polychromatic erythrocytes harvested from the bone marrow of male and female CD-1 mice. However, the test material caused three deaths out of eight mice in the 6000 mg/kg group by 48 h after injection.

These authors also noted that Methoxyisopropanol (concentration not stated) did not induce an increase in the frequency of micronuclei in V79 cells without metabolic activation and did not induce morphological transformations in Syrian hamster embryo (SHE) cells. The test material in each case contained 1.2% of the β-isomer (Elias et al. 1996).

OECD/SIDS (2001a) cited a study in which up to 5000 μg/plate Methoxyisopropanol was negative for mutagenicity and cytotoxicity in the Ames assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without S9 metabolic activation.

Methoxyisopropyl Acetate

Methoxyisopropyl Acetate was not mutagenic/genotoxic in bacterial and mammalian systems but showed some evidence of cytotoxicity at higher concentrations (OECD/SIDS 2001b; Tanaka et al. 1998).

OECD/SIDS (2001b) reported that 31.6 μM to 0.1 M Methoxyisopropanol did not induce unscheduled DNA synthesis in rat hepatocytes without metabolic activation. Cytotoxicity, as indicated by detachment of cells and/or granular appearance, was observed at the 0.0316 and 0.1 M concentrations.

Tanaka et al. (1998) reported that 313 to 5000 μg/plate Methoxyisopropyl Acetate did not induce mutations or toxicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 or in *Escherichia coli* WP2 uvrA, with or without S9 metabolic activation.

Tanaka et al. (1998) also reported that 0.33 to 1.3 mg/ml Methoxyisopropyl Acetate at 0.33 to 1.3 mg/ml did not induce chromosomal aberrations when incubated with Chinese hamster lung cells, with or without S9 metabolic activation.

CARCINOGENICITY

Methoxyisopropanol

Spencer et al. (2002) exposed F344 rats and B6C3F1 mice to 0, 300, 1000, or 3000 ppm Methoxyisopropanol by inhalation in whole-body exposure chambers 6 h per day, 5 days per week, for 1, 2, 13, 26, 52, 78, or 104 weeks (n = 10–20 animals/species/sex/dose level/exposure schedule). Animals were killed for necropsy and microscopic examination after their respective exposure periods ended. No toxicologically relevant increases in neoplasia occurred in either species.

CLINICAL ASSESSMENT OF SAFETY

Methoxyisopropanol

Stewart et al. (1970) exposed groups of male volunteers to 50 to 250 ppm Methoxyisopropanol for 1 to 7 h to simulate extreme conditions of Methoxyisopropanol vapor exposures in unventilated truck cabs. The odor of Methoxyisopropanol was

detectable at 10 ppm and became mildly irritating to the eyes, nose, and throat at 300 ppm. The vapor was extremely irritating at 750 ppm. However, tolerance to the odor of 100 ppm developed within 25 min of exposure. Within an hour of exposure to 250 ppm Methoxyisopropanol, most of the subjects had eye irritation, excessive blinking, nose irritation, throat irritation, and one subject had a severe headache. For 250 ppm exposures of 3 to 7 h, subjects had eye irritation, lacrimation, and rhinorrhea, but performance on coordination and neurological tests was not impaired.

Two subjects were placed in a chamber in which the concentration of Methoxyisopropanol vapor was gradually increased from 1 to 2000 ppm. The odor became objectionable at 50 to 75 ppm. At 300 to 400 ppm, both subjects became light-headed and experienced eye irritation. Rhinorrhea and lacrimation began at 700 ppm. One subject became incapacitated at 1000 ppm and discontinued participation in the study. Despite considerable discomfort, the remaining subject continued on to 2050 ppm, where he experienced severe lacrimation and blepharospasm. Breathing was painful. However, performance on neurological tests was normal. Nose and throat pain completely subsided 15 min after removal from the exposure chamber. Eye irritation subsided in 1 h, but nasal congestion persisted for 24 h (Stewart et al. 1970).

Emmen et al. (2003) exposed 12 healthy male volunteers to Methoxyisopropanol at concentrations of 0, 100, and 150 ppm in air for 2.5 h. Each subject was exposed to each of the concentrations with exposures 7 days apart. The sequences of exposures were counterbalanced, and treatments and measurements were conducted in a double-blind manner. In all exposures, 20 ppm diethyl ether was used as a masking agent to obscure detection of the Methoxyisopropanol. Irritation of the eyes and throat were determined by objective observations (redness, swelling, tearing, blinking, etc.) and subjective questionnaire of the subjects. Subjects exposed to 150 ppm Methoxyisopropanol described only very slight sensation of irritation of the eyes. However, there were no effects on objective parameters of eye irritation. No other subjective or objective adverse effects of 100 or 150 ppm Methoxyisopropanol were reported.

Occupational Safety

The National Institute of Occupational Safety and Health (NIOSH 2003) recommends an 8-h time weighted average (TWA) of Methoxyisopropanol of 100 ppm (360 mg/m^3) and a short-term exposure limit (STEL) of 150 ppm (540 mg/m^3).

MARGIN OF SAFETY ANALYSIS

Methoxyisopropanol

CTFA (2004) presented a margin of safety (MOS) approach to assess the risk of exposure to Methoxyisopropanol to human users of cosmetic products. Exposure calculations were based on the maximum reported concentration of use of Methoxyisopropanol, which was 35% in nail polish remover (CTFA 2003), and the 90th percentile of daily use of nail polish remover in a survey of 9684 women aged 13 to 61 years, which was 0.29 g nail polish remover/day (Environ Corporation 1985). The NOAEL of Methoxyisopropanol for developmental effects was 1 g/kg/day by inhalation (Tanaka et al. 1998). A conservative assumption of 100% dermal absorption of Methoxyisopropanol and an estimated consumer body weight of 50 kg were used. The calculation was:

$$\begin{aligned} 0.29\text{ g product/day} &\times 0.35\%\text{ Methoxyisopropanol} \\ &= 0.1015\text{ g Methoxyisopropanol/day} \\ 0.1015\text{g}/50\text{ kg/day} &= 0.002\text{ g/kg/day.} \end{aligned}$$

The NOAEL was divided by the daily dose to give the MOS:

$$1\text{g/kg/day(NOAEL)} \div 0.002\text{g/kg/day} = \text{MOS of 500.}$$

SUMMARY

Methoxyisopropanol and Methoxyisopropyl Acetate are also commonly known as propylene glycol monomethyl ether (PGME) and propylene glycol monomethyl ether acetate (PGMEA), respectively. Methoxyisopropanol is used in cosmetic products as a fragrance ingredient, a solvent, and a viscosity-decreasing agent. Data submitted by the FDA and CTFA based on voluntary industry reports indicate that Methoxyisopropanol was used in four cosmetic formulations at concentrations ranging from 4% to 35%. Methoxyisopropyl Acetate functions as a solvent in cosmetic products; however, it is not in current use.

Methoxyisopropanol and Methoxyisopropyl Acetate are expected to contain less than 0.5% of the β-isomers, 2-methoxy-1-propanol and 2-methoxy-1-propyl acetate, respectively.

Methoxyisopropanol is easily absorbed into the bloodstream upon inhalation or ingestion. In an in vitro dermal absorption study, the absorption rate of Methoxyisopropanol across human cadaver abdominal skin was 1.17 mg/cm^2/h, and the permeability constant was 12.5×10^{-4} cm/h. Methoxyisopropanol vapor at concentrations up to 95 ppm in air was not absorbed through human skin.

Methoxyisopropyl Acetate is readily metabolized to Methoxyisopropanol. The half-life of Methoxyisopropyl Alcohol conversion to Methoxyisopropanol in human whole blood was on the order of 30 min. Methoxyisopropanol can be excreted unchanged in the expired breath or in the urine as Methoxyisopropanol either free or as a sulfate or glucuronide conjugate, or as the primary metabolite propylene glycol. The half-life of Methoxyisopropanol excretion in urine is about 2 to 4 h.

In acute toxicity studies, the oral LD_{50} values of Methoxyisopropanol were 4.6 to 9.2 g/kg in rats, 4.6 to 9.2 g/kg in dogs, and 5.3 mg/kg in rabbits. Intravenous LD_{50} values were 4.9 g/kg in mice, 3.9 g/kg in rats, 1.1 g/kg in rabbits, and 1.8 to 2.3 g/kg in dogs. Subcutaneous LD_{50} values were 7.2 g/kg in

rats and 4.6 g/kg in rabbits. Dermal LD_{50} values in rabbits were 13 to 14 g/kg. In rats, the intraperitoneal LD_{50} values were 3.9 g/kg. Upon acute exposure to 10,000 to 15,000 ppm Methoxyisopropanol by inhalation, rats died within 4 to 6 h, and guinea pigs died within 7 to 10 h. Methoxyisopropyl Acetate had oral LD_{50} values of >10 g/kg in male rats and 8.5 g/kg in female rats. The dermal LD_{50} value of Methoxyisopropyl Acetate was >5 g/kg in rabbits.

Inhalation exposures of rats, mice, and rabbits to 3000 ppm Methoxyisopropanol for 6 h per day for 9 days to 13 weeks produced increased relative liver weights, signs of CNS depression, and in some cases, elevated serum alkaline phosphatase, alanine aminotransferase, or hepatocellular hypertrophy. The kidneys were unaffected by Methoxyisopropanol exposure at the concentrations tested. The NOAEL for 13-week inhalation exposures to Methoxyisopropanol was 1000 ppm in rats and rabbits. Similar inhalation exposures to Methoxyisopropyl Acetate to rats and mice produced similar results, with the addition of moderate degeneration of olfactory epithelium of the nasal cavities in rats exposed to 3000 ppm and in mice exposed to 300, 1000, or 3000 ppm Methoxyisopropyl Acetate vapor.

In a 90-day dermal exposure study using rabbits, 10 ml/kg undiluted Methoxyisopropanol produced narcosis and increased kidney weights. The NOAEL was 7.0 ml/kg.

Chronic (2-year) daily inhalation exposures of rats and mice to 3000 ppm Methoxyisopropanol produced signs of liver toxicity (rats and mice) and some evidence of renal toxicity in rats. The only observation at 1000 ppm was dark foci of the liver in male rats. For female rats and male and female mice, the NOAEL of this chronic inhalation study was 1000 ppm Methoxyisopropanol.

Methoxyisopropanol and Methoxyisopropyl Acetate were both found to be nonirritating to slightly irritating and nonsensitizing in rabbit and guinea pig skin. Repeated applications of undiluted Methoxyisopropanol to the eyes of rabbits produced transient slight to moderate irritation.

Pregnant rats exposed to 200 or 600 ppm Methoxyisopropanol on gestation days 6 to 17 had no effects on maternal health or normal fetal development. Adult male rats exposed to these concentrations had no effects on the reproductive organs. Pregnant rats and rabbits exposed to 500 to 3000 ppm Methoxyisopropanol by inhalation during gestation had no significant embryotoxic or fetotoxic effects. Only CNS depression and reduced body weight gain were observed in the 3000 ppm group.

In a two-generation inhalation study using rats, continuous inhalation of 3000 ppm Methoxyisopropanol produced CNS depression, prolonged estrous cycles, reduced fertility indices, reduced pup weights and pup survival, and delayed sexual development. The no observed adverse effect level (NOAEL) for reproductive and developmental effects of Methoxyisopropanol in this study was 1000 ppm, which corresponded to an exposure of 1.325 g/kg/day. In a continuous breeding protocol using mice, 2.0% Methoxyisopropanol in drinking water produced reduced growth, reduced relative epididymis weight, reduced relative prostate weight (males only), and increased liver weight (females only) in the offspring of exposed adults. No other reproductive or developmental effects were observed. The NOAEL for this study was 1% in drinking water, which corresponded to an exposure of 1.9 g/kg/day.

Daily oral doses of 1000 mg/kg/day Methoxyisopropyl Acetate given to adult male and female rats before mating and to dams during gestation produced no reproductive or developmental effects in the offspring. The only maternal effect at this dose level was reduced body weight gain. The NOAEL for reproductive toxicity in this study was 1 g/kg/day.

Exposure of mice or rats to 300 ppm to 3000 ppm Methoxyisopropanol by inhalation produced no signs of carcinogenicity. Methoxyisopropanol was negative for mutagenicity or genetic toxicity in the bacterial reverse mutation assay (≤ 5000 μg/plate), the unscheduled DNA synthesis (UDS) assay (≤ 0.1 M), V79 Chinese hamster lung assay (>100 mM), and in the Siberian hamster embryo assay (concentrations not reported). In other assays, 100 mM Methoxyisopropanol increased sister-chromatid exchanges in V79 cells, and 200 mM Methoxyisopropanol dose-dependently enhanced the genetic damage induced by methylmethanesulfonate. Some cytotoxicity was noted at the higher concentrations in these assays. Methoxyisopropyl Acetate was not mutagenic in bacterial or mammalian test systems, but some cytotoxicity was noted at higher concentrations.

In human inhalation exposure studies of 1 to 7 h duration, 50 to 75 ppm Methoxyisopropanol vapor had an objectionable odor, 150 ppm was slightly irritating to the eyes and throat; 250 ppm produced eye irritation, lacrimation, blinking, rhinorrhea, and headache; 300 ppm was mildly irritating to the eyes, nose, and throat; 750 ppm was extremely irritating; and 2050 ppm produced extreme discomfort with severe lacrimation, blepharospasm, and painful breathing. None of the concentrations tested impaired motor coordination or performance on neurological tests. The irritating effects subsided within 15 min to 24 h of removal from the inhalation chamber. NIOSH recommended an 8-h time-weighted average for occupational exposure of 100 ppm.

A margin of safety, based on a calculated exposure from the normal use of nail polish remover products and the NOAEL for reproductive toxicity, was 500.

DISCUSSION

Because Methoxyisopropanol is reportedly used only in nail products, and the absorption of this ingredient through the nail is likely to be extremely low, the Cosmetic Ingredient Review (CIR) Expert Panel did not expect Methoxyisopropanol to be significantly absorbed. The calculated margin of safety for the reproductive toxicity from use in nail products was 500, based on an assumed 100% absorption. Because Methoxyisopropanol is volatile, exposure by inhalation is possible. However, the odor of the ingredient became objectionable to human volunteers at

50 to 75 ppm in air, much lower than the NOAEL value of 1000 ppm in subchronic and developmental inhalation studies using rats and rabbits.

The Expert Panel noted that there are currently no reported uses of Methoxyisopropyl Acetate; were uses to occur in the future, the Expert Panel expects such uses to be in nail care products at concentrations similar to Methoxyisopropanol. Because Methoxyisopropyl Acetate is known to metabolize rapidly to Methoxyisopropanol in the body, the Expert Panel accepted toxicity data on the parent compound to assess the safety of the acetate.

CONCLUSION

The CIR Expert Panel concluded that Methoxyisopropanol and Methoxyisopropyl Acetate are safe for use in nail care products in the practices of use and concentration as described in this safety assessment.

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