

RE-REVIEW
Supplement Book 3

Alkyl Esters

CIR EXPERT PANEL MEETING
MARCH 5-6, 2012

ALKYL ESTERS RE-REVIEW – SUPPLEMENTAL BOOK 3

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Final Safety Assessment

On the Safety Assessment of Alkyl Glyceryl Ethers As Used in Cosmetics

December 19, 2011

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ABSTRACT Alkyl glyceryl ethers function mostly as skin conditioning agents in cosmetic products. Based on the available animal toxicity and clinical data, including the low dermal absorption, the CIR Expert Panel concluded that the alkyl glyceryl ethers are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The safety of the following ingredients in cosmetics is reviewed in this report:

- | | |
|---------------------------------------|-----------------------------|
| • Ethylhexylglycerin | • Glyceryl Allyl Ether |
| • Caprylyl Glyceryl Ether | • Glyceryl Lauryl Ether |
| • Glyceryl Capryl Ether | • Isodecyl Glyceryl Ether |
| • Cetyl Glyceryl Ether/Chimyl Alcohol | • Isostearyl Glyceryl Ether |
| • Batyl Alcohol | • Oleyl Glyceryl Ether |

These ingredients function mostly as surfactants or skin conditioning agents in cosmetic products. Cetyl glyceryl ether and chimyl alcohol are listed in The International Cosmetic Ingredient Dictionary and Handbook¹ as discrete chemicals. However, these two ingredients are identical chemicals. Accordingly, there are eleven ingredients listed in this review, but two of them represent the same entity. Since chimyl alcohol was the ingredient name first assigned in the International Cosmetic Ingredient Dictionary and Handbook, cetyl glyceryl ether will be referred to as chimyl alcohol throughout the report text.

CHEMISTRY

Definition and Structure

These ingredients are alkyl glyceryl ethers. Structurally, this means that an alkyl or alkenyl chain is terminated with glycerin at one end via an ether linkage. For example, caprylyl glyceryl ether is an 8-carbon, alkyl chain terminated with glycerin (Figure 1).

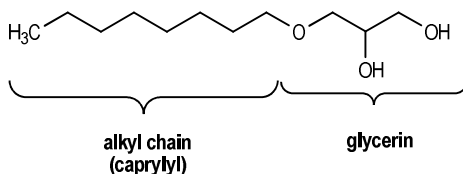


Figure 1. Caprylyl Glyceryl Ether

Substances with a similar structure, alkoxy lipids, are widely distributed in human and animal tissue and occur as neutral alkoxy lipids and ionic alkoxy lipids.^{2,3}

The ingredients reviewed in this safety assessment vary only by alkyl chain length, degree of chain branching, or the degree of unsaturation. Their gross structural characteristics are typical of a surfactant, that is, they contain a hydrophilic head group (i.e., glycerin) and a hydrophobic tail (i.e., the alkyl chain). The definitions, structures, and functions of these alkyl glyceryl ethers are included Table 1.¹

Physical and Chemical Properties

Chemical and physical properties of 6 of the 10 alkyl glyceryl ethers are included in Table 2. In general, these ingredients are solids at room temperature and have molecular weights that are < 400 g/mol. As would be expected, increased chain length translates into greater hydrophobicity. Ethylhexylglycerin, specifically, has “limited solubility in water (≈ 0.1%), is highly soluble in organic solvents,” and has an estimated octanol/water partition coefficient of Log P_{ow} = 2.4.

Method of Manufacture

The manufacture of alkyl glyceryl ethers can be accomplished by traditional etherification techniques. For example, one method of synthesis of chimyl alcohol involves reacting the sodium salt of acetone glycerol (a form of glycerin wherein 2 of the hydroxyl groups are protected and the third is activated as the sodium salt) with hexadecyl iodide in boiling glycol dimethyl ether, yielding the acetone compound of α -hexadecyl glycerol. Hydrolysis of the protecting group with acetic acid results in the formation of chimyl alcohol.⁴

Alternatively, these ingredients can be produced by the reduction of triglycerides. For example, long-chain alkyl glyceryl ethers can be synthesized via the treatment of a triglyceride with lithium aluminum hydride (LAH) + boron trifluoride etherate (BFE), followed by LAH hydrogenolysis.⁵ The major reaction products are the glyceryl monoether, glyceryl triether, and free alkanol.

One method for the synthesis of ethylhexylglycerin is via the catalytic splitting of ethylhexylglycidyl ether, followed by the addition of water.⁶ The product can then be purified by vacuum distillation.

Impurities

Sensiva® SC50 is one of the trade names under which ethylhexylglycerin is being marketed. According to Schülke and Mayr GmbH, Sensiva® SC 50 contains > 99% ethylhexylglycerin.⁶ Sensiva® SC 50 also contains a small amount of α -tocopherol, added to stabilize the molecule, and the impurities 2-ethylhexyl-glycidylether and water.⁷

Chimyl alcohol is approximately 98% pure and also contains approximately 2% batyl alcohol as an impurity. It has an acid value of approximately 0.001, which means that fatty acids are not present.⁸

USE

Cosmetic

These ingredients function mostly as surfactants or skin conditioning agents in cosmetic products.¹ These and additional functions are included in Table 1. Ethylhexylglycerin (Sensiva® SC 50) reportedly inhibits the growth and multiplication of odor-causing bacteria and enhances the efficacy of cosmetic preservatives, such as phenoxyethanol, methylisothiazolinone, or methylparaben. Preservatives defined as Sensiva® SC 50 + phenoxyethanol and Sensiva® SC 50 + methylisothiazolinone are being marketed.⁹

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), reported in 2011 FDA database, the following 4 ingredients were being used in personal care products: ethylhexylglycerin, glyceryl lauryl ether, chimyl alcohol, and isostearyl glyceryl ether.¹⁰ These data are summarized in Table 3. Surveys of ingredient use concentrations conducted by the Personal Care Products Council (also included in Table 3) provided use concentrations for these 5 ingredients: ethylhexylglycerin (up to 8% [maximum in rinse-off products]), chimyl alcohol (up to 0.5% [maximum in leave-on products]), batyl alcohol (up to 3% [maximum in leave-on products]), glyceryl lauryl ether (7% [in rinse-off products]), and isostearyl glyceryl ether (up to 0.02% [maximum in leave-on products]).^{11,12,13} Except for the use concentration data on glyceryl lauryl ether and batyl alcohol (collected in 2011), the data on these ingredients were collected in 2010.

Ethylhexylglycerin was reported as being used in 3 baby products in the VCRP, but use concentration data were not reported in the Council survey.¹¹

No uses of the remaining 5 ingredients reviewed in this safety assessment were reported in the VCRP database or in the Council survey.^{10,11}

Cosmetic products containing these ingredients may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Ethylhexylglycerin is used in hair sprays and, body and hand sprays, and effects on the lungs that may be induced by aerosolized products containing this ingredient are of concern. In practice, 95% to 99% of the aerosols released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 μm range.^{14,15} Therefore, most droplets/particles

incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., able to enter the lungs) to any appreciable amount.^{16,17} However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions may cause toxic effects, depending on their chemical and other properties.

Noncosmetic

The use of ethylhexylglycerin as an emollient in an alcohol-based surgical hand disinfectant (SurgiceptTM) has been reported.¹⁸

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Oral Studies

Chimyl Alcohol

The absorption and metabolism of chimyl alcohol was evaluated using adult male rats.¹⁹ (1-¹⁴C)-Chimyl alcohol (5 mg) in 0.5 ml olive oil was administered via stomach tube. Feces were collected in 24 h portions. The amount of chimyl alcohol absorbed was calculated as the difference between the amount of radioactivity administered and the amount recovered from the feces. The amount of [¹⁴C]-labeled chimyl alcohol absorbed after feeding was 95%, and the remainder was recovered in the unsaponifiable fraction of fecal lipids. The percentage of total absorbed activity (whole body) that was recovered in the lymph lipids was 45% (1 rat) and 59% (1 rat). The distribution of the activity between the different fractions in the lymph lipids was phospholipid fatty acids (3% and 4%) and glyceride fatty acids (45% and 51%). Also, in the lymph lipids, 45% and 51% of the activity was present as chimyl alcohol, of which free chimyl alcohol accounted for more than half. The remainder was esterified.

A similar study on the absorption and metabolism of chimyl alcohol using rats (strain not stated) was performed. α -(1-¹⁴C)-Chimyl alcohol was fed, by stomach tube, as free alcohol or as chimyl dioleate (in olive oil).²⁰ In one series of experiments, intestinal contents were analyzed during the absorption phase, 2-4 h after administration. In another series, the distribution of activity in expired CO₂ was determined at 24 h post-administration. In other experiments, the distribution of activity in lymph lipids was monitored after chimyl dioleate (in olive oil) was fed to rats with a thoracic duct fistula (for lymph collection). Results for dosing with free chimyl alcohol indicated the incorporation of free fatty acids into chimyl alcohol, with the formation of alkoxydiglycerides in lymph lipids. The results of analyses of intestinal contents together with lymph analyses clearly indicated the dynamic situation in the intestine. In the intestinal lumen, the ether linkage was intact during the entire absorption process, but, once absorbed into the intestinal mucosa, more than 50% of the compound was rapidly converted into palmitic acid.

Following administration of ¹⁴C-chimyl dioleate (chimyl alcohol esterified with oleic acid) in olive oil to rats by stomach tube, 8% of the total administered radioactivity was excreted as exhaled ¹⁴CO₂ in 24 h. Results also indicated that fatty acids in both the 1- and 2-position in the alkoxydiglyceride molecule were exchanged during hydrolysis by pancreatic enzymes *in vivo*. Apparently an equilibrium between the synthesis and hydrolysis of mono- and di-esterified chimyl alcohol and free chimyl alcohol was reached. Approximately 75% of radioactivity in the lymph was present as glyceride fatty acids and, approximately 2%, as phospholipid fatty acids. Approximately 25% of lymph activity was present as chimyl alcohol, of which more than two-thirds was present as esterified chimyl alcohol. More than half the radioactivity was associated with palmitic acid, indicating a splitting of the ether bond in mucosal cells. It was concluded that chimyl alcohol can be absorbed unchanged, but that it is already extensively metabolized in the mucosal cells, whether it is fed as free chimyl alcohol or as an alkoxydiglyceride.²⁰

Parenteral Studies

Chimyl Alcohol

The intravenous injection of ¹⁴C-chimyl alcohol (dose not stated) into rats of an unspecified strain resulted in excretion of 24% of the administered radioactivity as ¹⁴CO₂ in 24 h.²⁰

Male albino Sprague-Dawley rats (total of 40 used) were injected i.p. with 2-³H- α -1-¹⁴C- α -1-¹⁴C-2-³H-chimyl alcohol (5.60 mg) or β 1-¹⁴C-chimyl alcohol (6.30 mg).²¹ After dosing, the animals were killed and the entire liver and small intestine removed. Lipids were then extracted. The purpose of these timed experiments (4h or 8 h post-injection) was to

determine if these alcohols would be converted directly to alkyl glyceryl ether phospholipids in the liver and small intestines. Both labeled glyceryl ethers were converted to alkaline stable glyceryl ether phospholipids in the intestine. The β -ether was not incorporated into the glyceryl ether phospholipids as rapidly, when compared to the α -ether. This difference in incorporation of the β -glyceryl ethers might be explained by the fact that, in most acyl phospholipids, the fatty acid that is attached to the secondary carbon of glycerol is usually unsaturated.

For both the α - and β -chimyl alcohols, phosphatidyl choline was the major labeled intestinal fraction. For any of the liver lipid extracts, < 1% of alkaline stable glyceryl ether phospholipids was detected. In each experiment examining the metabolism of labeled glyceryl ethers, < 1% of the radioactivity was detected in each of the following: free fatty acids, long-chain alcohols, cholesterol esters, monoglycerides, and long-chain aldehydes. To substantiate that the glyceryl ether was converted to the glyceryl ether phospholipids, the rats were injected i.p. with double-labeled α -chimyl alcohol. At 4 h post-injection, very little tritium was detected in the total liver lipids, but was present in substantial quantities in the intestine. This finding was attributed to the degree of cleavage of the linkage in the liver and small intestines.²¹

The metabolism of chimyl alcohol was evaluated using 6 female rats of the Carworth Farm Nelson strain. ^{14}C -chimyl alcohol was injected i.v. (10 $\mu\text{Ci}/100\text{g}$ body weight) as a fat emulsion.^{22,22} Approximately 28% of the ^{14}C from chimyl alcohol was eliminated as $^{14}\text{CO}_2$ within 6 h post-injection. During the same period of time, the urine contained 1% of the ^{14}C from chimyl alcohol. Approximately 6 to 13% of the radioactivity was accounted for as lipid in the liver, and the remainder was associated with adipose tissue or transferred into a nonlipid metabolic pool. These *in vivo* results were confirmed in the *in vitro* liver slice system, in that the ^{14}C from chimyl alcohol was found in triglycerides, free fatty acids, fatty alcohols, glyceryl ether monoesters, lecithin, and cephalin. Less than 2% of the chimyl alcohol was oxidized to $^{14}\text{CO}_2$ during the 3-h incubation period. When bone marrow cells and spleen slices were studied *in vitro*, the bone marrow cells were less active in metabolizing the labeled chimyl alcohol. Less than 6% of the ^{14}C from ^{14}C -chimyl alcohol was incorporated into phospholipids by bone marrow cells or spleen slices during the 3-h incubation period.

The metabolism of chimyl alcohol and phosphatidylethanolamine (PE) in the brain was studied using 3 groups of male Sprague-Dawley rats (18 days old).²³ Use of a control group was not mentioned. Each rat was anesthetized and given an intracerebral injection of 0.375 ml of an emulsion consisting of: 20 mg of 6 μC chimyl alcohol- ^3H , 7.3 mg of 25 μC phosphatidylethanolamine (PE)- ^{14}C , and Tween 20 (36 mg/ml). The 3 groups of animals were killed after 4h, 8h, and 16 h, respectively, and brains removed. Ethanolamine phosphoglycerides were isolated and analyzed. It was evident that label from both substrates was incorporated into the brain lipids of the rats. A major portion of the ^{14}C activity (25-35%) appeared in the front fraction, defined as containing cholesterol, ceramide, cerebroside, choline phosphoglycerides, sphingomyelin and lyso phosphatidylcholine. The ^{14}C and ^3H activities in the dimethyl acetals derived from alkenyl acylethanolamine phosphoglycerides and in the glyceryl ethers derived from the alkyl acylethanolamine phosphoglycerides were measured. The absence of ^{14}C in the dimethyl acetals indicated that phosphatidylethanolamine was not transformed into phosphatidyl ethanolamine. The increase, with time, of the ^3H content of the glyceryl ethers and dimethyl acetals indicated that chimyl alcohol was a precursor of both types of phospholipids.²³

Batyl Alcohol

Male albino Sprague-Dawley rats (total of 40 used) were injected i.p. with α -1- ^{14}C -batyl alcohol (7.24 mg) or β -1- ^{14}C -batyl alcohol (10.37 mg).²¹ After dosing, the animals were killed and the entire liver and small intestine removed. Lipids were then extracted. After 8 h, 24.5% of the injected dose was present in the liver lipids. Approximately 15% of the α -1- ^{14}C -batyl alcohol liver lipid label was identified as intact free glyceryl ether. All of the liver lipid label was identified as esterified fatty acid, with the exception of the remaining free glyceryl ether that had been injected. No significant free fatty acid label was observed in any of the liver lipid fractions. A different labeling pattern was found for the intestinal lipids. At 8 h post-injection of α -1- ^{14}C -batyl alcohol, 65% of the intestinal lipid label was present as free glyceryl ether, and 8% of the injected dose was found in the small intestine. Only 7% of the dose was identified as esterified fatty acids. The major portion of the radioactive label in the intestine derived from α -1- ^{14}C -batyl alcohol was in the phospholipids. After 8 h, approximately 18% of the total lipid label was associated with the phospholipids. β -1- ^{14}C -batyl alcohol was not incorporated into the glyceryl ether phospholipids as rapidly as the α -ether.

The metabolism of batyl alcohol was evaluated using 6 female rats of the Carworth Farm Nelson strain. ^{14}C -batyl alcohol was injected i.v. (10 $\mu\text{Ci}/100\text{g}$ body weight) as a fat emulsion.²² Approximately 13% of the ^{14}C from batyl alcohol was eliminated as $^{14}\text{CO}_2$ within 6 h post-injection. During the same period of time, the urine contained 6.5% of the ^{14}C from batyl alcohol. Approximately 6 to 13% of the radioactivity was accounted for as lipid in the liver, and the remainder was associated with adipose tissue or transferred into a nonlipid metabolic pool. These *in vivo* results were confirmed in the *in vitro* liver slice system, in that the ^{14}C from batyl alcohol was found in triglycerides, free fatty acids, fatty alcohols, glyceryl

ether monoesters, lecithin, and cephalin. Less than 0.2% of the batyl alcohol was oxidized to $^{14}\text{CO}_2$ during the 3-h incubation period.

Human Study

Chimyl Alcohol

Two adult patients (1 male, 1 female) were used to evaluate the absorption of chimyl alcohol.²⁴ The female patient with chyluria was maintained on a liquid formula (administered orally) 5 times per day. The formula was enriched with corn oil containing 25 mg of ^{14}C -labeled chimyl alcohol. Urine was collected at 3-h intervals over a 12-h period. The male patient (with bilateral chylothorax secondary to carcinoma) was maintained on a mixed hospital diet, and, on day 1 the chest was emptied by thoracentesis. This process was followed by feeding with bread containing ^{14}C -labeled chimyl alcohol (18 mg). A second thoracentesis was performed 48 h later, prior to the removal of chylous fluid. In the female patient, 95% of administered labeled chimyl alcohol was absorbed and approximately 40% of the dose was recovered in the urine within 12 h post-administration. This indicated that this patient shunted approximately 40% of her intestinal lymph into the urinary tract. Approximately half of the radioactivity in the lymph was identified as chimyl alcohol, and the remaining 50% had been converted to palmitic acid, found in triglycerides, phospholipids, and free fatty acids. Essentially the same results were reported for the male patient. Study results also indicated that rupture of the ether linkage of chimyl alcohol can occur in the intestinal mucosa of man, and that the palmitoyl moiety is readily oxidized to palmitic acid.

Percutaneous Absorption

In Vivo Study

Ethylhexylglycerin

An acute toxicokinetic study on ethylhexylglycerin (Sensiva® SC 50) was performed using 2 groups of 5 rabbits of an unspecified strain.²⁵ The test substance was applied (single application) to the 2 groups at concentrations of 1% and 5% in corn oil, respectively. Each concentration was applied at a dose of 2 g/kg body weight, spread evenly over surgical gauze (25 x 25 mm). The occlusive dressing remained in place for 4 h. There were no signs of irritation at the application site as late as 60 min post-application of either concentration. Changes in body weight were unremarkable. Ethylhexylglycerin was detected in the plasma of 3 of 5 rabbits tested with the 5% concentration. The mean absorption through skin in this group was 0.02% at approximately 2 h after the beginning of exposure. Plasma concentrations in animals treated with 1% ethylhexylglycerin were below the limit of detection. In all blood samples collected after treatment ended, the concentrations of ethylhexylglycerin were below the limit of detection (1.03 µg/ml).

In Vitro Study

Ethylhexylglycerin

The skin penetration of ^{14}C -ethylhexylglycerin (Sensiva® SC 50) was also evaluated using human skin.²⁵ The experiments were performed after administration of the test substance at 3 concentrations formulated as solutions in ethanol:water, 10:90 v/v, and concentrations of the test substance that were determined using quantitative radiochemical analysis. The lowest test concentration was based on dermal application of the test substance at a concentration of 2% in cream (at 1.4 mg cream/cm² of skin). Based on concentrations determined in the receptor fluid, mean absorption values for ^{14}C -ethylhexylglycerin at the 3 concentrations evaluated were as follows: 44.65% (at 31 µg/cm²), 47.15% (at 60 µg/cm²), and 54.94% (at 151 µg/cm²). These 3 values corresponded to mean penetration rates of 2.38, 8.19, and 20.38 µg/cm²/h, respectively. Results indicated that the lag time was essentially the same for all concentration tested. The rate at which ^{14}C -ethylhexylglycerin moved from the outer skin surface (dissolved in ethanol:water (10:90 v/v)) to the receptor fluid appeared to have been linear.

Skin Penetration Enhancement

The penetration of indomethacin (from propylene glycol solutions) through rat abdominal skin *in vitro* was substantially increased in the presence of 0.2% or 1% (w/w) α -monoisoostearyl glyceryl ether.²⁶

TOXICOLOGY**Acute Inhalation Toxicity****Ethylhexylglycerin**

The acute inhalation toxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated in a study involving groups of 10 (5 males, 5 females/group) Sprague-Dawley rats.^{25,27} The animals were exposed to the aerosolized ethylhexylglycerin (nose only, mean achieved concentrations of 1.89, 2.96, and 4.98 mg/L) for 4 h according to the OECD TG 403 test method, using a continuous flow system. After exposure, the animals were observed for 14 days. The mean diameter of the aerosol particles was between 1.2 and 1.4 µm. Clinical observations included labored and noisy respiration and occasional sneezing (frequent when noted), ataxia, and gasping respiration. The acute inhalation LC50 was 3.07 mg/L (low to moderate toxicity), and the following mortalities were reported: 4.98 mg/L (4 males, 5 females), 2.96 mg/L (3 males, 2 females), and 1.89 mg/L (1 male). Morphological findings for the lungs were described as dark or abnormally reddened appearance, pale patches, enlargement, and an isolated incidence of hemorrhage. Thus, an irritant effect on the respiratory tract was evident. An abnormally dark liver (accentuated lobular pattern) was also reported for the male in the lowest dose group that died. The lung was described as a target organ, based on rapid deaths, severe respiratory changes, and abnormal coloration and enlargement of the lungs.

Acute Oral Toxicity**Ethylhexylglycerin**

In an acute toxicity study on undiluted ethylhexylglycerin (Sensiva® SC 50), 5 male and 5 female Wistar rats each received a single oral dose (2,000 mg/kg) by gavage according to the OECD TG 401 test method.^{25,27} An LD50 of > 2,000 mg/kg (low toxicity, no deaths) was reported, and clinical observations included irregular respiration and hemorrhagic nasal discharge for up to 24 h post-administration. No test-substance related morphological findings were reported.

Chimyl Alcohol

The acute oral toxicity of chimyl alcohol was evaluated using 6-week-old SD rats of the CrI:CD(SD) strain (5 males, 5 females).²⁸ Animals received a single oral dose of chimyl alcohol in a 1 w/v% Tween 80 solution (concentration = 200 mg/ml; dose volume = 10 ml/kg). None of the animals died. Diarrhea was observed after dosing; however, body weight gain was described as normal. Necropsy findings did not reveal any abnormalities. It was included that the acute toxicity induced by chimyl alcohol was extremely low (LD_{LO} > 2,000 mg/kg).

Acute Dermal Toxicity**Ethylhexylglycerin**

The acute dermal toxicity of undiluted ethylhexylglycerin (Sensiva® SC 50) was evaluated in a study involving 5 male and 5 female Wistar rats.^{27,25} The undiluted test substance was applied (2.17 ml on porous gauze/elastic dressing; dose = 2,000 mg/kg) to shaved, intact skin according to the OECD TG 402 test method. The application site was defined as a 5 x 10 cm area on the back, and the occlusive dressing remained in place for 24 h. No abnormal clinical signs or signs of erythema or edema were observed during the study. None of the animals died, and an acute dermal LD50 of > 2,000 mg/kg (non-toxic) was reported. Necropsy findings were described as normal.

Acute Subcutaneous Toxicity**Batyl Alcohol**

Single subcutaneous doses of batyl alcohol were administered to adult white mice (10 to 15, ages not stated), and deaths were reported at 24 h post-dosing.²⁹ A mean LD50 of > 8.8 mM/kg was reported. Details relating to the test protocol and study results were not included.

Repeated Dose Toxicity**Ethylhexylglycerin**

The oral toxicity of ethylhexylglycerin (Sensiva® SC 50, in polyethylene glycol 400) at doses of 100, 500, and 1,500 mg/kg was evaluated in a 28-day study using groups of 10 rats of an unspecified strain. The test substance was administered at a dose volume of 5 ml/kg.²⁵ There were no treatment-related mortalities. Body weight development was retarded in mid- and high-dose groups, and this finding was accompanied by a non-statistically significant reduction in food intake when compared to the control (polyethylene glycol 400) group. Both eye and ear functions remained unchanged during the study, and increased salivation (dose not stated) was the only clinical symptom observed. Hematological parameters were unaffected by treatment; however, serum analyses indicated changes in aminotransferase (above normal) in high-dose rats. Urinalysis and necropsy findings were unremarkable.

Increased liver and adrenal weights were reported for high-dose rats, especially females. Microscopic findings in the liver were described as follows: slight to moderate hypertrophy (rats from all dose groups), fatty infiltration of hepatocytes (high –dose males), and necrosis of hepatocytes (1 rat each from mid- and high-dose groups). A dose of 100 mg/kg was defined as the no-observed-adverse effect-level (NOAEL), assuming that the slight hepatocyte hypertrophy observed in 5 of 10 rats in this dose group was not toxicologically significant.²⁵

In a 13-week study, ethylhexylglycerin (Sensiva® SC 50, in polyethylene glycol [PEG] 400) was administered at oral doses of 0, 50, 200, and 800 mg/kg/day to groups of Sprague- Dawley rats (10 males, 10 females/group).^{25,30} A fourth group (control) was dosed with PEG 400 only. Testing was done in accordance with the OECD TG 407 test method. There was no evidence of treatment-related deaths or statistically significant changes in body weight gain. Furthermore, neurotoxicology testing and ophthalmoscopic examinations revealed no test-substance-related changes. Compared to controls, statistically significant changes in some clinical parameters (e.g., statistically significant decrease in lymphocytes) were observed, but were considered toxicologically insignificant. Abnormally noisy respiration and an increased incidence of subcutaneous masses were reported for the highest dose group. Noisy respiration was also observed in some animals in the mid dose group, and the incidence increased with time in mid- as well as high-dose groups. Treatment-related macroscopic effects were not found in animals killed at the end of dosing or the 4-week recovery period or in animals that died during the study.

In males of all dose groups and high-dose females, a statistically significant increase in absolute and relative-to-body weight liver weights was observed during dosing. Relative liver weights remained increased in males at the end of the recovery period. Increased liver weight was the only toxicologically significant finding that was also observed in the low-dose group. However, this finding was not accompanied by changes in clinical parameters associated with functional impairment of this organ. Increased absolute and relative kidney weights (statistically significant) were observed in females of low- and high-dose groups, but this finding was not observed at the end of the recovery period. Microscopic examination revealed generalized hepatocytic hypertrophy in the high-dose group. When compared to controls, this finding was statistically significant in high-dose male rats. An increased incidence of renal mineralization was observed in high-dose females, but this finding was not apparent at the end of the recovery period. According to the National Industrial Chemicals Notification and Assessment Scheme (NICNAS, Australia) summary of data from this 13-week study, it was not possible to establish a no-observed-adverse-effect level (NOAEL), in that increased liver weight was observed at all doses. The study authors considered 50 mg/kg/day to be an NOAEL, because this dose was associated with increased liver weights without any other effects.³⁰ In comparison, the NICNAS identified 50 mg/kg/day as a lowest observed adverse effect level (LOAEL), based on the increased liver weights reported in this study.²⁷

Batyl Alcohol

The hematopoietic activity of batyl alcohol was evaluated using male guinea pigs of the Dunkin-Hartley strain (ages not stated).³¹ One group of 12 guinea pigs was dosed subcutaneously (s.c.) with batyl alcohol (4 mg) in 1 ml of arachis oil on each of 5 consecutive days. The control group (10 guinea pigs) received s.c. injections of arachis oil. On day 6, the animals were killed and erythrocyte and leukocyte counts were performed on blood obtained from a small ear incision. Changes in bone marrow were also evaluated. Results suggested that batyl alcohol may be an erythropoietic stimulant. The authors suggested that batyl alcohol exerted an influence on the lymphocytic, but not the granulocytic, population of the bone marrow. The following changes were observed in the bone marrow: increased population of small lymphocytes ($p < 0.05$), increased bone marrow reticulocyte count ($p < 0.05$), increase in the number of cells intermediate between small lymphocytes and blast-like cells ($p \approx 0.05$), and an increase in the mean numbers of nucleated cells at each stage of the red cell series ($0.10 > p > 0.05$). Significant reticulocytosis ($p < 0.05$) in the blood was also observed. Stimulation of hematopoiesis was also observed in Wistar rats given 15 daily 50 mg doses of a 10% suspension of racemic batyl alcohol in distilled water,³²

and in Wistar rats that received 20 s.c. injections of peanut oil containing 12.5 mg or 25.0 mg of racemic batyl alcohol 5 days per week over a period of 4 weeks.³³ In the latter study, the erythrocytosis and reticulocytosis were more marked and appeared earlier in rats that received the higher dose.

Ocular Irritation

Ethylhexylglycerin

Undiluted ethylhexylglycerin (Sensiva® SC 50, 0.1 ml) was instilled into the left conjunctival sac of each of 3 New Zealand White rabbits (sex not specified), and animals were observed up to day 21 post-instillation.^{25,27} Right eyes served as untreated controls. Testing was in accordance with the OECD TG 405 test protocol. Conjunctival redness and chemosis were observed in all animals and irritation scores of 2 or 3 predominated. Conjunctival irritation persisted up to day 14, and, in one animal, corneal opacity persisted beyond the 21-day observation period. Thus, ethylhexylglycerin (Sensiva® SC 50) caused severe damage to the eyes of rabbits. When a 5% aqueous solution of the test substance was instilled into the eyes of 3 additional rabbits according to the same procedure, conjunctival erythema (score = 1) was observed in each animal at 1 h post-instillation. Conjunctival irritation had resolved completely within 24 h. There were no signs of irritation to the iris or cornea. Thus, the 5% aqueous solution of ethylhexylglycerin (Sensiva® SC 50) was mildly irritating to the eyes of rabbits.^{25,27}

Chimyl Alcohol

In the Draize test, the ocular irritation potential of chimyl alcohol was assessed using 6 male Japanese White rabbits of the Kbl: JW, SPF strain.³⁴ The test substance (0.1 g) was instilled into the right eye of each animal. The eyes of 3 rabbits were rinsed after instillation. In all unrinsed eyes, conjunctival redness and chemosis (score = 1) and discharge (score = 2 or 3) were observed at 1 h post-instillation. Reactions had cleared by 48 h post-instillation. Chimyl alcohol was classified as minimally irritating in unrinsed eyes (maximum mean Draize score = 9.3). Ocular reactions were not observed in rinsed eyes. Chimyl alcohol was classified as having minimal ocular irritation potential in this study.

Skin Irritation and Sensitization

Non-Human Studies

Ethylhexylglycerin

The skin irritation potential of ethylhexylglycerin (Sensiva® SC 50) was evaluated using 3 New Zealand White rabbits (sex not specified).²⁷ Undiluted test substance (0.5 ml) was applied to intact skin (shaved) and the test site was covered with a semi-occlusive dressing secured with elastic tape. Testing was in accordance with the OECD TG 404 test protocol. During the 4-day observation period, erythema (score = 1) was observed in 2 rabbits, but edema was not observed in any of the animals. Signs of erythema had cleared by day 4 post-application. Ethylhexylglycerin (Sensiva® SC 50) was classified as a mild skin irritant.

In another study, the skin irritation potential of undiluted ethylhexylglycerin (Sensiva® SC 50) was evaluated in 3 rabbits (strain not stated) according to the protocol stated in the preceding paragraph.²⁵ The test substance remained in contact with the skin for 4 h, and very slight erythema was observed in 2 of 3 rabbits at 24 h and 48 h post-application. It was concluded that ethylhexylglycerin could not be classified as a skin irritant.

In the maximization test (OECD TG 406 test method), the skin sensitization potential of ethylhexylglycerin (Sensiva® SC 50) was evaluated using 2 groups of 20 guinea pigs (10 males, 10 females/group); one of the 2 groups served as the negative control.^{25,27} The induction phase involved 10 test animals with 3 pairs of injection sites on the shaved neck according to the following procedure. Starting at day 0, 0.1 ml of the test substance was injected intradermally into the neck region (2 pairs of injection sites) at concentrations of 0.5% in peanut oil and 0.5% in Freund's complete adjuvant/saline 1:1, respectively. The third pair of sites was injected with Freund's complete adjuvant/water 1:1. On day 7, the undiluted test substance was applied (under occlusive dressing) to the neck for 48 h. On day 21, the animals were challenged with the test substance (50% in peanut oil, under occlusive dressing) for 24 or 48 h. Sensitization was not observed in any of the animals tested.

The sensitization potential of ethylhexylglycerin (Sensiva® SC 50) was evaluated in the local lymph node assay at concentrations up to 50%.²⁵ The test substance did not induce 3-fold increases (EC_3 -value) in tritiated thymidine (^{3} HTdR) incorporation at any concentration tested, and it was concluded that Ethylhexylglycerin was not a sensitizer.

Chimyl Alcohol

The skin irritation potential of chimyl alcohol was evaluated in the Draize test using 3 male Japanese White rabbits of the Kbl: JW, SPF strain (11 weeks old).³⁵ Chimyl alcohol (0.5 g) moistened with propylene glycol (0.5 ml) was applied to intact and abraded skin sites on each animal. Each application site was covered with an occlusive patch for 24 h. At 24 h post-application, all animals received an erythema score of 1 at intact and abraded skin sites. Reactions had cleared by 72 h post-application. Skin irritation was not observed at intact or abraded sites tested with propylene glycol (0.5 ml). Chimyl alcohol was classified as a mild irritant (primary irritation index [PII] = 0.5, intact and abraded skin).

A 14-day cumulative skin irritation study was performed using 3 male Japanese White rabbits of the Kbl: JW, SPF strain. Chimyl alcohol (10 w/v%, suspended in propylene glycol) was applied to the skin at a volume of 0.2 ml, without an occlusive patch.³⁶ Applications were made once daily for 14 days. Propylene glycol (solvent control) was applied to control sites. Skin irritation was not observed at sites treated with chimyl alcohol or control sites. It was concluded that chimyl alcohol did not have cumulative skin irritation potential.

Human Studies

Ethylhexylglycerin

The skin irritation and sensitization potential of a facial cream containing 0.4975% ethylhexylglycerin was evaluated in anRIPT using 600 subjects (ages not stated).³⁷ Occlusive patches (0.5" x 0.5") containing the test substance were applied (48 h) weekly for a total of 10 induction applications. Reactions were scored after patch removal. After a 2-week non-treatment period, challenge patches were applied for 48 h. As second challenge application (48 h) was made one week later. There was no evidence of primary irritation, skin fatiguing, or allergic eczematous dermatitis.

A foundation containing 0.4% ethylhexylglycerin was evaluated for skin irritation and sensitization potential in anRIPT involving 108 male and female (18 to 70 years old).³⁸ Partially-occlusive patches (2 cm x 2 cm) containing the test substance (~ 150 mg) were applied for 24 h, for a total of 9 induction applications. During the challenge phase (105 subjects), test sites were scored at the time of patch removal and 24 h and 48 h later. The induction application site and a new test site were challenged. The foundation was neither a skin irritant nor sensitizer.

A repeated insult patch test (RIPT) on a liquid eyeliner containing 0.5% ethylhexylglycerin was performed using 115 male and female subjects (16 to 79 years old).³⁹ Approximately 0.2 g of the test substance on a 1" x 1" semi-occlusive patch was applied (24 h) 3 times per week for a total of 9 induction applications. Reactions were scored after patch removal. After a 2-week non-treatment period, a challenge patch was applied to a new site adjacent to the original induction site. Challenge reactions were scored at 24 h and 72 h post-application. The product did not have skin irritation or allergic contact sensitization potential.

The skin irritation and sensitization potential of a makeup preparation containing 0.995% ethylhexylglycerin was studied in 111 male and female subjects (18 to 70 years old) using the same test procedure, except for the application of 100 μ l of test material to the partially-occlusive patch.⁴⁰ The number of subjects who participated in the challenge phase was 108. The makeup preparation was neither a skin irritant nor sensitizer.

AnRIPT on a fragranced body lotion containing 0.6965% ethylhexylglycerin was conducted using 108 subjects (between 18 and 70 years old).⁴¹ A semi-occlusive patch containing the test substance was applied (24 h) 3 times per week for a total of 9 induction applications. Reactions were scored after patch removal. After a 2-week non-treatment period, a challenge patch was applied to a previously untreated site for 24 h. Reactions were scored at 24 h, 48 h, and 72 h. The body lotion was not a skin irritant or sensitizer.

Skin Tanning

Chimyl Alcohol

A study was performed to achieve skin whitening via the control of cytokines by coating the skin with a chemical substance and the control of melanogenesis, in which inflammation of the skin became a trigger.⁴² The effect of chimyl alcohol on reduction of peroxisome proliferator activated receptor (PPAR) expression of normal human keratinocytes (NHK) by USB was evaluated in one of the experiments. The cells were cultured for 24 h in media containing chimyl alcohol at concentrations up to 10 μ M, and cultures were then exposed to UVB light (5.0 mJ/cm²). The participation of PPAR in the

control PGE₂ production due to chimyl alcohol was observed. Chimyl alcohol checked the reduction of expression of mRNA of PPAR γ due to UVB. This effect of chimyl alcohol was eliminated in the presence of a PPAR γ antagonist (GW9662). In another experiment, The effect on the erythema reaction caused by coating chimyl alcohol on the skin model was determined by changing the minimum erythema dose (MED), and the effect on pigmentation was visually determined. Study results suggested that chimyl alcohol had an inflammatory effect via PPARs of keratinocytes. Chimyl alcohol suppressed the production of chemical mediators of UVB-irradiated keratinocytes *in vitro*, possibly via the PPAR γ pathway and erythema in human skin. It substantially suppressed UV-induced tanning in human skin. The results of this study led to the proposal of chimyl alcohol as an ingredient of a new skin whitening agent.

Phototoxicity

Ethylhexylglycerin

The phototoxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated at concentrations ranging from 25% to 100% using albino guinea pigs (number not stated).²⁵ Each solution was applied to the flank, after which sites were irradiated with UVA light at a dose of 20 J/cm². The opposite flank (control) was treated with the test substance, but not irradiated. Study results indicated no evidence of phototoxic effects.

Photoallergenicity

Ethylhexylglycerin

Tests were also performed to evaluate the photoallergenicity of ethylhexylglycerin (Sensiva® SC 50).²⁵ Initially, albino guinea pigs (number not stated) were pretreated with Freund's adjuvant. The animals were then treated dermally (5 times in 14 days) with the undiluted test substance and irradiated with UVA and UVB light. None of the animals had reactions during the challenge phase that followed, and it was concluded that ethylhexylglycerin was not a photosensitizer.

Case Reports

Ethylhexylglycerin

A 57-year-old female developed perioral and periocular itchy erythematous edema of the eyelids after using a facial cream that contained ethylhexylglycerin.⁴³ Patch test results for 10% ethylhexylglycerin in petrolatum in this subject were positive (+) on days 2 and 4, but results were negative in 5 control subjects.

A 64-year-old female with chronic eczema was patch tested with ingredients provided by a product manufacturer. Reactions were scored on days 3 and 7.⁴⁴ A strong positive reaction (+++) to 5% ethylhexylglycerin in petrolatum was reported. A repeated open application test (ROAT, 7 days) was also performed. ROAT results for 5% ethylhexylglycerin were strongly positive on day 2, after only 4 applications. The reaction spread to the entire right arm and to the face. Patch test results were negative for 5% ethylhexylglycerin in 25 consecutive controls.

Recurrent and spreading facial dermatitis was observed in a 68-year-old, non-atopic female after using a cream containing ethylhexylglycerin.⁴⁵ Occlusive patches (Finn chambers) were applied for 2 days and reactions were scored on days 3 and 7. Results were positive for 5% ethylhexylglycerin in petrolatum. Patch test results were negative in 25 consecutive controls.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylhexylglycerin

The effects of ethylhexylglycerin (Sensiva® SC 50) on pregnancy and embryo-fetal development were evaluated in a prenatal developmental toxicity study involving groups of female rats of an unspecified strain (no. of animals not stated).²⁵ The test substance was administered by gavage at doses of 50, 200, and 800 mg/kg/day. None of the animals died. Salivation and rales were considered the most relevant signs observed in mid- and high-dose groups. There were no treatment-related effects on terminal body weight, uterine weight, or absolute weight gain. Litter data and the results of macroscopic examinations of females were also unaffected by treatment, and the malformations observed in 3 fetuses at external examination were considered incidental. The results of visceral and skeletal examinations did not reveal any changes between test and control groups that were considered treatment-related. Based on these results, the no-observed-

adverse-effect-level (NOAEL) was considered to be 800 mg/kg/day, and this was the highest dose tested in the one-generation developmental toxicity study summarized below.

The developmental toxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated in a one-generation developmental toxicity study using groups of male and female rats of an unspecified strain.²⁵ The test substance was administered orally at doses of 50, 200, and 800 mg/kg/day. Male rats were dosed daily for 10 weeks prior to pairing, after which dosing continued through the day before animals were killed. Female rats were dosed for 2 weeks prior to pairing and during gestation and post-partum periods; dosing ended on post-partum day 20. Treatment-related findings, rales and salivation, occurred only in males of mid- and high-dose groups. Two male rats were found dead (1 low-dose and 1 mid-dose; cause not stated) and 3 rats (2 high-dose males, 1 high-dose female) were killed for humane reasons. Necropsy findings in animals found dead or killed did not reveal any treatment-related changes in tissues/organs. On day 21 post-partum, there were 17 to 23 females per group with live pups. Twelve females did not become pregnant. Estrous cycles were comparable between groups, but the fertility index for high-dose animals was lower when compared to controls. Data on pre-birth loss and gestation length indicated no treatment-related effects on implantation. The no-observed-effect-level (NOEL) was 50 mg/kg/day for both sexes.

GENOTOXICITY

Ethylhexylglycerin

The genotoxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated in the Ames test (OECD TG 471 test method) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 with and without metabolic activation.^{25,27} The test substance was evaluated at concentrations up to 1.5 µg/plate. Toxicity was observed at the highest test concentration. Ethylhexylglycerin was not genotoxic with or without metabolic activation. Normal reversion rates were observed in negative control plates, and positive controls were genotoxic.

In another *in vitro* test (mouse lymphoma assay), the genotoxicity of ethylhexylglycerin (Sensiva® SC 50) was evaluated with and without metabolic activation using mouse lymphoma L5178Y cells.²⁵ Test concentrations were not stated. Negative results were reported for ethylhexylglycerin.

In the *in vivo* micronucleus assay, the genotoxicity of ethylhexylglycerin (Sensiva® SC 50) in mouse bone marrow cells was evaluated.^{25,27} According to the OECD TG 474 test method, 60 mice of the BOR:NMRI strain (30 males, 30 females) received single oral doses of 1,000 and 2,000 mg/kg by gavage. The examinations for cell nucleus changes in the bone marrow were performed on animals killed at 24 h and 48 h. Reduced activity, alterations in tone, and abnormal gait were among the findings observed up to 1 h post-dosing; however, none of the animals died. A statistically significant decrease in the numbers of polychromatic erythrocyte was observed in bone marrow cells from females of all dose groups. There were no statistically significant increases in micronucleated polychromatic erythrocytes at any timepoint, and it was concluded that ethylhexylglycerin was non-clastogenic.

Chimyl Alcohol

The genotoxicity of chimyl alcohol (in DMSO) was evaluated in the Ames pre-incubation test using the following bacterial strains, with and without metabolic activation:⁴⁶ *Salmonella typhimurium* strains TA100, TA 1535, TA98, and TA1537, and *Escherichia coli* strain WP2uvrA. Test concentrations up to 5,000 µg/plate were used. It was concluded that chimyl alcohol was not mutagenic to any of the strains tested. The numbers of revertant colonies in the negative (solvent) control and positive control cultures were within the acceptable ranges stipulated at the testing facility. In the *in vitro* chromosomal aberrations assay involving CHL/IU cells (derived from female Chinese hamster lungs), the genotoxicity of chimyl alcohol was evaluated with (concentrations up to 1,000 µg/ml) and without (concentrations up to 200 µg/ml) metabolic activation in short-term assays and at concentrations up to 100 µg/ml (with metabolic activation) in the 24-h assay.⁴⁷ In all assays, the incidence of cells with chromosomal aberrations was < 5% at each concentration tested, with or without metabolic activation. It was concluded that chimyl alcohol did not have the potential to induce chromosomal aberrations under the conditions used in this study.

Batyl Alcohol

Batyl alcohol was evaluated for genotoxicity in the Ames test (reverse mutation assay) using the following *Salmonella typhimurium* strains: TA 97a, TA 98, TA 100, TA 102, and TA 1535.⁴⁸ The test substance was evaluated with and without metabolic activation at doses up to 25 µg/plate. The following chemicals served as positive controls:

benzo[a]pyrene (with metabolic activation) and sodium azide; ICR 191; 2,4,7-trinitro-9-fluorene; and Mitomycin C (all without metabolic activation). Batyl alcohol was not genotoxic with or without metabolic activation.

Glyceryl Allyl Ether

The genotoxicity of glyceryl allyl ether was evaluated in the following battery of short-term tests: Ames test (*Salmonella typhimurium* strains TA98, TA100, and TA1538 and *Escherichia coli* strains WP₂ and WP₂ uvrA; test concentrations up to 4,000 µg/plate in plate incorporation assay, with and without metabolic activation), yeast assay for mitotic gene conversion (*Saccharomyces cerevisiae* strain JD1; 0.1 ml test substance added, with and without metabolic activation), and the rat-liver chromosome damage assay (RL₄ rat-liver cell line; tested up to 0.125 of the GI₅₀ [50% growth inhibition]).⁴⁹ Glyceryl allyl ether did not induce mutations in any of the bacterial strains tested, gene conversion in yeast (*S. cerevisiae*), or chromosome damage in RL₄ cells.

CARCINOGENICITY

Studies on the carcinogenicity of the alkyl glyceryl ethers reviewed in this safety assessment were not found in the published literature.

SUMMARY

The safety of the following ingredients in cosmetics is reviewed in this safety assessment: ethylhexylglycerin, caprylyl glyceryl ether, glyceryl capryl ether, chimyl alcohol, batyl alcohol, glyceryl allyl ether, glyceryl lauryl ether, isodecyl glyceryl ether, isostearyl glyceryl ether, and oleyl glyceryl ether. These ingredients function mostly as surfactants or skin conditioning agents in cosmetic products. Together, information supplied to FDA as part of the Voluntary Cosmetic Registration Program, reported in 2011 FDA database, and the results of Personal Care Products industry surveys conducted in 2010 and 2011 indicated use of the following ingredients in cosmetics: ethylhexylglycerin (0.000001% to 8%), chimyl alcohol (0.002% to 0.5%), glyceryl lauryl ether (7%), and isostearyl glyceryl ether (0.001% to 0.02%). The concentration of use survey for batyl alcohol is still underway.

Sensiva® SC 50, one of the trade names under which ethylhexylglycerin is being marketed contains > 99% ethylhexylglycerin.⁶ It also contains a small amount of α-tocopherol and the impurities, 2-ethylhexyl-glycidylether and water. Chimyl alcohol is approximately 98% pure and also contains approximately 2% batyl alcohol as an impurity.

Most of the (1-¹⁴C)-chimyl alcohol administered orally to rats was absorbed in 24 h (95% absorption), and the remainder was found in fecal lipids. Other results (rats) indicated that 8% of ¹⁴C-chimyl dioleate (esterified chimyl alcohol) administered orally was excreted as expired ¹⁴CO₂ in 24 h. Labeled chimyl alcohol was also detected in the lymph of rats dosed orally, and was also present in this form as well as in the form of its palmitic acid metabolite in intestinal mucosal cells. After dosing with free chimyl alcohol (rats, via stomach tube), alkoxydiglycerides resulted from the incorporation of free fatty acids into chimyl alcohol. At 8 h post-i.p. dosing of rats with α-1-¹⁴C-batyl alcohol, 24.5% of the injected dose was present in the liver lipids and 8% of the injected dose was found in the small intestine; 65% of the intestinal lipid label was present as free glyceryl ether. In another study involving rats, approximately 13% of the ¹⁴C from batyl alcohol was eliminated as ¹⁴CO₂ within 6 h post-injection and the urine contained 6.5% of the ¹⁴C from batyl alcohol.

Following oral administration of ¹⁴C-chimyl alcohol to human subjects, 95% of the labeled chimyl alcohol was absorbed, and approximately 40% of the dose was recovered in the urine within 12 h post-administration. Approximately half of the radioactivity in the lymph was identified as chimyl alcohol, and the remaining 50% had been converted to palmitic acid, found in triglycerides, phospholipids, and free fatty acids.

The i.p. dosing of rats with labeled α- and β-chimyl alcohols resulted in conversion to glyceryl ether phospholipids in the intestine. After i.v. dosing of rats with ¹⁴C-chimyl alcohol, approximately 28% of the ¹⁴C was eliminated as ¹⁴CO₂ within 6 h, and the urine contained 1%. Approximately 6 to 13% of the radioactivity was accounted for as lipid in the liver, and the remainder was associated with adipose tissue or transferred into a nonlipid metabolic pool. Similarly, 24% of ¹⁴C-chimyl alcohol injected i.v. was excreted as expired ¹⁴CO₂ in 24 h. After dosing with free chimyl alcohol (rats, via stomach tube), alkoxydiglycerides resulted from the incorporation of free fatty acids into chimyl alcohol. The incorporation of ³H-chimyl alcohol into brain lipids was apparent after intracerebral injection into rats.

In an acute toxicokinetic study *in vivo*, the mean absorption of ethylhexylglycerin through the skin of rabbits was 0.02% at approximately 2 h post-application and there were no signs of skin irritation. The quantity of ethylhexylglycerin in the plasma was below the detection limit at the end of the 4 h application period. Over a range of 3 concentrations (44.65, 47.15, and 54.94%) applied to human skin *in vitro*, mean penetration rates of 2.38, 8.19, and 20.38 $\mu\text{g}/\text{cm}^2/\text{h}$ were reported.

In an acute inhalation toxicity study using groups of rats exposed to ethylhexylglycerin (nose-only, mean achieved concentrations of 1.89, 2.96, and 4.98 mg/L), a concentration-related increase in mortality was observed. The lung was described as a target organ, based on rapid deaths, severe respiratory changes, and abnormal coloration and enlargement of the lungs.

No mortalities or exposure-related toxicological findings were observed in rats dosed orally with undiluted ethylhexylglycerin or chimyl alcohol. Subcutaneous administration of batyl alcohol to mice yielded an LD50 of > 8.8 mM/kg.

No mortalities or signs of skin irritation or abnormal necropsy findings were observed after undiluted ethylhexylglycerin was applied to the skin of rats. Necropsy findings were unremarkable and there were no treatment-related mortalities in rats dosed orally with ethylhexylglycerin at doses up to 1,500 mg/kg for 28 days. Increased liver and adrenal weights were observed in the highest dose group, and microscopic findings included slight to moderate liver hypertrophy in rats of all 3 dose groups. The 100 mg/kg dose was defined as the no-observed-adverse effect-level (NOAEL). Ethylhexylglycerin administered orally to rats, at doses up to 800 mg/kg/day, in a 13-week study did not result in any treatment-related deaths, macroscopic observations, or neurotoxicity. A statistically significant increase in absolute and relative-to-body weight liver weights was observed in males of all dose groups and females of the highest dose group. Generalized hepatocytic hypertrophy was observed at microscopic examination in the highest dose group, a finding that was statistically significant in males. Two summaries of this 13-week study were provided, and a dose of 50 mg/kg/day (lowest dose) was considered the lowest observed adverse effect level (LOAEL) in one summary and the NOAEL in the other summary. Batyl alcohol stimulated hematopoiesis (both red and white blood cells) in repeated dose studies involving rats and guinea pigs. In these studies, batyl alcohol (4 mg in arachis oil) was injected s.c. into guinea pigs for 5 days. Rats received 15 daily 50 mg doses of a 10% suspension of batyl alcohol in distilled water or 20 s.c. injections of 12.5 mg or 25.0 mg of batyl alcohol in peanut oil over a period of 4 weeks (5 days per week).

Undiluted ethylhexylglycerin was severely irritating, but 5% ethylhexylglycerin was mildly irritating, to the eyes of rabbits.

Undiluted ethylhexylglycerin was classified as a mild skin irritant in rabbits in one test and as a non-irritant in another test. Chimyl alcohol was classified as a mild skin irritant in rabbits after a single application, but was a non-irritating to the skin of rabbits in a cumulative skin irritation study. Skin sensitization was not observed in guinea pigs tested with 0.5% ethylhexylglycerin during induction and challenged with a higher concentration (50%) in the maximization test. Local lymph node assay results for ethylhexylglycerin at concentrations up to 50% were also negative. Products containing ethylhexylglycerin at concentrations ranging from 0.4% to ~1% were neither skin irritants nor sensitizers in RIPT's involving human subjects. Positive patch test results were reported for dermatitis patients patch tested with ethylhexylglycerin at concentrations up to 10%. However results were negative for control subjects.

Ethylhexylglycerin was not phototoxic or photoallergenic in guinea pigs when tested at concentrations up to 100% in the presence of UVA/UVB light. Chimyl alcohol suppressed the production of chemical mediators of UVB-irradiated keratinocytes *in vitro* and substantially suppressed UV-induced tanning in human skin. Based on these findings, a new concept for skin whitening via controlling keratinocyte function was proposed.

In a preliminary test, the results of visceral and skeletal examinations in litters of female rats given oral doses of ethylhexylglycerin (up to 800 mg/kg/day) were negative. None of the dosed animals died, and the no-observed-adverse-effect-level (NOAEL) for developmental toxicity was considered to be 800 mg/kg/day. In the one-generation developmental toxicity study (same doses) involving male and female rats, estrous cycles were comparable between groups, but the fertility index for rats of the highest dose group was lower when compared to controls. There were no treatment-related effects on implantation. Necropsy findings in dosed rats found dead or killed did not indicate any treatment-related changes. The no-observed-effect-level (NOEL) for developmental toxicity in both sexes was 50/mg/kg/day.

Ethylhexylglycerin was non-genotoxic in the Ames test (*Salmonella typhimurium* strains) and in the mouse lymphoma assay *in vitro*, both with and without metabolic activation. It was also non-clastogenic in the micronucleus assay *in vivo*. Chimyl alcohol was non-genotoxic (with and without metabolic activation) in the Ames test and in the chromosomal aberrations assay involving Chinese hamster lung cells. Batyl alcohol also was not genotoxic in the Ames test, with and without metabolic activation. Glyceryl Allyl Ether was non-genotoxic (with and without metabolic activation) in the Ames

test (*Salmonella typhimurium* and *E. coli* strains) and yeast assay for mitotic gene conversion (*Saccharomyces cerevisiae*). Results were also negative in the rat-liver chromosome damage assay (RL₄ rat-liver cell line). Studies on the carcinogenicity of the alkyl glyceryl ethers reviewed in this safety assessment were not found in the published literature.

DISCUSSION

The CIR Expert Panel considered the evidence of minimal percutaneous absorption of ethylhexylglycerin through rabbit skin *in vivo* and the relevance of such data to the entire group of ingredients. The Panel determined that the similar chemical structures of these alkyl glyceryl ethers and the similar ways in which they are used in cosmetics suggested that all of these ingredients would have minimal dermal penetration. Furthermore, a review of the available data on toxicity revealed: an absence of genotoxicity in studies using ethylhexylglycerin, chimyl alcohol, batyl alcohol, and glyceryl allyl ether; an absence of reproductive and developmental toxicity in oral studies using ethylhexylglycerin; negative skin irritation/sensitization data in studies using ethylhexylglycerin and chimyl alcohol; and negative phototoxicity/photoallergenicity data in studies using ethylhexylglycerin. Overall, the available toxicity data, coupled with the limited dermal penetration, suggested that these ingredients could be used safely in the present practices of use and concentration.

However, the Panel did note the skin penetration enhancement effect of isostearyl glyceryl ether, and emphasized that this should be taken into consideration when formulating cosmetic products that contain alkyl glyceryl ethers.

Because ethylhexylglycerin (up to 2%) can be used in cosmetics that may be sprayed, the Panel discussed the issue of incidental inhalation exposure. In the absence of sufficient inhalation data, the Panel considered that the available data from other routes of exposure that suggested an absence of genotoxicity, reproductive and developmental toxicity, dermal irritation and sensitization, and phototoxicity/photoallergenicity for this entire group of ingredients. The Panel noted that 95 – 99% of the droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

- | | |
|---------------------------------------|-----------------------------|
| • Ethylhexylglycerin | • Glyceryl Allyl Ether* |
| • Caprylyl Glyceryl Ether* | • Glyceryl Lauryl Ether |
| • Glyceryl Capryl Ether* | • Isodecyl Glyceryl Ether* |
| • Cetyl Glyceryl Ether/Chimyl Alcohol | • Isostearyl Glyceryl Ether |
| • Batyl Alcohol | • Oleyl Glyceryl Ether* |

Were ingredients in this group not in current use to be in the future (indicated by *), the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Table 1. Definitions, functions, and structures of alkyl glycerin ether ingredients in this safety assessment.¹

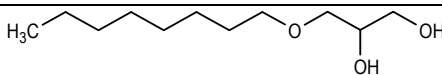
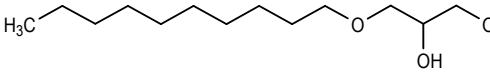
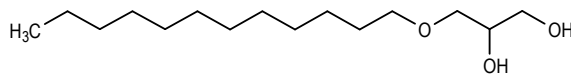
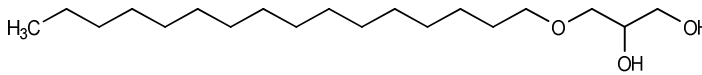
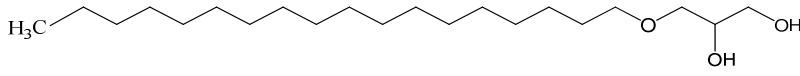
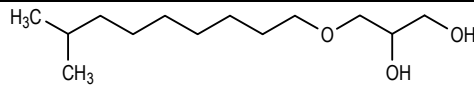
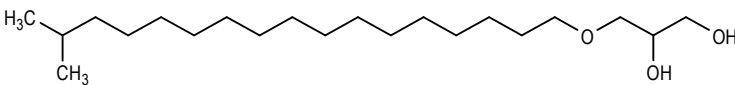
Ingredient CAS No.	Definition	Function(s)	Formula/structure
-Straight chain			
Caprylyl Glyceryl Ether 10438-94-5	Caprylyl Glyceryl Ether is the condensation product of octanol and glycerin.	Surfactants - Cleansing Agents; Surfactants - Foam Boosters	
Glyceryl Capryl Ether 10430-97-4 [current per CAS]	Glyceryl Capryl Ether is the condensation product of decanol and glycerin.	Surfactants - Cleansing Agents; Surfactants - Emulsifying Agents; Surfactants - Foam Boosters	
Glyceryl Lauryl Ether 1561-07-5 [current per CAS]	Glyceryl Lauryl Ether is the condensation product of dodecanol and glycerin.	Surfactants - Emulsifying Agents	
Chimyl Alcohol 506-03-6 [S isomer] 6145-69-3	Chimyl Alcohol is the condensation product of cetyl alcohol and glycerin. Chimyl Alcohol is synonymous with Cetyl Glyceryl Ether.	Skin-Conditioning Agents – Emollient	
Batyl Alcohol 544-62-7	Batyl Alcohol is the monooctadecyl ether of glycerin. Batyl alcohol is synonymous with 3-(Octadecyloxy)-1,2-Propanediol	Emulsion stabilizers; Skin-conditioning agents - occlusive	
-Branched			
Isodecyl Glyceryl Ether 84083-82-9 [current per CAS]	Isodecyl Glyceryl Ether is the condensation product of isodecanol and glycerin.	Surfactants - Foam Boosters	 one example of an “iso”
Isostearyl Glyceryl Ether 78145-84-3 [current per CAS]	Isostearyl Glyceryl Ether is the condensation product of isoostearyl alcohol and glycerin.	Skin-Conditioning Agents - Emollient	 one example of an “iso”

Table 1. Definitions, functions, and structures of alkyl glycerin ether ingredients in this safety assessment.¹

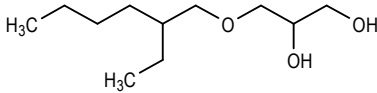
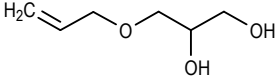
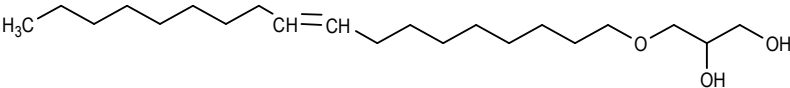
-Branched			
Ethylhexylglycerin 70445-33-9	Ethylhexylglycerin is the condensation product of 2-ethylhexanol and glycerin.	Deodorant Agents; Skin-Conditioning Agents – Miscellaneous	
-Unsaturated			
Glyceryl Allyl Ether 123-34-2 [current per CAS]	Glyceryl Allyl Ether is the condensation product of propenol and glycerin.	Skin-Conditioning Agents - Humectant	
Oleyl Glyceryl Ether [30524-89-1 per CAS]	Oleyl Glyceryl Ether is the condensation product of oleyl alcohol and glycerin.	Skin-Conditioning Agents - Emollient	

Table 2. Properties of Alkyl Glyceryl Ethers

Chemical	Molecular Weight	logP	Specific Gravity (SG)/Density (D)	Solubility	Boiling Point	Melting Point
Caprylyl Glyceryl Ether	204.31 ⁵⁰	2.6 +/- 0.5 ⁵⁰	0.9923 g/cm ³ (D) ⁵¹		135 to 136°C (@ 0.85 Torr) ⁵¹	68.5 to 69.5°C ⁵¹
Glyceryl Capryl Ether	232.36 ⁵⁰	3.6 +/- 0.5 ⁵⁰			361.7 +/- 22°C (@ 760 Torr) ⁵⁰	77 to 77.5°C ⁵²
Glyceryl Lauryl Ether	260.41 ⁵⁰	4.6 +/- 0.5 ⁵⁰	0.937 +/- 0.06 cm ³ (D) ⁵⁰		390.5 +/- 22.0°C (@ 760 Torr) ⁵⁰	62 to 63°C ⁵³
Chimyl Alcohol (S isomer, CAS No. 506-03-6)	316.52 ⁵⁰	6.7 +/- 0.5 ⁵⁰	0.920 +/- 0.06 g/cm ³ (D) ⁵⁰	Solubility in acetone, hexane, and chloroform ⁵⁴	445.2 +/- 25°C (@ 760 Torr) ⁵⁰	65 to 66°C ⁵⁵
Chimyl Alcohol (CAS No. 6145-69-3)	316.52 ⁵⁰	6.7 +/- 0.5 ⁵⁰	0.920 +/- 0.06 g/cm ³ (D) ⁵⁰		445.2 +/- 25°C (@ 760 Torr) ⁵⁰	64 to 66°C ⁵⁶
Batyl Alcohol (CAS No. 544-62-7)	344.57 ⁵⁰	7.7 +/- 0.5 ⁵⁰	0.914 +/- 0.06 g/cm ³ (D) ⁵⁰	Sparingly soluble in unbuffered water ⁵⁰	471.1 +/- 25°C (@ 760 Torr) ⁵⁰	68 to 69°C ⁵⁷
Ethylhexylglycerin	204.31 ⁵⁰	2.4 +/- 0.5 ⁵⁰	~0.95 g/cm ³ (D) ⁵⁰	limited solubility in water (≈ 0.1%); highly soluble in organic solvents, such as alcohols, glycols, and glycol ethers ⁹	145°C (@ 9 h Pa) ⁹	
Glyceryl Allyl Ether	132.16 ⁵⁰	- 0.1 +/- 0.5 ⁵⁰	1.0841 g/cm ³ (D) ⁵⁸		142°C (@ 28 Torr) ⁵⁹	-100°C to 90°C ⁵⁸

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2011¹⁰⁻¹³

	Ethylhexylglycerin		Chimyl Alcohol		Batyl Alcohol		Glyceryl Lauryl Ether	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type								
<i>Eye Area</i>	102	0.02 to 1	1	NR	26	0.5 to 1	NR	NR
<i>Incidental Ingestion</i>	23	0.08 to 0.5	NR	NR	6	0.5	NR	NR
<i>Incidental Inhalation-sprays</i>	114	0.01 to 2	NR	NR	1	NR	NR	NR
<i>Incidental Inhalation-powders</i>	11	0.2 to 0.5	NR	NR	NR	NR	NR	NR
<i>Dermal Contact</i>	952	0.000001 to 8	5	0.002 to 0.5	108	0.4 to 3	NR	NR
<i>Deodorant (underarm)</i>	89	0.04 to 2	NR	NR	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	63	0.0003 to 2	NR	NR	2	0.03 to 1	NR	NR
<i>Hair-Coloring</i>	NR	NR	NR	NR	NR	NR	44	7
<i>Nail</i>	3	0.1	NR	NR	NR	NR	NR	NR
<i>Mucous Membrane</i>	63	0.000001 to 0.5	NR	NR	6	0.5	NR	NR
<i>Baby Products</i>	7	NR	NR	NR	NR	NR	NR	NR
Duration of Use								
<i>Leave-On</i>	891	0.002 to 2	5	0.02 to 0.5	116	0.4 to 3	NR	NR
<i>Rinse off</i>	169	0.000001 to 8	NR	0.002	8	0.03 to 1	44	7
<i>Diluted for (bath) use</i>	6	0.1	NR	NR	NR	NR	NR	NR
Totals/Conc. Range	1066	0.000001 to 8	5	0.002 to 5	124	0.03 to 3	44	7
	Isostearyl Glyceryl Ether							
	# of Uses	Conc. (%)						
Exposure Type								
<i>Eye Area</i>	NR	NR						
<i>Incidental Ingestion</i>	NR	NR						
<i>Incidental Inhalation-sprays</i>	NR	NR						
<i>Incidental Inhalation-powders</i>	NR	NR						
<i>Dermal Contact</i>	5	0.001 to 0.02						
<i>Deodorant (underarm)</i>	NR	NR						
<i>Hair - Non-Coloring</i>	NR	NR						
<i>Hair-Coloring</i>	NR	NR						
<i>Nail</i>	NR	NR						
<i>Mucous Membrane</i>	1	NR						
<i>Baby products</i>	NR	NR						
Duration of Use								
<i>Leave-On</i>	4	0.01 to 0.02						
<i>Rinse off</i>	1	0.001						
<i>Diluted for (bath) use</i>	NR	NR						
Totals/Conc. Range	5	0.001 to 0.02						

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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5

Final Report on the Safety Assessment of Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol

Cetearyl, Cetyl, Isostearyl, Myristyl, and Behenyl Alcohols are long-chain aliphatic alcohols that are, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater. In acute dermal toxicity studies (rabbits), doses of up to 2.6 g/kg of Cetyl Alcohol and 2.0 g/kg of a product containing 0.8% Myristyl Alcohol were both practically nontoxic. Mild irritation was observed when a cream containing 3.0% Cetearyl Alcohol was applied to the skin of New Zealand albino rabbits. Cetyl Alcohol (50.0% in petrolatum) applied to abraded and intact skin of albino rabbits produced minimal to slight skin irritation. Cetyl Alcohol was considered to be practically nonirritating when instilled into the eyes of albino rabbits. An aerosol antiperspirant containing 3.0% Myristyl Alcohol induced mild to moderate irritation; a moisturizing lotion containing 0.8% Myristyl Alcohol was nonirritating to rabbit eyes. Corneal irritation was reported following an ocular test using a 5.0% Isostearyl Alcohol antiperspirant. Conjunctival irritation was observed 2 and 6 h after instillation of 1.0% Behenyl Alcohol. Isostearyl Alcohol (5.0% in propylene glycol) and an antiperspirant containing 5.0% Isostearyl Alcohol were not sensitizers in guinea pigs. Cetyl Alcohol was not mutagenic in *Salmonella typhimurium* LT2 mutant strains in the spot test. Clinical skin irritation and sensitization studies of product formulations containing up to 8.4% Cetyl Alcohol produced no evidence of irritation or sensitization. Moisturizing lotions containing 0.8% Myristyl Alcohol were nonirritating to human skin, and moisturizers containing 0.25% Myristyl Alcohol were neither irritants nor sensitizers. No signs of skin irritation or sensitization were observed in humans following the dermal application of 25% Isostearyl Alcohol. In a human skin sensitization study of a cream containing 3.0% Cetearyl Alcohol, none of the subjects had positive reactions. An analysis of the data and comparison with

data from other toxicity studies on long-chain aliphatic alcohols is presented. Based on the available data included in this report, it is concluded that Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol are safe as cosmetic ingredients in the present practices of use.

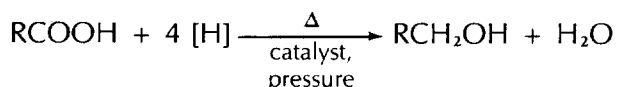
INTRODUCTION

The toxicity of long-chain aliphatic alcohols is reviewed in this report. In other toxicological reviews, the Cosmetic Ingredient Review Expert Panel has assessed the safety of related compounds: Stearyl Alcohol, Oleyl Alcohol, Octyl Dodecanol, Isopropyl Stearate, Isobutyl Stearate, Butyl Stearate, Octyl Stearate, Myristyl Stearate, Isocetyl Stearate, Cetyl Stearate, Isopropyl Palmitate, Octyl Palmitate, Cetyl Palmitate, Myristyl Lactate, Cetyl Lactate, Isopropyl Myristate, Myristyl Myristate, Cetearyl Octanoate, Isostearyl Neopentanoate, and Isostearic Acid.⁽¹⁻⁵⁾

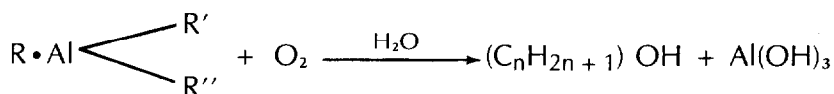
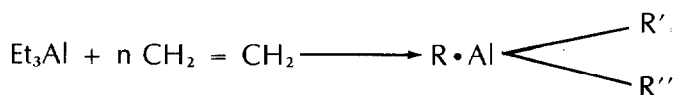
CHEMISTRY

Chemical and Physical Properties

Cetearyl, Cetyl, Myristyl, and Behenyl alcohols are straight-chain aliphatic alcohols. Isostearyl Alcohol is a branched-chain aliphatic alcohol. These long-chain aliphatic alcohols conform to the empirical formula, $C_nH_{2n+1}OH$, and have been produced via high-temperature, high-pressure, catalytic hydrogenation of fatty acids⁽⁶⁾:



A significant development since 1955 has been the manufacture of straight-chain primary alcohols by the Ziegler process⁽⁷⁾:



Branched-chain fatty alcohols may be produced by the Oxo process.⁽⁷⁾ This process involves the passage of olefin hydrocarbon vapors over cobalt catalysts

in the presence of carbon monoxide and hydrogen.⁽⁸⁾ Regardless of the method of production of the saturated fatty alcohols, they are sold either as high purity fractions or mixtures.⁽⁶⁾ Some of the physical and chemical properties of Cetearyl, Cetyl, Isostearyl, Myristyl, and Behenyl Alcohols are listed in Table 1.

Cetearyl Alcohol

Cetearyl Alcohol (CAS No. 8005-44-5) is a white, waxy solid, usually in flake form.⁽⁹⁾ It is a mixture of mostly cetyl (hexadecanol) and stearyl (octodecanol) alcohols.⁽¹⁰⁾ Cetearyl Alcohol is also known as cetostearyl alcohol and cetyl/stearyl alcohol.⁽¹⁰⁾ It is insoluble in water and soluble in alcohol and oils.⁽⁹⁾

Cetyl Alcohol

Cetyl Alcohol (CAS No. 36653-82-4) is a white, waxy solid in flake or powder form.⁽⁹⁾ It is a 16-carbon alcohol, known also as 1-hexadecanol and n-hexadecyl alcohol.⁽¹⁰⁾ Cetyl Alcohol is the oldest known of the long-chain alcohols, having been discovered by Chevreul in 1913. It is insoluble in water and soluble in alcohol and oils.⁽⁹⁾

Isostearyl Alcohol

Isostearyl Alcohol (CAS No. 27458-93-1 and 41744-75-6) is a clear water-white liquid, consisting essentially of a mixture of branched-chain, aliphatic 18-carbon alcohols.⁽¹³⁾ It is a primary alcohol having monomethyl branching randomly distributed along its C₁₇ straight chain.⁽⁶⁾ Isostearyl Alcohol is insoluble in water and miscible in most oils and waxes.⁽¹³⁾

Myristyl Alcohol

Myristyl Alcohol (CAS No. 112-72-1) or 1-tetradecanol is a white unctuous mixture of solid alcohols consisting chiefly of 14-carbon alcohols (n-tetradecanol); it is soluble in ether, slightly soluble in ethanol, and insoluble in water.⁽¹²⁾

Behenyl Alcohol

Behenyl Alcohol or n-docosanol (CAS No. 661-19-8) is a 22-carbon aliphatic alcohol. It is a colorless, waxy solid that is soluble in ethanol and chloroform and insoluble in water.⁽⁸⁾

Reactivity

No specific information concerning the chemical reactivity of long-chain aliphatic alcohols has been identified. However, it is believed that they are oxidized to their respective fatty acids.

Analytical Methods

Analytical methods that are used to detect and identify fatty alcohols include gas-liquid chromatography, liquid chromatography, thin-layer chromatography, gas chromatography, and mass spectrometry.⁽¹⁴⁻¹⁷⁾

TABLE 1. Properties of Long-Chain Aliphatic Alcohols

	Cetearyl Alcohol	Cetyl Alcohol	Isostearyl Alcohol	Myristyl Alcohol	Behenyl Alcohol
Formula	$\text{CH}_3(\text{CH}_2)_{15-17}\text{OH}^a$	$\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OH}^b$	$\text{C}_{18}\text{H}_{38}\text{O}^b$	$\text{CH}_3(\text{CH}_2)_{12}\text{CH}_2\text{OH}^b$	$\text{CH}_3(\text{CH}_2)_{20}\text{CH}_2\text{OH}^b$
Molecular weight		242.45 ^c	280 ^d	214.40 ^c	326.61 ^c
Form	White, waxy solid ^a	White, waxy solid ^a	Water-white liquid ^c	White solid ^e	Colorless, waxy solid ^f
Boiling point		344°C, bp ₁₅ 190°C ^c	bp _{0.7} 136–160°C ^d	263.2°C, bp ₁₅ 167°C ^c	bp _{0.22} 180°C ^c
Melting point	50–55°C ^a	50°C ^c	5°C ^d	39–40°C ^c	71°C ^c
Density		0.8176 ^c		0.8236 ^c	
Refractive index		1.4283 ^c	1.4615 at 20°C ^d		
Solubility	Alcohol, oils ^a	Alcohol, ether, ^c acetone, benzene	Oils, waxes ^e	Alcohol, ether, ^c acetone, benzene, chloroform	Alcohol, chloroform ^c
Acid value		0 ^g	1.0 maximum ^e		
Iodine value		3.0 maximum ^g	12.0 maximum ^e	1.0 maximum ^g	
Saponification value		1.0 maximum ^g	2.0 maximum ^e	1.0 maximum ^g	
Hydroxyl value		218–232 ^g	180–200 ^e	250–260 ^g	

^aRef. 9.^bRef. 10.^cRef. 11.^dRef. 6.^eRef. 13.^fRef. 8.^gRef. 12.

Impurities

Cetearyl Alcohol

Technical grade Cetearyl Alcohol contains approximately 65% to 80% stearyl and 20% to 35% cetyl alcohols.⁽¹⁸⁾ Though Cetearyl Alcohol consists mostly of cetyl and stearyl alcohols, small quantities of alcohols with longer and shorter chain lengths are usually present in this mixture.⁽⁹⁾ Additionally, the following impurities have been reported for Cetearyl Alcohol mixtures.⁽¹⁶⁾

Hydrocarbons (consisting principally of n-hexadecane and n-octadecane)	0.1–1.4%
Odd-numbered straight-chain alcohols	1–3.5%
Branched-chain primary alcohols	0.2–2%

Even-numbered straight-chain alcohols (C₈–C₂₂) comprise 90% to 95% of this mixture.⁽¹⁶⁾

Cetyl Alcohol

Cetyl Alcohol (National Formulary) contains a minimum of 90% Cetyl Alcohol.⁽⁹⁾ Cetyl Alcohol is generally believed to be 1-hexadecanol, but commercial grades often contain measurable amounts of stearyl alcohol and other long-chain aliphatic alcohols.⁽¹⁹⁾ The Cosmetic, Toiletry and Fragrance Association (CTFA) Specification for Cetyl Alcohol includes the following impurities⁽¹²⁾:

Hydrocarbons	1.5% maximum
Ash	0.05% maximum
Lead (as elemental lead)	20 ppm maximum
Arsenic (as elemental arsenic)	3 ppm maximum

Isostearyl Alcohol

Published data concerning impurities within Isostearyl Alcohol mixtures have not been identified.

Myristyl Alcohol

The CTFA Specification for Myristyl Alcohol includes the following impurities⁽¹²⁾:

Hydrocarbons	1.5% maximum
Ash	0.05% maximum
Lead (as elemental lead)	20 ppm maximum
Arsenic (as elemental arsenic)	3 ppm maximum

Behenyl Alcohol

Technical grade Behenyl Alcohol contains 99% Behenyl Alcohol.⁽⁸⁾ Published data concerning impurities within Behenyl Alcohol mixtures have not been identified.

USE

Purpose in Cosmetics

Long-chain aliphatic alcohols are widely used in skin lotions and creams; those most commonly used range from 12 to 18 carbons in length.⁽⁶⁾ In lotions, long-chain aliphatic alcohols serve as emollients, emulsion stabilizers, viscosity control agents, coupling agents, and foam stabilizers.⁽⁶⁾ Particularly, Cetyl Alcohol is used as an emollient to prevent drying and chapping of the skin because of its water-binding property.⁽²⁰⁾

The cosmetic product formulation listing that is made available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.⁽²¹⁾ Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration. See Table 2 for this list of cosmetic products containing long-chain aliphatic alcohols.

Surfaces to Which Applied

Cosmetic products containing long-chain aliphatic alcohols are applied to the skin, hair, nails, and vaginal mucosa and may come in contact with the eyes and nasal mucosa; small amounts of the ingredients may be ingested because of their presence in lipstick (Table 2).

Frequency and Duration of Application

Product formulations containing long-chain aliphatic alcohols may be applied once per week or as often as several times per day. Many of the products may be expected to remain in contact with the skin for as briefly as a few hours or as long as a few days. Each cosmetic product formulated with long-chain aliphatic alcohols may be used repeatedly over a period of many years (Table 2).

Noncosmetic Use

Long-chain aliphatic alcohols are used in pharmaceuticals as emulsifying and stiffening agents.⁽²²⁾ They occur in textile soaps as emulsifying agents and are components of synthetic fibers and lubricants.^(23,24) According to Section 172.864 of the Title 21 Code of Federal Regulations,⁽²⁵⁾ synthetic long-chain aliphatic alcohols may be used safely in food and in the synthesis of food compo-

nents. In keeping with this Section, Cetyl Alcohol must contain not less than 98% of total alcohols and not less than 94% of straight-chain alcohols; Myristyl Alcohol must contain not less than 99% of total alcohols and not less than 96% of straight chain alcohols.⁽²⁵⁾ Also, technical grade Cetearyl Alcohol, approximately 65% to 80% stearyl alcohol and 20% to 35% Cetyl Alcohol, is required for some indirect food additives.⁽¹⁸⁾

Of the ingredients reviewed in this report, Cetyl Alcohol is the only one listed in the 1984 FDA Over-The-Counter (OTC) Drug Review. The Miscellaneous External Drug Products Advisory Review Panel to the FDA lists Cetyl Alcohol as an ingredient of both external analgesics and skin protectants.⁽²⁶⁾ That panel has not issued a proposed or final ruling concerning the safety of Cetyl Alcohol in such compositions. However, before 1984, various advisory review panels to the FDA issued recommendations regarding the safety of Cetyl Alcohol; these recommendations appear in Table 3.⁽²⁷⁾

The uses of Cetearyl, Cetyl, and Myristyl Alcohols as direct and indirect food additives and any limitations existing for these ingredients are listed in Table 4.

BIOLOGICAL PROPERTIES

Antimicrobial Activity

The effect of Myristyl Alcohol on bacterial growth was assessed in *Streptococcus mutans* BHT.⁽³¹⁾ After a 4-h culture interval, the mean growth response in the presence of 12.4 mM Myristyl Alcohol was 45% of that in the untreated cultures. At the end of 6 h and throughout the remainder of the 24-h culture interval, the growth response to Myristyl Alcohol remained at 82–89% of that in untreated controls.

The inhibitory activity of Myristyl, Cetyl, and Behenyl Alcohols on the growth of *Mycoplasma gallisepticum* and *Mycoplasma pneumoniae* has been reported.⁽³²⁾ The proposed mechanism of action of these long-chain aliphatic alcohols is a change in cell membrane permeability that either blocks absorption of essential nutrients or causes the outward diffusion of vital cellular components. Growth was indicated by a decrease in pH and was monitored by the change in percent transmittance at 560 nm, using a spectrophotometer. The effect of treatment with long-chain aliphatic alcohols (64 μ M) on *Mycoplasma* growth for 6 days is as follows:

Alcohol	% Inhibition	
	<i>M. gallisepticum</i>	<i>M. pneumoniae</i>
Myristyl	0	20.7
Cetyl	97.9	90.8
Behenyl	0	44.9

Inhibition of Lipolysis

The inhibition of methyl oleate hydrolysis by pancreatic lipase has been demonstrated in a solution of rat pancreatic juice.⁽³³⁾ Approximately 15.8 μ moles of Cetyl Alcohol added to the reaction mixture (225 μ moles of methyl oleate/55 ml of pancreatic juice) caused 50% inhibition of hydrolysis.

TABLE 2. Product Formulation Data ⁽¹⁷⁰⁾

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			> 10-25	> 5-10	> 1-5	> 0.1-1
<i>Cetearyl Alcohol</i>						
Eye makeup remover	81	1	-	-	1	-
Mascara	397	1	-	-	1	-
Hair conditioners	478	6	-	1	4	1
Hair straighteners	64	3	-	3	-	-
Hair rinses (noncoloring)	158	1	-	-	-	1
Hair shampoos (noncoloring)	909	1	-	-	1	-
Makeup foundations	740	2	-	-	-	2
Rouges	211	1	-	-	-	1
Other makeup preparations (not eye)	530	1	-	-	1	-
Bath soaps and detergents	148	1	1	-	-	-
Other personal cleanliness products	227	1	-	1	-	-
Aftershave lotions	282	2	-	-	-	2
Shaving cream (aerosol, brushless, and lather)	114	4	-	-	1	3
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4	-	-	2	2
Face, body, and hand skin care preparations (excluding shaving preparations)	832	11	-	1	9	1
Moisturizing skin care preparations	747	7	1	1	3	2
Night skin care preparations	219	2	-	-	2	-
Paste masks (mud packs)	171	4	-	1	3	-
Other skin care preparations	349	3	1	-	2	-
1982 TOTALS		56	3	8	30	15

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			> 25-50	> 10-25	> 5-10	> 1-5	> 0.1-1	≤ 0.1
<i>Cetyl Alcohol</i>								
Baby lotions, oils, powders, and creams	56	12	-	-	-	8	4	-
Bath oils, tablets, and salts	237	8	-	-	-	4	2	2
Other bath preparations	132	4	-	-	-	2	2	-
Eyebrow pencil	145	6	-	-	-	6	-	-
Eyeliner	396	30	-	-	-	16	11	3
Eye shadow	2582	169	-	-	7	94	67	1
Eye lotion	13	1	-	-	-	-	1	-
Eye makeup remover	81	4	-	-	-	3	1	-
Mascara	397	8	-	-	-	5	3	-
Other eye makeup preparations	230	26	-	-	-	13	13	-
Colognes and toilet waters	1120	12	-	2	-	6	4	-
Perfumes	657	7	1	-	-	6	-	-
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	4	-	-	-	1	3	-
Sachets	119	59	4	-	9	20	26	-
Other fragrance preparations	191	26	-	-	1	10	14	1
Hair conditioners	478	163	-	3	10	104	37	9
Hair sprays (aerosol fixatives)	265	2	-	-	-	1	-	1
Hair straighteners	64	32	-	6	8	1	17	-
Permanent waves	474	3	-	-	-	-	2	1
Hair rinses (noncoloring)	158	52	-	-	-	20	29	3
Hair shampoos (noncoloring)	909	9	-	-	-	3	4	2
Tonics, dressings, and other hair grooming aids	290	17	-	-	2	5	8	2
Other hair preparations (noncoloring)	177	9	-	-	-	2	3	4
Hair dyes and colors (all types requiring caution statement and patch test)	811	1	-	-	-	-	1	-
Hair shampoos (coloring)	16	2	-	-	-	-	2	-
Hair bleaches	111	12	-	-	4	3	5	-
Other hair coloring preparations	49	5	-	2	-	2	1	-
Blushers (all types)	819	40	-	1	-	14	24	1
Face powders	555	24	-	-	-	10	14	-
Makeup foundations	740	68	-	-	1	12	53	2

TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1
Leg and body paints	4	3	—	—	—	—	3	—
Lipstick	3319	573	—	2	11	538	20	2
Makeup bases	831	134	—	—	1	23	108	2
Rouges	211	13	—	—	—	8	4	1
Makeup fixatives	22	2	—	—	—	—	1	1
Other makeup preparations (not eye)	530	11	—	—	—	5	6	—
Cuticle softeners	32	6	—	—	—	3	3	—
Nail creams and lotions	25	8	—	—	1	4	3	—
Other manicuring preparations	50	2	—	—	—	1	1	—
Bath soaps and detergents	148	1	—	—	1	—	—	—
Deodorants (underarm)	239	20	—	—	—	16	4	—
Feminine hygiene deodorants	21	1	—	—	—	—	1	—
Other personal cleanliness products	227	29	—	—	2	19	8	—
Aftershave lotions	282	11	—	—	—	3	6	2
Preshave lotions (all types)	29	1	—	—	—	—	1	—
Shaving cream (aerosol, brushless, and lather)	114	25	—	—	—	1	22	2
Other shaving preparation products	29	10	—	—	—	5	5	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	169	—	1	3	79	81	5
Depilatories	32	9	—	—	4	5	—	—
Face, body, and hand skin care preparations (excluding shaving preparations)	832	322	—	1	3	153	160	5
Foot powders and sprays	17	2	—	—	—	1	1	—
Hormone skin care preparations	10	3	—	—	1	1	1	—

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TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>1-5	>0.1-1	≤0.1
<i>Myristyl Alcohol</i>					
Hair conditioners	478	1	1	—	—
Hair shampoos (noncoloring)	909	1	—	1	—
Makeup foundations	740	1	1	—	—
Makeup bases	831	4	4	—	—
Cuticle softeners	32	1	1	—	—
Aftershave lotions	282	1	—	1	—
Beard softeners	4	2	2	—	—
Shaving cream (aerosol, brushless, and lather)	114	1	1	—	—
Other shaving preparation products	29	2	1	1	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	1	—	—	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	5	2	3	—
Moisturizing skin care preparations	747	8	3	5	—
Night skin care preparations	219	1	—	1	—
Paste masks (mud packs)	171	1	—	1	—
Other skin care preparations	349	1	1	—	—
1982 TOTALS		31	17	13	1

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>25-50	>10-25	>5-10
<i>Behenyl Alcohol</i>					
Eyebrow pencil	145	4	—	4	—
Eyeliner	396	18	3	14	1
Eye shadow	2582	9	2	7	—
Lipstick	3319	11	1	10	—
Other makeup preparations (not eye)	530	1	—	1	—
1982 TOTALS		43	6	36	1

Absorption, Metabolism, and Excretion

Summaries of various studies indicate that long-chain aliphatic alcohols are oxidized to their corresponding fatty acids in mammalian tissues.^(4,5) Much of the data concerning the absorption, metabolism, and excretion of long-chain aliphatic alcohols has been accumulated for Cetyl (C₁₆) and Stearyl (C₁₈) Alcohols. The Federation of American Societies for Experimental Biology (FASEB) has

TABLE 3. OTC Panel Recommendations for Cetyl Alcohol⁽²⁷⁾

<i>Advisory review panel</i>	<i>Date of action</i>	<i>Reference document</i>	<i>Recommended category^a</i>	<i>Final conditions</i>
Hemorrhoidal Drug Panel	3/9–10/74	OTC Panel (6th meeting)	I	Pharmaceutical necessity (stabilizant and emulsification aid) for use as an emulsifying aid based on hydrating properties; dispersant abilities and stabilizing properties for washable ointment base
Hemorrhoidal Drug Panel	5/12–14/74	OTC Panel (7th meeting)	III	Tentatively
Miscellaneous External Drug Products	8/3–4/79	OTC Panel (32nd meeting)	I	For safety as an active ingredient in concentrations of 8% or less
Miscellaneous External Drug Products	8/3–4/79	OTC Panel (32nd meeting)	I	For effectiveness for antimicrobial action
Miscellaneous External Drug Products	4/20–21/80	OTC Panel (38th meeting)	I	For safety in any concentration for topical application and for effectiveness in low concentration as a pharmaceutical aid; has no function as a "skin antiseptic"

^aCategory I: Conditions under which OTC drug products are generally recognized as safe and effective and are not misbranded. Category II: Conditions under which OTC drug products are not generally recognized as safe and effective or are misbranded. Category III: Conditions for which the available data are insufficient to permit final classification at this time as category I or II.

published an evaluation of stearyl alcohol.⁽³⁴⁾ That document contains a review of the literature, dating from 1933 to 1978, concerning the absorption, metabolism, and excretion of Stearyl Alcohol. Because Cetyl and Stearyl Alcohols have structural similarities, the FASEB literature review may be applicable to Cetyl Alcohol. The absorption, metabolism, and excretion of Cetyl Alcohol are discussed below.

In one study, tracer doses (0.2 mg of Cetyl Alcohol-1-¹⁴C) were dissolved in 0.5 ml of corn oil and administered by stomach tube to male Sprague-Dawley rats in which the thoracic duct had been cannulated; the rats were killed after 24 h.⁽³⁵⁾ Results from this study indicate that 75% of the absorbed radioactivity appeared in the thoracic duct lymph. Furthermore, 85% of the Cetyl Alcohol was converted during lymphatic absorption to saponifiable material, presumed to be palmitic acid. Similar findings were reported in an earlier study by Bloomstrand and Rumpf.⁽³⁶⁾ In that study, radioactively labeled Cetyl Alcohol was fed to rats (strain not identified) with thoracic duct fistulas. Most of the radioactivity

TABLE 4. Direct and Indirect Food Additives

<i>Ingredient</i>	<i>Noncosmetic use</i>	<i>Limitations</i>	<i>Reference</i>
Cetearyl Alcohol	Indirect food additives: Adhesives and components of coatings	—	18
Cetyl Alcohol	Direct food additives: Synthetic flavoring sub- stances and adjuvants	—	28
	Indirect food additives: Adhesives and components of coatings	—	18
	Indirect food additives: Surface lubricants used in the manufacture of metallic articles	—	29
Myristyl Alcohol	Indirect food additives: Adhesives and components of coatings	—	18
	Indirect food additives: defoaming agents used in the manufacture of paper and paperboard	—	30
Myristyl Alcohol (in primary al- cohol mixtures containing not more than 5% C ₁₁ -C ₁₅ alco- hols)	Indirect food additives: Surface lubricants used in the manufacture of metallic articles	For use at a level not to exceed 8% by weight of the finished lubricant for- mulation	29

(63–96%) appeared in the lymph, indicating good absorption. Approximately 15% of the alcohol was unchanged during its passage through the mucosal cells of the small intestine; most of the Cetyl Alcohol was oxidized to palmitic acid and incorporated into triglycerides and phospholipids. Consequently, the extent of fatty acid absorption may depend on the animal species. For example, Yoshida et al.⁽³⁷⁾ reported that alcohols containing more than 14 carbon atoms were poorly used in poultry because of their low absorbability. The value reported for the absorption of Cetyl Alcohol was 26%.

Cetyl Alcohol has been isolated from sterile feces of infants and in sterile experimental intestinal loops of dogs.⁽³⁸⁾ The presence of Cetyl Alcohol in the feces may result from the conversion of fatty acids to corresponding long-chain aliphatic alcohols, which enter the intestinal lumen. Bandi and Mangold⁽³⁹⁾ demonstrated the interconvertibility of fatty acids and alcohols by the rat. Cetyl Alcohol was detected in the feces of rats whose dietary lipids contained palmitic

acid (C_{16}). It has been concluded that the conversion of fatty acids to long-chain aliphatic alcohols occurs during their passage through the intestinal mucosal cells.⁽³⁶⁾ Cetyl Alcohol was also excreted in the urine as conjugated glucuronic acid and as expired carbon dioxide.⁽⁴⁰⁾

ANIMAL TOXICOLOGY

Inhalation Toxicity

Cetyl Alcohol

A study involving a single 6-h exposure of groups of 10 mice, rats, and guinea pigs to Cetyl Alcohol vapors (26 ppm) under dynamic conditions, followed by a 24-h holding period, was reported⁽⁴¹⁾ (Table 5). Necropsies were performed on the animals at the end of the holding period. Local irritation due to the alcohol vapor was slight and involved the mucous membranes of the eyes, nose, throat, and respiratory passages. There were no signs of systemic toxicity, and no deaths were reported. In a second inhalation study,⁽⁴¹⁾ a group of 10 rats and 10 guinea pigs was exposed to Cetyl Alcohol vapor (10-min exposures of 9.6 mg/L) every 30 min for a period of 4 h (Table 5). A comparable control group was exposed to room air for the same period. Half of the animals were killed immediately after the exposures, and the rest were killed after a 14-day holding period. The lungs of some of the exposed animals had lesions indicative of chronic respiratory disease (rats) and interstitial or bronchial pneumonia (guinea pigs). The incidence and severity of these changes were comparable to such observations in the control group. No effects related to Cetyl Alcohol exposure were noted. Alternatively, the inhalation of 2220 mg/m³ of synthetic Cetyl Alcohol for 6 h has resulted in the death of all exposed rats⁽⁴⁰⁾ (Table 5).

Myristyl Alcohol

Ten young adult Albino rats of the Sprague-Dawley Strain (average weight, 250 g) were exposed to an aerosol containing 3.0% Myristyl Alcohol. Exposures were conducted in a 0.038 m³ glass chamber and comprised 20 10-sec aerosol bursts (one burst every 3 min) during a 1-h period. Approximately 7.4 g of the test substance were delivered with each burst, and the average test substance concentration was approximately 192 mg/L of air. Following 10 min of exposure, ataxia and moderate nasal irritation were noted in all animals and persisted throughout the remainder of the exposure period. These reactions were also noted in all animals up to 4 h after their removal from the chamber. No deaths were reported⁽⁴²⁾ (Table 5).

Acute Oral Toxicity

According to Egan and Portwood,⁽⁶⁾ long-chain aliphatic alcohols are non-toxic when administered orally, as defined by the Federal Hazardous Substances Labeling Act (FHS�A). The results from oral toxicological studies of long-chain aliphatic alcohols are indicated below.

Cetyl Alcohol

In a study by Scala and Burtis,⁽⁴¹⁾ Cetyl Alcohol was administered via stomach tube as a corn oil suspension to groups of 5 fasted Sprague-Dawley rats (No. of groups not stated) (Table 6). Observations for signs of toxicity were made for a period of 7–14 days postadministration. The LD₅₀ was not achieved at a dose of 8.2 g/kg, the highest dose administered. The principal effects noted were central nervous system depression and labored respiration.

Ten fasted rats of the Harlan Wistar strain (weight range, 110–135 g) each received an oral dose (13,000 mg/kg) of a formulation containing 4.0% Cetyl Alcohol. The animals were observed for signs of toxicity during a 7-day period. No deaths were reported, and there were no signs of toxicity during the observation period⁽⁴³⁾ (Table 6). In another study, the protocol outlined in Title 16 Part 1500.3 (6)(6)(i)(A) of the Code of Federal Regulations was used to assess the acute oral toxicity of a lipstick product containing 4.0% Cetyl Alcohol. A group of 10 or more laboratory white rats, each weighing between 200 and 300 g, were given a single dose of 50 mg/kg of the product via oral intubation. An LD₅₀ of 5.0 g/kg was reported⁽⁴⁴⁾ (Table 6).

The acute oral toxicity of a lotion containing 3.25% Cetyl Alcohol was investigated using 10 fasted rats of the Wistar strain. The animals were approximately 6 to 9 weeks old and weighed between 200 and 300 g. Doses were administered via intragastric feeding, and observations for signs of toxicity were made at 1, 3, 6, and 24 h postadministration and at least once daily thereafter for a total of 14 days. Necropsies were performed at the end of the 14-day period. The product induced toxicity at a dose of 5 g/kg if 50% or more of the animals died. One rat died at this dose and had fibrous tissue encasing the heart and lungs at necropsy. No other gross changes were reported⁽⁴⁵⁾ (Table 6). No deaths were reported in a similar study (same protocol) in which 10 fasted Wistar rats received 5 g/kg of the same product. The only gross changes reported (1 animal) were a consolidated right lung and a fluid-filled fibrous tissue sac encasing the heart and lungs⁽⁴⁶⁾ (Table 6). In another study (same protocol), 1 of the 10 rats receiving 5 g/kg of the product died (day 13 of observation period) and had fibrous tissue encasing the heart and lungs. Identical gross changes were noted in another animal.⁽⁵⁴⁾ Gross changes were not observed in another study (same protocol) in which 5 g/kg of the product were administered to 10 albino rats of the Wistar strain.⁽⁵⁵⁾

An oral dose (7 ml/kg) of a formulation containing 2.0% Cetyl Alcohol was administered to each of 10 fasted rats of the Harlan Wistar strain. No signs of toxicity were noted during a 7-day period postadministration⁽⁴⁷⁾ (Table 6). In another study, 10 rats (same strain) received a single dose of 33 ml/kg of a product containing 2.0% Cetyl Alcohol. The only effects noted during the 7-day observation period were transient appearances of poor grooming⁽⁴⁸⁾ (Table 6). Identical results were reported in another study in which 10 fasted rats of the Fischer 344 strain (weight range, 115–170 g) each received an oral dose (10 ml/kg) of a moisturizer containing 2.0% Cetyl Alcohol⁽⁴⁹⁾ (Table 6).

Myristyl Alcohol

The acute oral toxicity of Myristyl Alcohol was assessed in Holtzman albino

TABLE 5. Acute Inhalation Toxicity

<i>Ingredient</i>	<i>Alcohol concentration and vehicle</i>	<i>No. of animals</i>	<i>Procedure</i>	<i>Results</i>	<i>Reference</i>
Cetyl Alcohol	26 ppm vapor	10 mice, 10 rats, 10 guinea pigs	Single 6-h exposure	Local irritation of eyes, nose, throat, and respiratory passages	41
Cetyl Alcohol	9.6 mg/L of vapor	10 rats, 10 guinea pigs	8 10-min exposures over 4 h	No exposure-related effects	41
Cetyl Alcohol	2220 mg/m ³ of vapor	Rats (no. not stated)	Single 6-h exposure	Death of all animals	40
Myristyl Alcohol	3.0% in aerosol (192 mg/L)	10 rats	20 10-sec bursts over 1 h	Ataxia and moderate nasal irritation (all animals)	42

TABLE 6. Acute Oral Toxicity

<i>Ingredient</i>	<i>Alcohol concentration and vehicle</i>	<i>No. of animals</i>	<i>Procedure</i>	<i>Results</i>	<i>Reference</i>
Cetyl Alcohol	Corn oil suspension (concentration not stated)	Groups of 5 rats (no. not stated)	Intragastric feeding	LD ₅₀ > 8.2 g/kg	41
Cetyl Alcohol	4.0% in formulation	10 rats	Single oral dose	LD ₅₀ > 13.0 g/kg	43
Cetyl Alcohol	4.0% in lipstick	10 rats	Single oral dose	LD ₅₀ = 5.0 g/kg	44
Cetyl Alcohol	3.25% in lotion	10 rats	Single oral dose	LD ₅₀ > 5.0 g/kg	45
Cetyl Alcohol	3.25% in lotion	10 rats	Intragastric feeding	LD ₅₀ > 5.0 g/kg	46
Cetyl Alcohol	2.0% in formulation	10 rats	Single oral dose	LD ₅₀ > 7.0 ml/kg	47
Cetyl Alcohol	2.0% in formulation	10 rats	Single oral dose	LD ₅₀ > 33.0 ml/kg	48
Cetyl Alcohol	2.0% in moisturizer	10 rats	Single oral dose	LD ₅₀ > 10.0 ml/kg	49
Myristyl Alcohol	100%	Rats (no. not stated)	Single oral dose	LD ₅₀ > 8.0 g/kg	6
Myristyl Alcohol	0.8% in moisturizing lotion	10 rats	Single oral dose	LD ₅₀ > 5.0 g/kg	50
Isostearyl Alcohol	100%	Rats (no. not stated)	Single oral dose	LD ₅₀ > 20.0 g/kg	6
Isostearyl Alcohol	27.0% in lipstick	5 rats	Single oral dose	LD ₅₀ > 15.0 g/kg	51
Isostearyl Alcohol	25.0% in lipstick	5 rats	Single oral dose	LD ₅₀ > 15.0 g/kg	52
Behenyl Alcohol	Olive oil (concentration not stated)	10 mice	Intragastric feeding	LD ₅₀ < 1.0 g/kg	53

rats. The number of animals involved in the study was not stated. The LD₅₀ was not achieved at a dose of 8.0 g/kg⁽⁶⁾ (Table 6).

The Protocol stated in Title 16 Part 1500.3 (b)(6)(i)(A) of the Code of Federal Regulations was used to assess the acute oral toxicity of a moisturizing lotion containing 0.8% Myristyl Alcohol. A group of 10 or more laboratory white rats, each weighing between 200 and 300 g, was used in the study. The LD₅₀ was not achieved at a dose of 5.0 g/kg⁽⁵⁰⁾ (Table 6).

Isostearyl Alcohol

The acute oral toxicity of Isostearyl Alcohol was assessed in adult Sprague-Dawley rats. The number of animals involved in the study was not stated. The LD₅₀ was not achieved at a dose of 2.0 g/kg⁽⁶⁾ (Table 6).

The acute oral toxicity of a lipstick product containing 27.0% Isostearyl Alcohol was determined using 5 female albino rats (ages not stated). Each animal was given 15.0 g/kg of the product via stomach tube. All animals appeared normal throughout the study, and no gross lesions were found at necropsy on day 7 postadministration⁽⁵¹⁾ (Table 6).

The acute oral toxicity of another lipstick product containing 25.0% Isostearyl Alcohol was evaluated in 5 female albino rats (ages not stated) according to the protocol stated immediately above. All animals appeared clinically normal throughout the study, and no gross lesions were found at necropsy⁽⁵²⁾ (Table 6). Identical results were reported in another study (same protocol) involving a different lipstick product containing 25.0% Isostearyl Alcohol.⁽⁵⁶⁾

Behenyl Alcohol

The acute oral toxicity of Behenyl Alcohol was evaluated using 10 adult mice of the CF₁ strain (average weight, 25 g). The test substance was diluted with olive oil, heated, and administered (dose, 1.0 g/kg) via stomach tube. None of the animals died during the 8-day observation period. The LD₅₀ was not achieved at the administered dosage⁽⁵³⁾ (Table 6).

Acute Dermal Toxicity

Cetyl Alcohol

Cetyl Alcohol was applied full-strength to the clipped intact abdominal skin of 16 albino rabbits. The animals were divided equally into four treatment groups: 0.10, 0.316, 1.00, and 3.16 ml/kg doses. Each exposed area was covered with an occlusive binding of dental damming that remained in place for 24 h. Observations for signs of toxicity were made for a total of 7 days postapplication. The LD₅₀ was reported to be greater than 2.6 g/kg. One of the four animals in the 3.16 ml/kg group had decreased activity and labored respiration⁽⁴¹⁾ (Table 7).

The procedures outlined in Title 16 Parts 1500.3(c)(1)(ii)(c) and 1500.40 of the Code of Federal Regulations were used to assess the acute dermal toxicity of a lipstick product containing 4.0% Cetyl Alcohol.⁽⁵⁷⁾ The test substance was

TABLE 7. Acute Dermal Toxicity

<i>Ingredient</i>	<i>Alcohol concentration and vehicle</i>	<i>No. of rabbits</i>	<i>Procedure</i>	<i>Results</i>	<i>Reference</i>
Cetyl Alcohol	100%	16	Applied to abdominal skin	LD ₅₀ > 2.6 g/kg	41
Cetyl Alcohol	4.0% in lipstick	5	24-h skin application	LD ₅₀ > 2.0 g/kg	58
Myristyl Alcohol	0.8% in moisturizing lotion	5	24-h skin application	LD ₅₀ > 2.0 g/kg	59

held in contact with either clipped skin (5 rabbits) or clipped abraded skin (5 rabbits) by means of an "impervious sleeve" and removed after 24 h. An LD₅₀ of >2.0 g/kg was reported⁽⁵⁸⁾ (Table 7).

Myristyl Alcohol

The acute dermal toxicity of a moisturizing lotion containing 0.8% Myristyl Alcohol was evaluated in 5 rabbits according to the protocol stated immediately above. An LD₅₀ of >2.0 g/kg was reported⁽⁵⁹⁾ (Table 7).

Subchronic Dermal Toxicity

Cetyl Alcohol

Five-tenths milliliter of a heated Cetyl Alcohol mixture (30% Cetyl Alcohol in methyl alcohol and propylene glycol) was massaged into a 10 × 10 cm depilated area on the right flanks of five 6-month-old female albino rabbits. The animals were treated daily for 30 days. Punch biopsies of the treated areas were taken, and tissues were examined histologically. Microscopic alterations (after 10 days) were infiltrates of lymphomononuclear cells and histiocytes in superficial portions of the dermis⁽⁶⁰⁾ (Table 8).

An oil-in-water cream base containing 11.5% Cetyl Alcohol was applied (concentration, 400 mg/kg) to a 5 cm diameter area of clipped skin in the lumbar region of the backs of 20 New Zealand white rabbits (2.5–3 kg). The animals were divided into groups of 4 and treated five times daily for 20 days. At necropsy, tissue specimens of skin were fixed in 10% neutral formalin and stained with hematoxylin and eosin. The following gross observations were made of the alterations in skin at treated sites:

1. By the second full day of treatment, erythema was seen in all treated groups.
2. On the third day, transverse wrinkling and an apparent thickening of the treated area were observed.
3. On the fourth day, cracking or fissuring along the wrinkle or fold lines was apparent.

The principal histological changes seen in the skin consisted of acanthosis, para-

TABLE 8. Subchronic Dermal Toxicity

<i>Ingredient</i>	<i>Alcohol concentration and vehicle</i>	<i>No. of rabbits</i>	<i>Procedure</i>	<i>Results</i>	<i>Reference</i>
Cetyl Alcohol	30.0% in methyl alcohol and propylene glycol	5	Applied to depilated skin during 30-day period	No substantial macroscopic changes, dermal infiltration with histiocytes	60
Cetyl Alcohol	11.5% in cream base	20	Applied to dorsal clipped skin during 20-day period	Erythema, parakeratosis, hyperkeratosis, papillary projections of epidermis	61
Cetyl Alcohol	11.5% in cream base	48	Applied to shaved and abraded dorsal skin	Exfoliative dermatitis	62
Cetyl Alcohol	2.0% in moisturizer	20	Applied to skin during 3-month period	Mild inflammation at application site	63

keratosis, hyperkeratosis, and papillary projections of the epidermis, all of which are features of exfoliative dermatitis. Intracellular and intercellular edema were prominent in the basal layer of the stratum germinativum of some of the papillary projections⁽⁶¹⁾ (Table 8).

In another study, 400 mg/kg of a cream base containing 11.5% Cetyl Alcohol was applied to a 5 cm diameter area in the lumbar region of the backs of 48 New Zealand rabbits (average weight, 2.5 kg). The animals were divided into two groups of 24 each. In one group, the backs were shaved and abraded. In the other group, the backs were shaved only. Subgroups of 4 rabbits with abraded or intact skin were treated five times daily for 20 days. At the end of the study, the animals were necropsied, and tissues were examined histologically. Hemograms were also obtained. Terminal hemogram and necropsy findings were negative for systemic effects, but rabbits of both groups (abraded skin and intact skin) developed exfoliative dermatitis within 2 to 3 days of treatment⁽⁶²⁾ (Table 8).

A 3-month dermal toxicity study of a moisturizer containing 2.0% Cetyl Alcohol was conducted with two groups of New Zealand white rabbits (5 males, 5 females/group) ranging in age from 12 to 16 weeks. Doses of 5.5 and 8.8 mg/cm² were applied daily to the clipped dorsal skin of animals in groups 1 and 2, respectively. Applications were made to 8.4% of the body surface area. All animals survived the 3-month test period, except 1 that was killed because of a severe head tilt caused by otitis media. The treatment-related changes were mild inflammation at the application site. Hematological and clinical chemistry values were within the normal range. The authors concluded that there was no evidence of systemic toxicity that would contraindicate use of the moisturizer⁽⁶³⁾ (Table 8).

Skin Irritation

Cetearyl Alcohol

A skin irritation study of a cream containing 3.0% Cetearyl Alcohol was conducted with 6 New Zealand albino rabbits (3 males, 3 females) weighing from 3.5–4.2 kg. The product was applied to intact and abraded skin of each animal during 5 consecutive days. After each application, an occlusive dressing was placed over the test site and removed after an 8-h period. Sites were graded for signs of irritation at 8 and 24 h postapplication. Mean erythema scores for intact skin ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.67 at 24 h postapplication. For abraded skin, mean erythema scores ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.50 at 24 h. It was concluded that the cream was mildly irritating to the skin⁽⁶⁴⁾ (Table 9).

Cetyl Alcohol

The skin irritation potential of Cetyl Alcohol was evaluated in 9 female albino rabbits. One-tenth milliliter of the test substance was applied at a concentration of 50.0% in petrolatum to the dorsal shaved skin of each animal via an occlusive dressing. Patches remained for 24 h, and reactions were graded at 24 and 72 h postapplication. The test substance produced minimal to slight irritation⁽⁶⁵⁾ (Table 9). Identical results were reported in a similar study.⁽⁶⁶⁾

The skin irritation potential of a cream containing 4.0% Cetyl Alcohol was evaluated in 6 New Zealand albino rabbits (male and female). The backs of 3 animals were shaved, and the backs of the remaining 3 were shaved and abraded. Five-tenths milliliter of the cream was then applied, and the sites were rinsed with water 1 h after treatment. Observations for signs of skin irritation and systemic toxicity were conducted during a 7-day period after application. Slight to well-defined erythema was observed in all animals 24–48 h after the first application, and slight edema was observed in 3 animals within 2–3 days. Irritation persisted in 5 animals for the remainder of the test period. Slight desquamation developed in all animals within 4–7 days. The irritation index was 1.4 out of a maximum possible score of 8⁽⁶⁷⁾ (Table 9).

In another study, the skin irritation potential of a lipstick product containing 4.0% Cetyl Alcohol was evaluated according to the methods stated in Title 16 parts 1500.3(c)(4) and 1500.41 of the Code of Federal Regulations. The product (0.5 g) was administered to both abraded and intact clipped skin of albino rabbits (a minimum of six) via a surgical gauze patch. Patches remained for 24 h, after which reactions were evaluated. Subsequent evaluations occurred 48 h later. The lipstick was nonirritating to abraded and intact skin⁽⁶⁸⁾ (Table 9).

Five-tenths milliliter of a conditioner containing 3.25% Cetyl Alcohol (pH 5.7) was applied to abraded and intact clipped skin (two test sites per animal) of each of 6 New Zealand white rabbits (weight, approximately 2 kg; age, 3 months). Each site was covered for 1 h with an occlusive dressing, and grading for signs of irritation occurred at 1, 24, and 72 h postapplication according to the Draize (1975) scale for skin irritation. Reactions of very slight erythema and edema (5 animals) predominated in abraded and intact skin during the observation period. The primary irritation index was 0.90. A primary irritation index of

TABLE 9. Skin Irritation

Ingredient	Alcohol concentration and vehicle	No. of rabbits	Procedure	Results	Reference
Cetearyl Alcohol	3.0% in cream	6	8-h occlusive dressings applied during 5-day period	Mild irritation	64
Cetyl Alcohol	100%	9	24-h occlusive dressing	Minimal to slight irritation	65
Cetyl Alcohol	4.0% in cream	6	Applied to shaved and abraded dorsal skin	Slight to well-defined erythema and slight desquamation	67
Cetyl Alcohol	4.0% in lipstick	6	24-h surgical gauze patch	No irritation	68
Cetyl Alcohol	3.25% in conditioner	6	1-h occlusive dressing	Very slight erythema and edema predominated (5 animals)	69
Cetyl Alcohol	2.0% in formulation	3	Applied to skin once daily for 4 days	Slight erythema (2 animals); well-defined erythema (1 animal)	70
Cetyl Alcohol	2.0% in cream	3	Applied to skin once daily for 4 days	Well-defined erythema and mild edema	71
Myristyl Alcohol	0.8% in moisturizing lotion	6	24-h surgical gauze patch	No irritation	72
Isostearyl Alcohol	27.0% in lipstick	9	24-h occlusive dressing	Barely perceptible erythema predominated	73
Isostearyl Alcohol	25.0% in lipstick	9	24-h occlusive dressing	Barely perceptible erythema predominated	74
Isostearyl Alcohol	5.0% in antiperspirant	6	24-h occlusive dressing	Mild irritation	75

5.0 or more would have identified the product as a primary dermal irritant⁽⁶⁹⁾ (Table 9). In three other studies (same protocol) of different skin conditioners containing 3.25% Cetyl Alcohol, primary irritation indexes of 0.15, 0.95, and 1.25 were reported, respectively.⁽⁷⁶⁻⁷⁸⁾

A skin irritation study of a formulation containing 2.0% Cetyl Alcohol was conducted with 3 albino rats. Five-tenths milliliter of the formulation was applied to the shaved back of each animal once daily for 4 days. Slight erythema developed within 24 h after the first application and persisted throughout the 7-day observation period. In 1 animal, erythema became well defined, and slight edema was observed. Mild desquamation was noted on day 7. The irritation index was 1.6⁽⁷¹⁾ (Table 9).

In another study, the skin irritation potential of a cream containing 2.0% Cetyl Alcohol was evaluated in 3 albino rabbits during a 7-day study. The product (0.5 ml) was applied to the shaved dorsal skin of each animal for a total of four daily applications. Well-defined erythema and mild edema persisted throughout the study. The irritation index was 2.9⁽⁷²⁾ (Table 9).

Myristyl Alcohol

The protocol outlined in Title 16 Parts 1500.3(c)(4) and 1500.41 of the Code of Federal Regulations was used to assess the primary irritation potential of a moisturizing lotion containing 0.8% Myristyl Alcohol. The product (0.5 ml) was applied to abraded and intact clipped skin of albino rabbits (a minimum of 6) via a surgical gauze patch. Patches remained for 24 h, after which reactions were evaluated. Subsequent evaluations occurred 48 h later. The product did not induce irritation in either abraded or intact skin⁽⁷²⁾ (Table 9).

Isostearyl Alcohol

The skin irritation potential of a lipstick product containing 25.0% Isostearyl Alcohol was evaluated in 9 female albino rabbits. One-tenth milliliter of the product was applied to the dorsal shaved skin of each animal by means of an occlusive dressing that remained for 24 h. Reactions were evaluated 24 and 72 h after application. The following results were reported: barely perceptible erythema (7 animals), mild erythema (1 animal), and no erythema (1 animal). The primary irritation index was 0.50.⁽⁷⁴⁾ Results from another study (same protocol) of a lipstick product containing 25.0% Isostearyl Alcohol were as follows: barely perceptible erythema (6 animals) and mild erythema (3 animals)⁽⁷⁹⁾ (Table 9). In a similar study involving a lipstick product containing 27.0% Isostearyl Alcohol (same protocol), the following results were reported: barely perceptible erythema (7 animals), mild erythema (1 animal), and no erythema (1 animal)⁽⁷³⁾ (Table 9).

A skin irritation study of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was conducted with 6 New Zealand white rabbits (3 males, 3 females) according to the method of Draize.⁽⁸⁰⁾ Five-tenths milliliter of the product was applied to each animal by means of an occlusive dressing. Patches remained for 24 h, and reactions were scored 24 and 72 h after application. It was concluded that the product was mildly irritating to the skin⁽⁷⁵⁾ (Table 9).

Mucous Membrane Irritation

Cetyl Alcohol

One-tenth milliliter of a formulation containing 2.0% Cetyl Alcohol was applied topically to the genital mucosa of each of 6 albino rabbits. There were no signs of irritation during the 7-day study.⁽⁸¹⁾

Ocular Irritation

Cetearyl Alcohol

The ocular irritation potential of a cream containing 3.0% Cetearyl Alcohol was assessed in 9 albino rabbits. One-tenth milliliter of the product was instilled into one eye of each animal. The eyes of 3 animals were rinsed 30 sec after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days postinstillation. The product was classified as a nonirritant⁽⁸²⁾ (Table 10).

Cetyl Alcohol

The ocular irritation potential of Cetyl Alcohol (100.0%) was evaluated in 6 New Zealand albino rabbits (male and female) according to a modification of the procedure by Draize.⁽⁸⁰⁾ One-tenth milliliter of the test substance was instilled into one eye of each animal. Ocular irritation was scored according to the Draize scale (0–110) at 1, 2, 3, 4, and 7 days postinstillation. An average score of 1 was reported on day 1, and signs of irritation had cleared by day 2. The test material was practically nonirritating⁽⁸³⁾ (Table 10). In a similar study of Cetyl Alcohol, an average score of 1 was reported at day 1 postinstillation, and signs of ocular irritation had cleared by day 3. The test substance was either minimally irritating or nonirritating.⁽⁸⁴⁾ Similar results were reported in another study of 100.0% Cetyl Alcohol involving 6 rabbits.⁽⁴¹⁾

In another ocular irritation study, 0.1 ml of a moisturizing cream containing 6.36% Cetyl Alcohol was instilled into the eyes of 9 albino rabbits according to the procedure of Draize.⁽⁸⁰⁾ The 9 animals comprised three treatment groups: eyes rinsed 10 sec postinstillation (3 animals), eyes rinsed 20 sec postinstillation (3 animals), eyes not rinsed (3 animals). Ocular irritation was scored at 1, 2, 3, 4, and 7 days postinstillation according to the Draize⁽⁸⁰⁾ scale. There were no observations of ocular irritation⁽⁸⁵⁾ (Table 10).

The ocular irritation potential of a cream containing 5.0% Cetyl Alcohol was evaluated in 9 New Zealand white rabbits (male and female). One hundred milligrams of the product were instilled into one eye of each animal. The eyes of 3 animals were rinsed 30 sec after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days postinstillation on a scale of 0–110. Five of the six animals not subjected to ocular rinsing first had ocular irritation at day 1 postinstillation, and one animal had ocular irritation at day 2. Signs of irritation had cleared by day 3. The 3 animals subjected to ocular rinsing first had ocular irritation at day 1. Signs of irritation had cleared by day 2 in 2 animals and by day 4 in 1 animal. A score of 2 was the maximum reported for any animal during the study. The product was classified as a nonirritant⁽⁸⁶⁾ (Table 10).

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TABLE 10. Ocular irritation

Ingredient	Alcohol concentration and vehicle	No. of rabbits	Procedure	Results	Reference
Cetearyl Alcohol	3.0% in cream	9	Instilled into one eye; eyes rinsed (3 animals)	No irritation	82
Cetyl Alcohol	100%	6	Instilled into one eye	Practically no irritation	83
Cetyl Alcohol	6.36% in moisturizing cream	9	Instilled into one eye; eyes rinsed (6 animals)	No irritation	85
Cetyl Alcohol	5.0% in cream	9	Instilled into one eye; eyes rinsed (3 animals)	No irritation	86
Cetyl Alcohol	5.0% in facial makeup product	6	Instilled into one eye; eyes rinsed (3 animals)	No irritation	87
Cetyl Alcohol	4.0% in cream	6	Instilled into one eye	Transient conjunctivitis	88
Cetyl Alcohol	4.0% in formulation	6	Instilled into one eye	No irritation	89
Cetyl Alcohol	3.25% in conditioner	9	Instilled into one eye; all eyes rinsed	No irritation	90
Cetyl Alcohol	3.25% in conditioner	9	Instilled into one eye; all eyes rinsed	No irritation	91
Cetyl Alcohol	2.85% in cleansing cream	9	Instilled into one eye; eyes rinsed (6 animals)	No irritation	92
Cetyl Alcohol	2.7% in night cream	9	Instilled into one eye; eyes rinsed (6 animals)	No irritation	93
Cetyl Alcohol	2.0% in formulation	6	Instilled into one eye	Transient conjunctival redness	94
Cetyl Alcohol	2.0% in moisturizer	6	Instilled into one eye	Transient conjunctival hyperemia	95
Cetyl Alcohol	2.0% in moisturizer	6	Instilled into one eye	Transient conjunctival hyperemia	95
Myristyl Alcohol	3.0% in antiperspirant	9	Instilled into one eye; eyes rinsed (6 animals)	Mild irritation (rinsed eyes); moderate irritation (unrinsed eyes)	96
Myristyl Alcohol	0.8% in moisturizing lotion	6	Instilled into one eye	No irritation	97
Isostearyl Alcohol	27.0% in lipstick	6	Instilled into one eye	Mild irritation	98
Isostearyl Alcohol	25.0% in lipstick	6	Instilled into one eye	Minimal irritation	99
Isostearyl Alcohol	25.0% in lipstick	6	Instilled into one eye	Minimal irritation	100
Isostearyl Alcohol	10.0% in antiperspirant	5	Sprayed into one eye	Transient corneal, conjunctival, and iridial irritation	101
Isostearyl Alcohol	5.0% in antiperspirant	6	Instilled into one eye	Transient iridial and conjunctival irritation, persistent corneal irritation	102
Behenyl Alcohol	1.0% in oil	5	Instilled into one eye	Transient conjunctival irritation	53

In another study, 0.1 g of a facial makeup product containing 5.0% Cetyl Alcohol was instilled into the eyes of 6 female rabbits of the New Zealand strain. Three animals were subjected to ocular rinsing 4 sec after instillation. Ocular reactions were scored according to the scale by Draize.⁽⁸⁰⁾ The product was classified as a nonirritant⁽⁸⁷⁾ (Table 10).

A cream containing 4.0% Cetyl Alcohol was evaluated for its ocular irritation potential in 6 New Zealand albino rabbits (3 males, 3 females). One-tenth milliliter of the product was instilled into one eye of each animal. Signs of ocular irritation were scored at 1 h and days 1, 2, 3, and 7 postinstillation. Slight conjunctivitis was observed in all animals at day 1 postinstillation and cleared within 1 to 3 days. There were no signs of corneal irritation or iritis⁽⁸⁸⁾ (Table 10). In another study, the ocular irritation potential of a lipstick product containing 4.0% Cetyl Alcohol was determined according to the procedures outlined in Title 16 Parts 1500.3(c)(4) and 1500.42 of the Code of Federal Regulations. One-tenth milliliter of the product was instilled into one eye of each of 6 albino rabbits. The grading of keratitis, iritis, and conjunctival redness occurred at 1, 2, and 3 days after instillation. Positive reactions were not noted, and it was concluded that the product was nonirritating under the conditions of testing⁽⁸⁹⁾ (Table 10).

One-tenth milliliter of a conditioner containing 3.25% Cetyl Alcohol was instilled into one eye of each of 9 New Zealand white rabbits. The eyes of 6 and 3 animals were rinsed 24 h and 15 sec after instillation, respectively. Signs of ocular irritation were scored at 1, 2, 3, 4, and 7 days postinstillation according to the scale by Draize⁽⁸⁰⁾ (0–110). For the 6 animals subjected to a 24-h rinsing, mean irritation scores of 5.7, 1.7, 1.7, and 0.7 were recorded on days 1, 2, 3, and 4, respectively. A mean score of 0.7 was reported on days 1, 2, and 3 postinstillation for the 3 animals subjected to a 15-sec rinsing⁽⁹⁰⁾ (Table 10). Similar results were reported in an identical study involving another conditioner containing 3.25% Cetyl Alcohol.⁽¹⁰³⁾ The protocol previously mentioned was used in two other studies, each involving a different conditioner (pH 5.7) containing 3.25% Cetyl Alcohol. In one of the studies, mean irritation scores (6 animals) of 13.7, 3.7, 2.3, 2.0, and 0.7 were reported on days 1, 2, 3, 4, and 7, respectively (24-h rinse group). Mean irritation scores (3 animals) of 4.0, 1.3, 0.7, 0.7, and 0.7 were also reported on days 1, 2, 3, 4, and 7, respectively (15-sec rinse group)⁽⁹¹⁾ (Table 10). Results from the second study were as follows: mean scores (6 animals) of 12.0, 4.7, 2.3, and 1.3 on days 1, 2, 3, and 4, respectively (24-h rinse group) and mean scores (3 animals) of 3.3 and 0.7 on days 1 and 2, respectively.⁽¹⁰⁴⁾

One-tenth milliliter of a cleansing cream containing 2.85% Cetyl Alcohol was instilled into the eyes of 9 albino rabbits according to the procedure of Draize.⁽⁸⁰⁾ The 9 animals comprised three treatment groups: eyes rinsed 10 sec postinstillation (3 animals), eyes rinsed 20 sec postinstillation (3 animals), eyes not rinsed (3 animals). Ocular irritation was scored at 1, 2, 3, 4, and 7 days postinstillation according to the Draize⁽⁸⁰⁾ scale. There were no observations of ocular irritation⁽⁹²⁾ (Table 10). In another study, the ocular irritation potential of a night cream containing 2.7% Cetyl Alcohol was evaluated in 9 albino rabbits according to the protocol previously mentioned. There were no signs of ocular irritation⁽⁹³⁾ (Table 10).

The ocular irritation potential of a formulation containing 2.0% Cetyl Alco-

hol was evaluated in 6 albino rabbits. one-tenth milliliter of the product was instilled into one eye of each animal. Observations for signs of irritation occurred over a period of 7 days. Slight conjunctival redness was observed 1 h after treatment (number of animals not stated) and cleared after 24 h. Signs of irritation were not observed in the cornea and iris⁽⁹⁴⁾ (Table 10). Another product (cream) containing 2.0% Cetyl Alcohol was evaluated according to the protocol previously mentioned. Slight conjunctivitis was observed within 1 h postinstillation (number of animals not stated) and cleared by 24 h. Signs of irritation were not observed in the cornea and iris.⁽¹⁰⁵⁾ In two other studies, a moisturizer containing 2.0% Cetyl Alcohol was evaluated for its ocular irritation potential. One-tenth milliliter of the product was instilled into one eye of each of 6 New Zealand albino rabbits in the first study. Ocular reactions were scored at 1 h and days 1, 2, 3, and 7 postinstillation. Slight conjunctival hyperemia was observed within 1 h after instillation in 3 animals and had cleared by 3 days. In the second study, one-tenth milliliter of the product was instilled into the eyes of six New Zealand albino rabbits daily for a period of 14 days. Slight conjunctival hyperemia was observed intermittently during the first week of treatment. Signs of irritation were not observed in the cornea and iris⁽⁹⁶⁾ (Table 10).

Myristyl Alcohol

One-tenth milliliter of an aerosol antiperspirant containing 3.0% Myristyl Alcohol was instilled into one eye of each of 9 albino rabbits. The 9 animals comprised three treatment groups: eyes rinsed 2 sec postinstillation (3 animals), eyes rinsed 4 sec postinstillation (3 animals), eyes not rinsed (3 animals). Ocular irritation was scored according to the scale by Draize⁽⁸⁰⁾ (0–110) at 1 h and 1, 2, 3, 4, and 7 days after instillation. An average irritation score of 19.7 (2-sec rinse group) was reported at 1 h postinstillation, and signs of irritation had cleared by day 4. In the 4-sec rinse group, an average score of 21.3 was reported at 1 h postinstillation, and signs of irritation had also cleared by day 4. An average irritation score of 42.3 was reported at 1 h postinstillation for animals not subjected to ocular rinsing; signs of irritation had cleared by day 7. It was concluded that the product was mildly irritating to eyes that were rinsed and moderately irritating to eyes that were not rinsed⁽⁹⁶⁾ (Table 10).

The ocular irritation potential of a moisturizing lotion containing 0.8% Myristyl Alcohol was determined according to the procedures outlined in Title 16 Parts 1500.3(c)(4) and 1500.42 of the Code of Federal Regulations. One-tenth milliliter of the product was instilled into one eye of each of 6 albino rabbits. The scoring of ocular reactions occurred 1, 2, and 3 days after instillation. Positive reactions were not observed, and it was concluded that the product was nonirritating⁽⁹⁷⁾ (Table 10).

Isostearyl Alcohol

One-tenth milliliter of a lipstick product containing 27.0% Isostearyl Alcohol was instilled into the eyes of 6 New Zealand albino rabbits (male and female).

Signs of ocular irritation were scored at 1, 2, 3, 4, and 7 days postinstillation according to the scale by Draize⁽⁸⁰⁾ (0–110). An average irritation score of 5 was reported on day 1, and all signs of irritation had cleared by day 4. The product was considered to be a mild eye irritant⁽⁹⁸⁾ (Table 10). In two similar studies (same protocol), one-tenth milliliter of two different lipstick products containing 25.0% Isostearyl Alcohol was instilled into the eyes of 6 New Zealand albino rabbits. On day 1 postinstillation, average scores of 2 and 1 (Draize scale, 0–110) were reported in the two studies, respectively. Signs of irritation had cleared by day 3. The products were considered to be minimally irritating to the eye^(99,100) (Table 10).

The ocular irritation potential of a pump spray antiperspirant containing 10.0% Isostearyl Alcohol was evaluated in 5 adult New Zealand albino rabbits (male and female). The aerosol was sprayed into one eye of each animal at a distance of 6 inches (1-sec exposure). Gross signs of ocular irritation were scored at 1 h and 1, 2, 3, 4, and 7 days postinstillation according to the scale by Draize⁽⁸⁰⁾ (0–110). The following reactions were observed at 1 h postinstillation: corneal irritation (1 animal; score, 5), conjunctival irritation (5 animals; score range 10–12), iridial irritation (4 animals; scores, 5). All reactions had cleared by day 4 postinstillation⁽¹⁰¹⁾ (Table 10). In a similar study, 0.1 ml of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was instilled into the eyes of 6 albino rabbits (male and female). Reactions were scored at 1 h and 1, 2, 3, 7, and 14 days postinstillation according to the scale by Draize.⁽⁸⁰⁾ Corneal irritation was first observed at day 1 postinstillation (average score, 6.7) and persisted to day 14 (average score, 2.5). Iridial irritation was observed at 1 h postinstillation (average score, 0.8) and cleared 23 h later. Conjunctival irritation was also observed at 1 h postinstillation and cleared by day 14. It was concluded that the product induced moderate ocular irritation⁽¹⁰²⁾ (Table 10).

Behenyl Alcohol

The ocular irritation potential of Behenyl Alcohol was evaluated using 5 adult New Zealand rabbits. A 1% dilution of the test substance in oil was heated and instilled (50 μ l) into the right eye of each animal. The left eye served as the control. Conjunctival irritation was scored at 2, 6, 24, and 48 h postinstillation according to the scale by Draize⁽⁸⁰⁾ (0–20). Mean conjunctival irritation scores (5 animals) at 2 and 6 h postinstillation were 18 and 10, respectively. There were no signs of conjunctival irritation at 24 and 48 h. Irritation was not observed in the cornea or iris⁽⁵³⁾ (Table 10).

Skin Sensitization

Isostearyl Alcohol

The sensitization potential of Isostearyl Alcohol was evaluated according to the Magnusson-Kligman maximization procedure⁽¹⁰⁶⁾ using albino guinea pigs

of the Hartley strain (300–350 g). The procedure was divided into four phases: (1) induction phase, (2) dose range phase, (3) booster phase, and (4) challenge phase. During induction, 0.05 ml of 5.0% Isostearyl Alcohol in propylene glycol (site 1) and 5.0% Isostearyl Alcohol in 50.0% aqueous Freund's complete adjuvant (site 2) were applied intradermally to the upper back of each of 20 animals. Occlusive patches were then placed over the shaved sites 1 week later and removed after 48 h. In the dose range phase, 5, 10, 25, and 100% concentrations of the test substances were applied to the shaved flanks of 50 extra guinea pigs to determine the subirritating concentration to be used during the challenge phase and a slightly irritating concentration for use in one booster phase. Ten percent aqueous sodium lauryl sulfate was applied to induction sites of the 20 animals (initial study group) before application of test substance boosters because significant irritation was not observed during the dose range phase. The booster phase was initiated 1 week after induction. Occlusive pads containing 100.0% Isostearyl Alcohol were placed over the induction site and removed after 48 h. The challenge phase began 2 weeks after the end of the booster phase. Five percent Isostearyl Alcohol in petrolatum (0.5 ml) was applied via an occlusive patch to a new site on the flank of each animal. Patches remained for 24 h, and sites were scored for erythema at 24 and 48 h after removal according to the scale: 1 (weak) to 5 (extreme). Isostearyl Alcohol did not have any discernible potential for allergic skin sensitization⁽¹⁰⁷⁾ (Table 11). The same conclusion was stated in a similar study (same protocol).⁽¹⁰⁸⁾

A pump spray antiperspirant containing 5.0% Isostearyl Alcohol was tested at a concentration of 4.0% in ethanol (effective Isostearyl Alcohol concentration, 0.2%) in a sensitization study involving 10 adult albino guinea pigs (weight, approximately 300 g). A semiocclusive coverlet containing 0.1 ml of the test substance was applied to two sites, one shaved and the other shaved and abraded, on the back of each animal. Patches were removed after 5 h. Each animal was given a total of nine doses (one dose/day). The challenge phase was initiated 2 weeks after the last induction exposure. Abraded and intact sites were scored for signs of irritation at 24 and 48 h postapplication. The product did not induce sensitization in any of the animals⁽¹⁰⁹⁾ (Table 11).

TABLE 11. Skin Sensitization

<i>Ingredient</i>	<i>Alcohol concentration and vehicle</i>	<i>No. of animals</i>	<i>Procedure</i>	<i>Results</i>	<i>Reference</i>
Isostearyl Alcohol	5.0% in propylene glycol	20 guinea pigs	48-h induction patches; 24-h challenge	No sensitization	107
Isostearyl Alcohol	5.0% in Freund's complete adjuvant	20 guinea pigs	48-h induction patches; 24-h challenge	No sensitization	107
Isostearyl Alcohol	0.2% in ethanol	10 guinea pigs	5-h induction patches; 24-h challenge	No sensitization	109

Mutagenicity

Mutagenicity tests for Cetyl Alcohol were conducted with five mutant strains of *Salmonella typhimurium* LT2. These mutant strains were selected because of their ability to revert to prototrophy in the presence of a broad spectrum of mutagens and their sensitivity to mutagens. Spot tests were performed according to the methods described by Ames et al.⁽¹¹⁰⁾ Results indicate that Cetyl Alcohol was not mutagenic to any of the strains in the presence or absence of metabolic activation.⁽¹¹¹⁾

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

Cetyl Alcohol

The skin irritation potential of Cetyl Alcohol (100.0%) was evaluated in 20 subjects (18–65 years old). One-tenth milliliter of the test substance was applied via an occlusive patch to the volar surface of the forearm of each subject; each patch remained for 24 or 48 h. Skin reactions were scored 2 and 24 h after patch removal according to the scale 0.5 (barely perceptible irritation) to 4.0 (severe irritation). No erythematous reactions were elicited by the test substance⁽¹¹²⁾ (Table 12). The same finding was reported in a similar study of Cetyl Alcohol⁽¹¹³⁾ (Table 12).

A topical tolerance study involving an 11.5% Cetyl Alcohol cream base was conducted with 80 male subjects, ranging in age from 21 to 52 years and in weight from 120 to 220 pounds⁽⁶²⁾ (Table 12). The 80 subjects were assigned at random to eight treatment groups of 10 each. The cream base was applied (gentle rubbing) to the left forearm (700 mg/202 cm² area) in four groups and to the left lower facial region (250 mg/70 cm² area), including the left side of the lips, in the other four groups. The preparations were applied five times daily (every 3 hours) for 10 days. One subject had erythema, folliculitis, and pustule formation (forearm site).

A formulation containing 6.0% Cetyl Alcohol was tested for its skin irritation potential in 20 subjects according to the protocol stated above. The product did not induce skin irritation⁽¹¹⁴⁾ (Table 12). In another study, the skin irritation potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 12 female subjects (≤ 18 – ≥ 60 years old). An occlusive patch containing 0.3 ml of the product was applied to the back of each subject. Patches were removed 23 h after application, and sites were bathed immediately. Reactions were scored 1 h after patch removal. The product was applied to the same test site for 21 consecutive days. The grading scale for cumulative irritation ranged from 0 to 630 (primary irritation). The total irritation score (all panelists) for the 21 applications was 418, indicating mild cumulative irritation⁽¹¹⁵⁾ (Table 12).

The skin irritation potential of a cream containing 5.0% Cetyl Alcohol was evaluated in 9 female subjects (30–65 years old). A closed patch containing the

product (amount sufficient to cover patch) was applied to the back of each subject. Patches were removed 23 h after application, and sites were bathed immediately. Reactions were scored 1 h after patch removal. The product was applied to the same site for 21 consecutive days. The grading scale for cumulative irritation ranged from 0 to 630 (primary irritation). The total irritation score (9 subjects) was 1, interpreted as no evidence of cumulative irritation. The product was classified as a mild material⁽¹¹⁶⁾ (Table 12). In another study (same protocol), 0.2–0.3 ml of a cream containing 4.0% Cetyl Alcohol was applied to 12 male and female subjects (10–>60 years old) via semioclusive patches. The total irritation score (12 subjects) was 211, and the product was classified as a slight irritant⁽¹¹⁷⁾ (Table 12).

A lipstick product containing 4.0% Cetyl Alcohol was applied to the face and lips of 52 subjects over a period of 4 weeks. The detailed experimental procedure was not stated. Reactions were graded according to the scale by Wilkinson et al.⁽¹⁶¹⁾: 1 (weak nonvesicular reaction) to 3 (bullous or ulcerative reaction). None of the subjects had signs of skin irritation⁽¹¹⁸⁾ (Table 12).

The irritation potential of a hair conditioner containing 3.25% Cetyl Alcohol was evaluated in 75 female subjects (15–30 years old) during a 30-day home use study. Subjects were instructed to shampoo and condition their hair daily. Scalp irritation was evaluated by a dermatologist before the beginning of the study and after 2 and 4 weeks of product use according to the scale 0 to 4 (erythema and excoriations). There were no significant irritation reactions that were attributed to 4 weeks of use of the conditioner⁽¹¹⁹⁾ (Table 12). In another study, two conditioners containing 3.25% Cetyl Alcohol were applied to the back of each of 15 adult subjects (21–65 years old). Each patch (0.2 ml of product) was removed after 24 h, and sites were then scored according to the scale 0 to 4 (intense erythema, edema, and vesicles). Fresh applications were then made to the same sites, and scoring occurred 24 h after patch removal. Patches applied on Friday were removed on the following Monday. This procedure was repeated for a total of 21 days. A cumulative score of less than 90 was interpreted as an insignificant level of irritation. Cumulative scores ranging from 91 to 180 were interpreted as very mild irritation. A cumulative (21 days) irritation score of 95 was reported for one of the products and 80 for the other⁽¹²⁰⁾ (Table 12).

In three separate studies, three different products containing 2.0% Cetyl Alcohol were tested according to the protocol stated immediately above. In one of the studies, 0.3 ml of a lotion was applied to 9 subjects (18–>60 years old) via closed patches. The total irritation score (9 subjects) was 9, interpreted as essentially no evidence of cumulative irritation. The product was classified as a mild material⁽¹²¹⁾ (Table 12). In the second study, approximately 0.2 ml of a cream was applied to 11 female subjects (18–59 years old) via closed patches. The total irritation score was 105, indicating that the product was slightly irritating⁽¹²²⁾ (Table 12). In the third study, 0.2 ml of a cream was applied to 11 male and female subjects (18–>60 years old) via closed patches. A total irritation score of 55 was reported, indicating evidence of a slight potential for very mild cumulative irritation⁽¹²³⁾ (Table 12).

TABLE 12. Clinical Assessment of Safety

Type of study	Ingredient	Alcohol concentration and vehicle	No. of subjects	Procedure	Results	Reference
Skin irritation	Cetyl Alcohol	100%	20	24-48 h occlusive patch test	No irritation	112
Skin irritation	Cetyl Alcohol	100%	20	24-48 h occlusive patch test	No irritation	113
Skin irritation	Cetyl Alcohol	11.5% in cream base	80	10-day cumulative irritation test	Erythema, folliculitis, pustules (1 subject)	62
Skin irritation	Cetyl Alcohol	6.0% in formulation	20	24-48 h occlusive patch test	No irritation	114
Skin irritation	Cetyl Alcohol	6.0% in cream	12	21-day cumulative irritation test	Potential for mild cumulative irritation	115
Skin irritation	Cetyl Alcohol	5.0% in cream	9	21-day cumulative irritation test	No cumulative irritation	116
Skin irritation	Cetyl Alcohol	4.0% in cream	12	21-day cumulative irritation test	Slight irritation	117
Skin irritation	Cetyl Alcohol	4.0% in lipstick	52	4-week application period	No irritation	118
Skin irritation	Cetyl Alcohol	3.25% in hair conditioner	75	30-day home use test	No significant irritation	119
Skin irritation	Cetyl Alcohol	3.25% in conditioner	15	24-h patch test	Mild irritation	120
Skin irritation	Cetyl Alcohol	3.25% in conditioner	15	21-day cumulative irritation test	No significant irritation	120
Skin irritation	Cetyl Alcohol	2.0% in lotion	9	21-day cumulative irritation test	No cumulative irritation	121
Skin irritation	Cetyl Alcohol	2.0% in cream	11	21-day cumulative irritation test	Slight irritation	122
Skin irritation	Cetyl Alcohol	2.0% in cream	11	21-day cumulative irritation test	Potential for mild cumulative irritation	123
Skin irritation	Myristyl Alcohol	0.8% in moisturizing lotion	53	4-week application period	No irritation	124
Skin irritation	Myristyl Alcohol	0.25% in moisturizing lotion	51	1-month home use test	No irritation	125
Skin irritation	Isostearyl Alcohol	100%	20	24-48 h application	No irritation	126
Skin irritation	Isostearyl Alcohol	28.0% in lipstick	20	24-48 h application	No irritation	127

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Skin irritation	Isostearyl Alcohol	27.0% in lipstick	19	24-48 h application	No irritation	128
Skin irritation	Isostearyl Alcohol	25.0% in lipstick	19	24-48 h application	No irritation	129
Skin irritation	Isostearyl Alcohol	5.0% in antiperspirant	11	21-day cumulative irritation test	Severe irritation	130
Skin irritation and sensitization	Cetyl Alcohol	8.4% in formulation	110	10 48-h induction patches; 1 48-h challenge	No irritation or sensitization	131
Skin irritation and sensitization	Cetyl Alcohol	6.36% in moisturizing cream	229	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	132
Skin irritation and sensitization	Cetyl Alcohol	6.0% in cream	52	9 24-h induction patches; 1 48-h challenge	Barely perceptible to mild erythema during induction (33 subjects); no sensitization	133
Skin irritation and sensitization	Cetyl Alcohol	4.0% in lipstick	103	24-h induction patch; 24-h challenge	No irritation or sensitization	134
Skin irritation and sensitization	Cetyl Alcohol	4.0% in skin cleanser	200	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	135
Skin irritation and sensitization	Cetyl Alcohol	4.0% in skin cleanser	200	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	136
Skin irritation and sensitization	Cetyl Alcohol	3.3% in lipstick	78	9 24-h induction patches; 1 24-h challenge	Mild erythema during induction (2 subjects); no sensitization	137
Skin irritation and sensitization	Cetyl Alcohol	3.25% in conditioner	53	10 48- to 72-h induction patches; 1 48-h challenge	Erythema during induction (6 subjects); no sensitization	138
Skin irritation and sensitization	Cetyl Alcohol	3.0% in hand cream	116	9 24-h induction patches; 1 24-h challenge	Mild to moderate erythema during induction (1 subject); no sensitization	139
Skin irritation and sensitization	Cetyl Alcohol	2.85% in cleansing cream	204	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	165
Skin irritation and sensitization	Cetyl Alcohol	2.7% in night cream	208	10 24-h induction patches; 2 48-h challenges	Mild to intense erythema during induction (1 subject); no sensitization	140

TABLE 12. (Continued)

Type of study	Ingredient	Alcohol concentration and vehicle	No. of subjects	Procedure	Results	Reference
Skin irritation and sensitization	Cetyl Alcohol	2.0% in moisturizer	239	10 24-h induction patches; 1 48-h challenge	No irritation or sensitization	166
Skin irritation and sensitization	Cetyl Alcohol	2.0% in formulation	210	10 24-h induction patches; 1 48-h challenge	No strong irritation or sensitization	142
Skin irritation and sensitization	Cetyl Alcohol	2.0% in cream	205	10 24-h induction patches; 1 48-h challenge	No strong irritation or sensitization	143
Skin irritation and sensitization	Cetyl Alcohol	2.0% in skin cream	90	9 24-h induction patches; 1 24-h challenge	Barely perceptible to mild erythema during induction (68 subjects); no sensitization	144
Skin irritation and sensitization	Cetyl Alcohol	1.0% in skin care preparation	804	24-h induction patch; 24-h challenge	Strong edematous reaction during induction (1 subject); no sensitization	145
Skin irritation and sensitization	Cetyl Alcohol	1.0% in skin care preparation	407	10 24-h induction patches; 1 48-h challenge	No irritation or sensitization	145
Skin irritation and sensitization	Myristyl Alcohol	0.25% in moisturizing lotion	229	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	146
Skin irritation and sensitization	Myristyl Alcohol	0.10% in moisturizing lotion	106	24-h induction patch; 24-h challenge	No irritation or sensitization	147
Skin irritation and sensitization	Myristyl Alcohol	0.10% in moisturizing lotion	52	10 24-h induction patches; 1 48-h challenge	No irritation or sensitization	147
Skin irritation and sensitization	Isostearyl Alcohol	25.0% in 95.0% isopropyl alcohol	12	9 24-h induction patches; 1 24-h challenge	Slight erythema during induction (3 subjects); no sensitization	148
Skin sensitization	Cetearyl Alcohol	3.0% in cream	25	5 48-h induction patches; 1 48-h challenge	No sensitization	149

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Skin sensitization	Cetyl Alcohol	30.0% in white petrolatum	330	Method of Fregert et al., 1969	No sensitization	150
Skin sensitization	Cetyl Alcohol	5.0% in cream	25	5 48-h induction patches; 1 48-h challenge	No sensitization	151
Skin sensitization	Cetyl Alcohol	5.0% in facial makeup product	150	9 24-h induction patches; 2 48-h challenges	No sensitization	152
Skin sensitization	Cetyl Alcohol	4.78% in facial makeup product	150	9 24-h induction patches; 2 48-h challenges	No sensitization	141
Skin sensitization	Cetyl Alcohol	4.5% in facial makeup product	206	9 24-h induction patches; 2 48-h challenges	No sensitization	153
Skin sensitization	Cetyl Alcohol	2.59% in hand lotion	650	9 24-h induction patches; 4 24-h challenges	No sensitization	154
Skin sensitization	Cetyl Alcohol	2.0% in hand lotion	650	9 24-h induction patches; 4 24-h challenges	No sensitization	154
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	148	9 24-h induction patches; 1 24-h challenge	Sensitization in 6 subjects	155
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	60	9 24-h induction patches; 1 24-h challenge	Sensitization in 5 subjects	155
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	148	9 24-h induction patches; 4 24-h challenges	Reactions in 75, 65, 83, and 69 subjects after 1st, 2nd, 3rd, and 4th challenges, respectively	156
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	148	9 24-h induction patches; 1 24-h challenge	Sensitization in 4 subjects	157
Photosensitization	Cetyl Alcohol	4.0% in lipstick	52	—	No photosensitization	158
Photosensitization	Cetyl Alcohol	1.0% in skin care preparation	407	—	No photosensitization	159
Photosensitization	Myristyl Alcohol	0.10% in moisturizing lotion	52	—	No photosensitization	160

Myristyl Alcohol

A moisturizing lotion containing 0.80% Myristyl Alcohol was applied to the face of each of 53 subjects over a period of 4 weeks. The detailed experimental procedure was not stated. Reactions were graded according to the scale by Wilkinson et al.⁽¹⁶⁾: 1 (weak nonvesicular reaction) to 3 (bullous or ulcerative reaction). None of the subjects had signs of skin irritation⁽¹²⁴⁾ (Table 12).

In another study, the irritation potential of a moisturizing lotion containing 0.25% Myristyl Alcohol was evaluated in 51 subjects. The subjects used the product daily during a 1-month period. A burning sensation was experienced by 1 of the subjects 1 day after initial use of the product. None of the subjects had signs of skin irritation⁽¹²⁵⁾ (Table 12).

Isostearyl Alcohol

The skin irritation potential of Isostearyl Alcohol was evaluated in 19 male and female subjects (18–65 years old) at a concentration of 25.0% in petrolatum. One-tenth milliliter of the test substance was applied to the volar surface of the forearm of each subject and removed after 24 or 48 h. It was not stated whether or not patches were placed over the test sites. Skin reaction were scored 2 and 24 h after removal according to the scale: 0.5 (barely perceptible erythema) to 4.0 (severe erythema). The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05)⁽¹²⁶⁾ (Table 12). In three similar studies, three different lipstick products containing 25.0, 27.0, and 28.0% Isostearyl Alcohol, respectively, were tested according to the same protocol. The three products did not induce skin irritation^(127–129) (Table 12).

An antiperspirant containing 5.0% Isostearyl Alcohol was applied to 11 subjects (21–60 years old) according to the procedure by Philips et al.⁽¹⁶²⁾ An occlusive patch containing 0.4 ml of the product was applied to the back of each subject and removed after 24 h. Sites were scored 30 min after removal, and fresh patches were then applied to the same sites. This procedure was repeated daily for 21 days. The product was classified as a severe irritant, based on a 21-day cumulative irritation score of 49.60 (scale: 0–60)⁽¹³⁰⁾ (Table 12).

Skin Irritation and Sensitization

Cetyl Alcohol

The skin irritation and sensitization potential of a product containing 8.4% Cetyl Alcohol was evaluated in 110 female subjects. The product was applied to the upper back of each subject, and sites were covered with a patch plaster. Patches remained in place for 48 h, after which sites were scored according to the scale 0 to 3 (vesiculation with edema). This procedure was repeated 10 times. Fourteen days after scoring of the tenth application site, a challenge patch was applied to each subject and removed after 48 h; sites were scored after patch removal. The product did not induce primary irritation or sensitization⁽¹³¹⁾ (Table 12).

A moisturizing cream containing 6.36% Cetyl Alcohol was applied to the backs of 229 male and female subjects via occlusive patches. Patches remained for 24 h, after which reactions were scored according to the scale: 0 to 4 (in-

tense erythema with edema and vesicles). The product was applied to the same site for a total of 10 induction applications. After a 2-week nontreatment period, the product was again applied to each subject (first challenge). Challenge patches remained for 48 h, after which sites were scored. One week later, challenge patches were reapplied; sites were scored 48 and 72 h postapplication. The product did not induce irritation or sensitization in any of the subjects⁽¹³²⁾ (Table 12).

The skin irritation and sensitization potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 52 male and female subjects. One-tenth milliliter of the product was applied to the upper back of each subject via a patch made of nonwoven cotton fabric. Patches were removed after 24 h, and sites were scored according to the scale 0 to 4 (deep red erythema with vesiculation). This procedure was repeated (same test sites) every Monday, Wednesday, and Friday for 3 consecutive weeks. The challenge phase was begun 2 weeks after scoring of the last induction site. Challenge patches were applied to new sites and removed after 24 h. Sites were scored 24 and 48 h after patch removal. Subjects having reactions that were indicative of possible sensitization underwent follow-up testing after a 1-week nontreatment period. During this procedure, the product was applied via an occlusive patch and removed after 24 h. Skin reactions were noted in 33 subjects during the induction phase and were limited to barely perceptible and mild erythema. Five subjects had barely perceptible to mild erythema during the challenge phase. Reactions were not observed in the 5 subjects during follow-up testing. The authors stated that the original challenge reactions were of a nonspecific (irritant) nature. It was concluded that the product did not have any potential for inducing allergic sensitization⁽¹³³⁾ (Table 12).

A lipstick product containing 4.0% Cetyl Alcohol was applied to 103 subjects according to the procedure of Schwartz and Peck.⁽¹⁶³⁾ During the first phase of testing, patches (one open, one closed) were applied to each subject and removed after 24 h. Sites were then scored according to the scale by Wilkinson et al.⁽¹⁶¹⁾: 1 (weak nonvesicular reaction) to 3 (bullous ulcerative reaction). After a 10- to 14-day nontreatment period, the procedure was repeated (2nd phase). Two subjects had a weak vesicular reaction at the closed patch site during the first phase of testing. No reactions to the product were noted during the second phase⁽¹³⁴⁾ (Table 12). The same product was tested for its irritation and sensitization potential in another study, according to a modification of the procedure by Shelanski and Shelanski.⁽¹⁶⁴⁾ During the induction phase, the product was applied (one open and one closed patch) to the skin of each of 52 subjects; patches were removed after 24 h. Reactions were then scored according to the scale by Wilkinson et al.,⁽¹⁶¹⁾ after which a 24-h nontreatment period was observed. This procedure was repeated for a total of 10 exposures. After a 2- to 3-week nontreatment period, the product was reapplied (open and closed patches) and removed after 48 h. Reactions were scored immediately after patch removal. A weak (nonvesicular) reaction was observed in 8 subjects after the first induction and in 1 subject after the tenth induction. One subject had a strong vesicular reaction after the ninth induction. After the 48-h challenge, a weak (nonvesicular) reaction (1 subject) and a strong vesicular reaction (1 subject) were observed. It was concluded that the product was neither an irritant nor a sensitizer⁽¹³⁴⁾ (Table 12).

A skin cleanser containing 4.0% Cetyl Alcohol was applied to the back of each of 200 male and female subjects (18–65 years old) via open patches. During induction, applications were made every Monday, Wednesday, and Friday for 3½ weeks (total of 10 applications); patches were removed after 24 h. Sites were graded immediately after patch removal according to the scale: 0 to 4 (marked edema and vesicles). The challenge phase was begun 10 to 14 days after scoring of the tenth induction site. An open challenge patch was applied to each subject and removed after 48 h. Sites were then scored according to the same grading scale. Patches were reapplied 7–10 days later, and sites were scored 48 and 72 h after patch removal. None of the subjects had reactions to the product during the study. Within the limits imposed by the sample size and test procedure, it was concluded that the product was neither a strong irritant nor an allergic sensitizer⁽¹³⁵⁾ (Table 12). Identical results were reported in another study in which a different skin cleanser containing 4.0% Cetyl Alcohol was applied to 200 subjects according to the same protocol⁽¹³⁶⁾ (Table 12).

The irritation and sensitization potential of a lipstick product containing 3.3% Cetyl Alcohol was evaluated in 78 subjects (21–70 years old). During induction, 0.1 ml of the product was applied to the back of each subject via an occlusive patch every Monday, Wednesday, and Friday for 3 consecutive weeks; patches were removed after 24 h. Reactions were scored 24 h after patch removal according to the scale 0 to 4 (severe erythema with vesiculation). The challenge phase was initiated 2 weeks after scoring of the last induction sites. Challenge patches were applied to new test sites and removed after 24 h. Reactions were scored immediately after patch removal and 48 h later. Mild erythema was noted in 1 subject after the second induction, and in another subject, after the sixth, seventh, and ninth inductions. None of the subjects had reactions to the product during the challenge phase⁽¹³⁷⁾ (Table 12).

Five-hundredths milliliter of a conditioner containing 3.25% Cetyl Alcohol was applied to the back of each of 53 male and female subjects (12 years old and older) via occlusive patches. During the induction phase, patches applied on Mondays and Wednesdays remained for 48 h. Patches applied on Fridays remained for 72 h. Sites were graded within 15 min after patch removal according to the scale: 0 to 3 (erythema, edema, and vesiculation). This procedure was repeated for a total of 10 applications. Challenge applications of the product were made after a 2-week nontreatment period. Occlusive patches were applied to new test sites and removed after 48 h. Sites were scored at 48 and 72 h postapplication. Six subjects had erythema during the induction phase. Three subjects had erythema 72 h after challenge patch application, two of whom did not have reactions during induction. One of these two subjects was rechallenged with the product and had no evidence of sensitization. The authors concluded that there was definite evidence of the product causing skin irritation but no evidence of sensitization⁽¹³⁸⁾ (Table 12).

The skin irritation and sensitization potential of a hand cream containing 3.0% Cetyl Alcohol was evaluated in 116 subjects (18–70 years old). During induction, 0.1 ml of the product was applied to the back of each subject via an occlusive patch every Monday, Wednesday, and Friday for 3 consecutive weeks; patches remained for 24 h. Reactions to the product were scored 24 h after patch removal according to the scale 0 to 4 (severe erythema and vesicula-

tion). The challenge phase was initiated 3 weeks after grading of the last induction sites. Challenge patches were applied to new test sites and removed after 24 h. Reactions were scored immediately after patch removal and 48 h later. One subject had mild to moderate erythema during the induction phase. None of the subjects had reactions during the challenge phase⁽¹³⁹⁾ (Table 12).

An irritation and sensitization study of a cleansing cream containing 2.85% Cetyl Alcohol was conducted with 204 male and female subjects (18–65 years old). The product was applied to each subject via an occlusive patch every other day for 10 days. Patches remained for 24 h, after which sites were scored according to the scale 0 to 4 (intense erythema with edema and vesicles). After a 13-day nontreatment period, a challenge patch was applied to the back of each subject and removed after 48 h. A second challenge patch was applied 7 days after application of the first. Sites were graded immediately after patch removal and 1 h later. Mild erythema was noted in 16 subjects: 6 subjects (induction phase), 7 subjects (challenge phase), and 3 subjects (induction and challenge phase). One subject had mild to intense erythema during the induction phase. It was concluded that the product was neither an irritant nor an allergen.⁽¹⁶⁵⁾ The irritation and sensitization potential of a night cream containing 2.7% Cetyl Alcohol was evaluated in 208 subjects (18–64 years old) according to the same protocol. One subject had mild erythema and intense erythema with edema during induction. Mild erythema was also noted in this subject during the challenge phase. It was concluded that the product was neither an irritant nor an allergen⁽¹⁴⁰⁾ (Table 12).

A moisturizer containing 2.0% Cetyl Alcohol was tested for its irritation and sensitization potential in a study involving 239 male and female subjects (18–65 years old). One-tenth gram of the product was applied to the back of each subject via an occlusive patch on Mondays, Wednesdays, and Fridays during a 4-week induction period. Patches were removed after 24 h, after which sites were graded according to the scale 0 to 4 (erythema, edema/induration, blisters). The tenth (final) induction site was scored 24 and 48 h after patch application. The 48-h reading was followed by an 11-day nontreatment period. Challenge patches were then applied to new test sites and removed after 48 h. Sites were scored 48 and 72 h postapplication. One subject had erythema during induction. None of the subjects had reactions during the challenge phase. Within the limits imposed by the population size and test procedure, it was concluded that the product was neither a primary irritant nor an allergic sensitizer⁽¹⁶⁶⁾ (Table 12).

In another study, the irritation and sensitization potential of a product (type not stated) containing 2.0% Cetyl Alcohol was evaluated in 210 male and female subjects (18–65 years old). The product was applied via an occlusive patch every Monday, Wednesday, and Friday during a 3½ week induction period (total of 10 applications). Patches were removed after 24 h and sites were then scored according to the scale 0 to 4 (marked edema and vesicles). The challenge phase was begun 10–14 days after scoring of the tenth insult. Patches remained for 48 h, after which sites were immediately scored. Patches were again applied 7 to 10 days after scoring of the first challenge and removed after 48 h. Sites were scored immediately after patch removal and 24 h later. Two subjects had erythema and papules during induction. One of the two also had these reactions during the challenge phase. Within the limits imposed by the population

size and test procedure, the product was neither a strong irritant nor a strong contact sensitizer⁽¹⁴²⁾ (Table 12). In a similar study (same protocol), a cream containing 2.0% Cetyl Alcohol was applied to 205 male and female subjects (18–65 years old). The following observations were made during the induction phase: erythema (2 subjects), erythema and papules (1 subject), and erythema, papules, and vesicles (1 subject). Reactions were also noted during the challenge phase: erythema (4 subjects), erythema and papules (1 subject), erythema, papules, and vesicles (1 subject). None of the subjects with reactions during the challenge phase had them during induction. It was concluded that the product was neither a strong irritant nor a gross allergic sensitizer⁽¹⁴³⁾ (Table 12).

The skin irritation and sensitization potential of a skin cream containing 2.0% Cetyl Alcohol was evaluated in 90 male and female subjects (18–70 years old). One-tenth milliliter of the product was applied to the back of each subject via an occlusive patch. During induction, applications were made every Monday, Wednesday, and Friday for 3 consecutive weeks. Patch removals occurred 24 h postapplication, after which sites were scored according to the scale 0 to 4 (severe erythema with vesiculation). Reactions of barely perceptible and mild erythema were observed in 68 subjects during the induction phase. Because of the fairly large number of irritant responses observed during induction, a 50.0% aqueous solution of the product was applied during the challenge phase. A 2-week nontreatment period preceded the challenge phase. Challenge patches were applied to new sites and remained for 24 h. Reactions were scored 24 and 48 h after patch removal. Twenty-two of the subjects with reactions during induction also had these reactions during the challenge phase. Within the limits imposed by the sample size and test procedure, the product did not exhibit any potential for inducing allergic sensitization⁽¹⁴⁴⁾ (Table 12).

A skin care preparation containing 1.0% Cetyl Alcohol was applied to 804 subjects according to the procedure of Schwartz and Peck.⁽¹⁶³⁾ Patches (one open, one closed) were applied to each subject and removed after 24 h. Sites were then scored according to the scale of Wilkinson et al.⁽¹⁶¹⁾: 1 (weak non-vesicular reaction) to 3 (bullous or ulcerative reaction). Patches were reapplied after a 10–14 day nontreatment period and remained for 24 h; sites were then scored. One subject had a strong edematous reaction at the closed patch site during the first phase of testing. None of the subjects had reactions during the second phase. The product was neither an irritant nor a sensitizer⁽¹⁴⁵⁾ (Table 12). The same product was tested for its irritation and sensitization potential according to a modification of the procedure by Shelanski and Shelanski.⁽¹⁶⁴⁾ During the induction phase, patches (one open, one closed) were applied to 407 subjects. Patches remained for 24 h, after which sites were scored according to the scale by Wilkinson et al.⁽¹⁶¹⁾ mentioned above. Scoring was followed by a 24-h nontreatment period. This procedure was repeated for a total of 10 applications. After a 2–3-week nontreatment period, the product was reapplied (open and closed patches) and remained for 48 h. Challenge sites were scored immediately after patch removal. One subject had a strong edematous reaction (closed patch site) during the induction phase. Reactions were not observed in subjects during the challenge phase. The product was neither an irritant nor a sensitizer⁽¹⁴⁵⁾ (Table 12).

Myristyl Alcohol

A moisturizing lotion containing 0.25% Myristyl Alcohol was applied to the backs of 229 male and female subjects via occlusive patches. Patches remained for 24 h, after which sites were scored according to the scale 0 to 4 (intense erythema with edema and vesicles). The product was reapplied to the same sites following a 24-h nontreatment period. This procedure was repeated Monday through Friday for a total of 10 induction applications. After a 2-week nontreatment period, two 48-h challenge patches were applied. The two applications were separated by a 1-week nontreatment period. Sites were scored 48 h after patch application (first challenge) and 48 and 72 h postapplication (second challenge). None of the subjects had reactions to the product. The product was considered neither an irritant nor an allergen⁽¹⁴⁶⁾ (Table 12).

A moisturizing lotion containing 0.10% Myristyl Alcohol was applied to 106 subjects according to the procedure of Schwartz and Peck.⁽¹⁶³⁾ During the first phase of testing, patches (one open, one closed) were applied to each subject and removed after 24 h. Sites were then scored according to the scale of Wilkinson et al.⁽¹⁶¹⁾: 1 (weak nonvesicular reaction) to 3 (bullous, ulcerative reaction). This procedure was repeated after a 10–14-day nontreatment period (second phase). Five subjects had a weak vesicular reaction at the closed patch site during the first phase of testing. Two subjects had this reaction during the second phase. The product was neither an irritant nor a sensitizer.⁽¹⁴⁷⁾ The same product was tested for its irritation and sensitization potential in another study according to a modification of the procedure by Shelanski and Shelanski.⁽¹⁶⁴⁾ During induction, the product was applied (one open and one closed patch) to the skin of each of 52 subjects; patches remained for 24 h. Reactions were then scored according to the scale by Wilkinson et al.,⁽¹⁶¹⁾ after which a 24-h nontreatment period was observed. This procedure was repeated for a total of 10 exposures. After a 2–3-week nontreatment period, the product was reapplied (open and closed patches) and removed after 48 h. Reactions were scored immediately after patch removal. Weak nonvesicular reactions were observed at closed patch sites during the fifth (2 subjects) and sixth (2 subjects) inductions. A strong vesicular reaction at the closed patch site was noted in 1 subject during the seventh induction. None of the subjects had reactions to the product during the challenge phase. It was concluded that the product was neither an irritant nor a sensitizer⁽¹⁴⁷⁾ (Table 12).

Isostearyl Alcohol

The irritation and sensitization potential of Isostearyl Alcohol (25% V/V in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21–>60 years old). Each patch (type not stated, moistened with 0.5 ml of the solution, was applied to the upper arm of each subject and remained for 24 h. Applications were made to the same site for a total of 9 days. The third, sixth, and ninth induction sites were scored 48 h after patch removal, and the remaining sites were scored 24 h after removal. The grading scale ranged from 0 to 6 (strong reaction, spreading beyond test site). Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch. Patches re-

mained for 24 h, and sites were scored 24 and 48 h after removal. Three of the 12 subjects had slight erythema during induction, and there was no evidence of sensitization⁽¹⁴⁸⁾ (Table 12).

Skin Sensitization

Cetearyl Alcohol

The sensitization potential of a cream containing 3.0% Cetearyl Alcohol was evaluated in 25 subjects (18–25 years old). Three-tenths gram of the product was applied to the forearm (volar aspect) of each subject via an occlusive patch covered with a 15 mm aluminum chamber and removed after 48 h. Patches were reapplied after a 24-h nontreatment period. This procedure was repeated for a total of five applications. Since the product was nonirritating, 2.5% sodium lauryl sulfate was applied before each induction application. Following a 10-day nontreatment period, occlusive challenge patches were applied to new sites and removed after 48 h. A 5.0% aqueous solution of sodium lauryl sulfate was applied before application of the challenge patches. Sites were scored immediately after patch removal and 24 h later according to the scale 0 to 3 (strong sensitization). Sensitization reactions were not observed in any of the subjects⁽¹⁴⁹⁾ (Table 12).

Cetyl Alcohol

A total of 330 male and female patients (age range, 19–60 years) with eczematous lesions (88 suffered from leg ulcers and 242 had eczematous dermatitis) were tested with 30% Cetyl Alcohol in white petrolatum⁽¹⁵⁰⁾ (Table 12). This study contains the results of 3 years of patch tests in dermatological patients. More often, the tests were undertaken because of slow healing, aggravation, or recurrence of lesions. Patch tests were placed on the back and removed after 48 h. Results were read at 48 and 72 (or 96) h after application. All tests were in accordance with the technique described by Fregert et al.⁽¹⁶⁷⁾ Of the 330 patients, 11.2% had allergic reactions to Cetyl Alcohol (positive patch tests). The authors mentioned that the large number of allergic reactions reported in this study was not consistent with results from other studies in the literature. For example, Hjorth and Trolle-Lassen⁽¹⁶⁸⁾ identified only 2 positive reactions among 1664 consecutive patients. Fisher et al.⁽¹⁶⁹⁾ did not identify any positive reactions among 100 patients. The greater number of positive patch tests in the study by Blondeel et al.⁽¹⁵⁰⁾ may be attributed to the preferential choice of cream containing Cetyl Alcohol for the treatment of outpatients.

The sensitization potential of a cream containing 5.0% Cetyl Alcohol was evaluated in 25 male and female subjects (18–30 years old). Three-tenths gram of the product was applied to the forearm (volar aspect) of each subject via an occlusive dressing for a total of five 48-h exposures; the dressing remained for 48 h. The dressing was reapplied after a 24-h nontreatment period. This procedure was repeated for a total of five applications. Since the product was nonirritating, 1.5% sodium lauryl sulfate was applied before each induction application. After a 10-day nontreatment period, occlusive challenge patches were

applied to new sites and removed after 48 h. A 10.0% aqueous solution of sodium lauryl sulfate was applied before application of the challenge patches. Sites were scored immediately after patch removal and 24 h later according to the scale 0 to 3 (strong sensitization). None of the subjects had sensitization reactions⁽¹⁵¹⁾ (Table 12).

The sensitization potential of a facial makeup product containing 5.0% Cetyl Alcohol was evaluated in 150 male and female subjects (18–65 years old). The product was applied to the back of each subject via an occlusive patch on Monday, Wednesday, and Friday for 3 consecutive weeks. Patches remained for 24 h, after which sites were scored according to the scale 0 to 4 (bullae or extensive erosions). The challenge phase was preceded by a 2-week nontreatment period. Two consecutive 48-h challenge patches were applied to the back of each subject. Sites were scored at 48 and 96 h postapplication. Faint erythema was noted in 2 subjects during the induction phase. None of the subjects had positive reactions during the challenge phase⁽¹⁵²⁾ (Table 12). A facial makeup product containing 4.78% Cetyl Alcohol was applied to 154 male and female subjects (18–65 years old) according to the same protocol. Faint erythema was observed in 1 subject during the induction phase. None of the subjects had positive responses during the challenge phase⁽¹⁴¹⁾ (Table 12). In another study (same protocol), the sensitization potential of a facial makeup product containing 4.5% Cetyl Alcohol was evaluated in 206 male and female subjects (18–65 years old). Two subjects had equivocal reactions during the challenge phase. The product was not a sensitizer⁽¹⁵³⁾ (Table 12).

The sensitization potential of two hand lotions, one containing 25.9% Cetyl Alcohol and the other 2.0% Cetyl Alcohol, was evaluated in 650 male and female subjects (18–60 years old). Three-tenths milliliter of both products was applied to the arm of each subject via an occlusive patch for a total of nine induction applications (3 days/week for 3 weeks). Patches remained for 24 h, after which sites were scored according to the scale 0 to 7 (strong reaction spreading beyond test site). The challenge phase was preceded by a 10–14-day nontreatment period. A total of four applications were made to original and adjacent sites: first challenge (original), second challenge (adjacent), third challenge (original), and fourth challenge (adjacent). Patches remained for 24 h, after which sites were scored. After applications of both products, reactions of minimal erythema predominated throughout the induction phase. Reactions to the 2.59% product were noted in 3 subjects (minimal erythema) and in 1 subject (definite erythema) after the first challenge. None of the subjects had reactions to the 2.0% product during the challenge phase. The products were not sensitizers⁽¹⁵⁴⁾ (Table 12).

Isostearyl Alcohol

The sensitization potential of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was evaluated using 148 male and female subjects. The product was applied via an occlusive patch to the upper arm for a total of nine induction applications (3 times/week for 3 weeks). Each patch remained for 24 h, and sites were scored immediately before subsequent applications. During the

challenge phase, a patch was applied to the induction site and to a new site on the opposite arm of each subject. Reactions were scored 48 and 96 h after application. Ten of the twelve subjects with reactions suggestive of sensitization were rechallenged with the product 2 months later. Patches remained for 24 h, and sites were scored at 48 and 96 h postapplication. Six subjects had reactions during the rechallenge. Four of the six subjects were then tested with 5.0% Isostearyl Alcohol in solution with ethanol 6 weeks after scoring of the first rechallenge; all had positive responses. Negative responses were reported when the product (without Isostearyl Alcohol) and 100.0% ethanol each were tested⁽¹⁵⁵⁾ (Table 12). In a second study, the same product was applied to 60 male and female subjects (same protocol). Five of the subjects had positive responses after the first challenge. One of the five was rechallenged with 5.0% Isostearyl Alcohol in ethanol solution, and a positive reaction was observed⁽¹⁵⁵⁾ (Table 12).

The sensitization potential of another pump spray antiperspirant containing 5.0% Isostearyl Alcohol was evaluated in 148 male and female subjects (21–60 years old). The product contained 10 times the normal concentration of perfume. Four-tenths milliliter of the product was applied to the upper arm of each subject via a topical patch for a total of nine induction applications (3 days/week for 3 weeks). Patches remained for 24 h, after which sites were scored according to the scale 0 to 7 (strong reaction spreading beyond test site). The challenge phase was preceded by a 10–14-day nontreatment period. A total of four applications were made to original and adjacent sites: first challenge (original), second challenge (adjacent), third challenge (original), and fourth challenge (adjacent). Patches remained for 24 h, after which reactions were scored. Following the first and ninth inductions, 27 and 63 subjects, respectively, had reactions ranging from minimal erythema to erythema, edema, and papules. Reactions ranging from minimal erythema to a strong reaction spreading beyond the test site were observed after each of the four challenges: first challenge (75 subjects), second challenge (65 subjects), third challenge (83 subjects), and fourth challenge (69 subjects). The authors stated that the exaggerated amount of perfume in the product may have induced sensitization⁽¹⁵⁶⁾ (Table 12). The validity of this assumption was tested in a subsequent study involving 148 subjects (same protocol). Subjects were rechallenged with the following substances: pump spray antiperspirant containing 5.0% Isostearyl Alcohol (week of 1/10/77), pump spray without perfume (week of 2/21/77), pump spray without perfume or Isostearyl Alcohol (week of 5/9/77) and 5.0% Isostearyl Alcohol (week of 6/13/77). Sites were scored 48 and 96 h after patch application. The incidence of sensitization reactions was as follows: 4 subjects (pump spray antiperspirant), 2 subjects (pump spray without perfume), 1 subject (pump spray without perfume or Isostearyl Alcohol), and 4 subjects (5.0% Isostearyl Alcohol). The most severe reactions were observed when samples containing Isostearyl Alcohol were applied. The sensitization reactions resulting from application of the antiperspirant were suspected of being due to its Isostearyl Alcohol content⁽¹⁵⁷⁾ (Table 12).

Photosensitization

Cetyl Alcohol

The photosensitization potential of a lipstick product containing 4.0% Cetyl

Alcohol was evaluated in 52 subjects. The experimental procedure was not stated. Photosensitization reactions were not noted in any of the subjects⁽¹⁵⁸⁾ (Table 12). In another study, a skin care preparation containing 1.0% Cetyl Alcohol did not induce photosensitization in the 407 subjects tested. The experimental procedure was not stated⁽¹⁵⁹⁾ (Table 12).

Myristyl Alcohol

A moisturizing lotion containing 0.10% Myristyl Alcohol was evaluated for its photosensitization potential in a study involving 52 subjects. The experimental procedure was not stated. The product did not induce photosensitization in any of the subjects⁽¹⁶⁰⁾ (Table 12).

SUMMARY

The long-chain aliphatic alcohols are alcohols resulting from the reduction of corresponding fatty acids.

Noncosmetic uses of long-chain aliphatic alcohols include emulsifying agents in textile soaps, components of synthetic fibers and lubricants, and food additives. Data submitted to the FDA by cosmetic firms participating in the voluntary cosmetic registration program indicate that long-chain aliphatic alcohols were used in at least 63 cosmetic products during 1982, ranging in concentration from $\leq 0.1\%$ to 50%. These cosmetic formulations are applied to the skin and may come in contact with the eyes.

The inhalation of Cetyl Alcohol vapor (26 ppm) by mice, rats, and guinea pigs caused slight irritation of the mucous membranes of the eyes, nose, throat, and respiratory passages. There were no signs of systemic toxicity, and no deaths were reported. Alternatively, exposure to a Cetyl Alcohol concentration of 2220 mg/m³ resulted in death of all animals. Ataxia and moderate nasal irritation were observed in albino rats exposed to bursts of a 3.0% Myristyl Alcohol aerosol. No deaths were reported.

The oral LD₅₀ of Cetyl Alcohol in fasted rats was > 8.2 g/kg. The animals had signs of central nervous system depression and labored respiration. In acute oral toxicity studies (rats) of formulations containing 2.0, 3.25, and 4.0% Cetyl Alcohol, there were predominantly no toxic effects.

The oral administration of Myristyl Alcohol and a product containing 0.8% Myristyl Alcohol to albino rats resulted in LD₅₀s of > 8.0 and > 5.0 g/kg, respectively.

The oral administration of up to 20.0 g/kg of Isostearyl Alcohol to rats failed to cause a significant number of deaths that would have permitted calculation of an LD₅₀.

No mortalities were noted following the intragastric administration of a heated mixture of 1.0% Behenyl Alcohol in olive oil (dose, 10.0 g/kg).

In acute dermal toxicity studies (rabbits), doses of up to 2.6 g/kg of Cetyl Alcohol and 2.0 g/kg of a product containing 4.0% Cetyl Alcohol induced little toxicity, as did 2.0 g/kg of a product containing 0.8% Myristyl Alcohol.

Following the subchronic dermal administration of Cetyl Alcohol (30.0% in methyl alcohol and propylene glycol) to albino rabbits, dermal infiltrates of histiocytes were observed. Exfoliative dermatitis, parakeratosis, and hyperkeratosis were observed in New Zealand white rabbits after the subchronic dermal administration of 11.5% Cetyl Alcohol cream bases. In another subchronic dermal toxicity study, mild inflammation was observed at application sites after the administration of a 2.0% Cetyl Alcohol moisturizer.

Mild irritation was observed when a cream containing 3.0% Cetearyl Alcohol was applied to the skin of New Zealand albino rabbits. Following the administration of Cetyl Alcohol (50.0% in petrolatum) to abraded and intact skin of albino rabbits, minimal to slight skin irritation was observed. Slight to well-defined erythema and slight desquamation were observed in albino rabbits after application of a cream containing 4.0% Cetyl Alcohol. A lipstick product containing 4.0% Cetyl Alcohol was nonirritating to abraded and intact skin of albino rabbits. Slight erythema and edema (abraded and intact skin) were observed in New Zealand white rabbits receiving cutaneous applications of a conditioner containing 3.25% Cetyl Alcohol. In a skin irritation study of a product containing 2.0% Cetyl Alcohol, observations of slight erythema predominated. Applications of a cream containing 2.0% Cetyl Alcohol resulted in well-defined erythema and mild edema.

A moisturizing lotion containing 0.8% Myristyl Alcohol was nonirritating to abraded and intact skin of albino rabbits.

Observations of barely perceptible erythema predominated in skin irritation studies of lipstick products containing 27.0 and 25.0% Isostearyl Alcohol. Following the cutaneous administration of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol to New Zealand white rabbits, mild skin irritation was observed.

A product formulation containing 2.0% Cetyl Alcohol was nonirritating to the genital mucosa of albino rabbits.

A cream containing 3.0% Cetearyl Alcohol was considered to be a nonirritant when instilled into the eyes of albino rabbits.

Product formulations containing 6.36, 5.0, 4.0, 3.25, 2.85, 2.7, and 2.0% Cetyl Alcohol were instilled into the eyes of albino rabbits. The products were nonirritating in most of the studies.

The instillation of an aerosol antiperspirant containing 3.0% Myristyl Alcohol into the eyes of albino rabbits induced mild to moderate irritation. A moisturizing lotion containing 0.8% induced mild to moderate irritation. A moisturizing lotion containing 0.8% Myristyl Alcohol was nonirritating when instilled into the eyes of albino rabbits.

Reactions of minimal to mild irritation were observed after the ocular administration of lipstick products containing 27.0 and 25.0% Isostearyl Alcohol into the eyes of albino rabbits. Transient iridial and conjunctival irritation was observed in albino rabbits during ocular irritation studies of two pump spray antiperspirants (5.0 and 10.0% Isostearyl Alcohol). Corneal irritation was noted at the conclusion of the study involving the 5.0% Isostearyl Alcohol antiperspirant.

Conjunctival irritation was observed 2 and 6 hours after instillation of a 1.0% Behenyl Alcohol in oil mixture into the eyes of New Zealand rabbits. Reactions had cleared by 24 h postinstillation. Irritation was not noted in the cornea or iris.

Applications of Isostearyl Alcohol (5.0% in propylene glycol) and an antiperspirant containing 5.0% Isostearyl Alcohol to albino guinea pigs resulted in no skin sensitization reactions.

Cetyl Alcohol was not mutagenic in *Salmonella typhimurium* LT2 mutant strains in the spot test. In human skin irritation studies, Cetyl Alcohol produced no erythematous reactions. Product formulations containing 11.5%, 6.0%, 5.0%, 4.0%, 3.25%, and 2.0% Cetyl Alcohol were, at most, mild irritants.

The results of human skin irritation studies of two moisturizing lotions (0.25% and 0.8% Myristyl Alcohol) indicated no signs of irritation.

No signs of skin irritation were observed in humans when Isostearyl Alcohol (25.0% in petrolatum) was applied. Results of clinical skin irritation studies of lipstick products containing 28.0%, 27.0%, and 25.0% Isostearyl Alcohol were negative, whereas an antiperspirant containing 5.0% Isostearyl Alcohol was classified as a severe irritant.

Clinical skin irritation and sensitization studies of product formulations containing 8.4%, 6.36%, 6.0%, 4.0%, 3.3%, 3.25%, 3.0%, 2.85%, 2.0%, and 1.0% Cetyl Alcohol produced no substantial evidence of irritation or sensitization.

Moisturizing lotions containing 0.10 and 0.25% Myristyl Alcohol were found to be neither irritants nor sensitizers in human skin irritation and sensitization studies.

The application of Isostearyl Alcohol (25.0% in Isopropyl Alcohol) to human subjects produced no substantial evidence of skin irritation or sensitization.

In a human skin sensitization study of a cream containing 3.0% Cetearyl Alcohol, none of the subjects had positive reactions. In a human skin sensitization study of Cetyl Alcohol (30.0% in petrolatum), sensitization reactions were observed in 11.0% of the subjects. Human sensitization studies of product formulations containing 5.0%, 4.78%, 4.5%, 2.59%, and 2.0% Cetyl Alcohol revealed no positive reactions in any of the subjects.

Positive reactions were observed in the four human sensitization studies of pump spray antiperspirants containing 5.0% Isostearyl Alcohol.

Clinical photosensitization studies of a lipstick product containing 4.0% Cetyl Alcohol and a skin care preparation containing 1.0% Cetyl Alcohol resulted in no positive reactions. Identical results were reported in a study of a moisturizing lotion containing 0.10% Myristyl Alcohol.

ANALYSIS

The toxicity of long-chain aliphatic alcohols, esters of fatty acids and alcohols, and a fatty acid (Isostearic Acid) has been reviewed. Long-chain aliphatic alcohols (C_{18} and C_{20}) induced minimal ocular and skin irritation but no sensitization or comedogenicity in rabbits; no mutagenic effects were noted in the Ames assay. In a subchronic percutaneous toxicity study, a product formulation (C_{18} -alcohol content) induced erythema and mild desquamation. Clinical studies of long-chain alcohols (C_{18} and C_{20}) indicated a low order of skin irritation and sensitization. Also, results were negative in clinical phototoxicity and photosensitization studies of products containing these alcohols.⁽⁴⁾ Esters of stearic acid

(C₂₁–C₃₄) were essentially nonirritating to rabbit eyes when tested at and above concentrations used in cosmetic products. Cosmetic use concentrations were, at most, minimally irritating to rabbit skin. In clinical studies, the stearates and cosmetic products containing them were, at most, minimally to mildly irritating to the skin. Comedogenicity is a potential health effect that should be considered when stearates are used in cosmetic formulations.⁽⁴⁾ Isopropyl palmitate (C₁₉), octyl palmitate (C₂₄), and cetyl palmitate (C₃₂), esters of palmitic acid, did not induce subchronic oral toxicity in rats (C₃₂) or subchronic dermal toxicity in rabbits (C₁₉ and C₂₄). In rabbit skin irritation studies, the palmitates were neither sensitizing nor irritating but induced ocular irritation (none to slight) in Draize rabbit eye irritation tests. In clinical studies, formulations containing the palmitates induced minimal skin irritation but no sensitization, phototoxicity, or photocontact allergenicity.⁽¹⁾

In most of the Draize tests, cetyl lactate (C₁₉) and myristyl lactate (C₁₇), esters of Cetyl Alcohol and Myristyl Alcohol, respectively, were minimally irritating to rabbit skin. Cetyl lactate was either nonirritating or slightly irritating and myristyl lactate was nonirritating in Draize ocular irritation tests. In clinical studies, minimal and no skin irritation were induced by cetyl lactate and myristyl lactate, respectively. Neither of the two were sensitizers.⁽¹⁾ Myristyl myristate (C₂₈), ester of myristic acid, induced minimal to mild skin irritation and minimal ocular irritation in rabbits; results were negative in a guinea pig sensitization study. A product formulation containing myristyl myristate did not induce sensitization in humans.⁽²⁾ Cetearyl octanoate (C₂₄–C₂₆), ester of Cetearyl Alcohol, induced, at most, mild ocular irritation and no skin irritation in rabbits. Subchronic dermal toxic effects were not noted. Formulations containing cetearyl octanoate did not induce phototoxicity or sensitization in guinea pigs. A low incidence of moderate irritation was noted in a human skin irritation study of cetearyl octanoate. Also, product formulations containing this ingredient did not induce skin sensitization, photocontact allergenicity, or phototoxicity.⁽²⁾

Isostearyl neopentanoate (C₂₃), ester of Isostearyl Alcohol, was not toxic to rats in a subchronic oral toxicity study. It was a mild eye irritant but not a skin irritant in rabbits; sensitization was not induced in guinea pigs. Low level sensitization was induced by cosmetic formulations containing Isostearyl Alcohol. However, this was not considered to be due to the alcohol but to other ingredients in the formulation. Also, this ingredient was not considered to be a significant comedogenic agent in rabbits. In a clinical study, isostearyl neopentanoate induced a very low incidence of slight noninflammatory skin changes. At most, mild skin irritation was noted in subjects tested with formulations containing this ingredient.⁽⁵⁾ Isostearic acid (C₁₈) induced no significant skin or ocular irritation in rabbits in Draize irritation tests. In a clinical study, isostearic acid was not irritating to the skin. Also, product formulations containing this ingredient did not cause skin irritation.⁽³⁾

Generically, much is known about the biological activities of fatty acids and long-chain aliphatic alcohols and esters. For the long-chain aliphatic alcohols, there is little information on their subchronic or chronic toxicities, genotoxicity, or photosensitization potential. However, based on their close structural similarities to fatty acids and long-chain aliphatic esters, the long-chain aliphatic alcohols are expected to have similar biological activities. Therefore, further tox-

icity testing of these long-chain aliphatic alcohols is not necessary for judging their safety as ingredients in cosmetics.

DISCUSSION

The toxicological data for the five long-chain aliphatic alcohols included in this report revealed no significant toxicity. Assuming that the five ingredients are of the same grade of purity, the similar chemical structure permits extrapolation of data for one of the alcohols to the remaining four alcohols. Based on these factors, the Expert Panel considered it reasonable to assume that the alcohols reviewed in this report have equivalent biological activity.

CONCLUSION

Based on the available data included in this report, the Expert Panel concludes that Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol are safe as cosmetic ingredients in the present practices of use.

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Final Report of the Addendum to the Safety Assessment of *n*-Butyl Alcohol as Used in Cosmetics¹

n-Butyl Alcohol is a primary aliphatic alcohol historically used as a solvent in nail care cosmetic products, but new concentration of use data indicate that it also is being used at low concentrations in eye makeup, personal hygiene, and shaving cosmetic products. *n*-Butyl Alcohol has been generally recognized as safe for use as a flavoring substance in food and appears on the 1982 Food and Drug Administration (FDA) list of inactive ingredients for approved prescription drug products. *n*-Butyl Alcohol can be absorbed through the skin, lungs, and gastrointestinal tract. *n*-Butyl Alcohol may be formed by hydrolysis of butyl acetate in the blood, but is rapidly oxidized. The single oral dose LD₅₀ of *n*-Butyl Alcohol for rats was 0.79 to 4.36 g/kg. The dermal LD₅₀ for rabbits was 4.2 g/kg. Inhalation toxicity studies in humans demonstrate sensory irritation of the upper respiratory tract, but only at levels above 3000 mg/m³. Animal studies demonstrate intoxication, restlessness, ataxia, prostration, and narcosis. Exposures of rats to levels up to 4000 ppm failed to produce hearing defects. High concentrations of *n*-Butyl Alcohol vapors can be fatal. Ocular irritation was observed for *n*-Butyl alcohol at 0.005 ml of a 40% solution. The behavioral no-effect dose for *n*-Butyl Alcohol injected subcutaneously (s.c.) was 120 mg/kg. Fetotoxicity has been demonstrated, but only at maternally toxic levels (1000 mg/kg). No significant behavioral or neurochemical effects were seen in offspring following either maternal or paternal exposure to 3000 or 6000 ppm. *n*-Butyl Alcohol was not mutagenic in Ames tests, did not induce sister-chromatid exchange or chromosome breakage in chick embryos or Chinese hamster ovary cells, did not induce micronuclei formation in V79 Chinese hamster cells, did not have any chromosome-damaging effects in a mouse micronucleus test, and did not impair chromosome distribution in the course of mitosis. Clinical testing of *n*-Butyl Alcohol for nonimmunological contact urticaria was negative in 105 subjects. Repeat-insult patch test (RIPT) studies of nail colors and enamels containing 3% *n*-Butyl Alcohol in one study produced reactions on challenge, but further study linked significant positive reactions to another solvent. In other RIPT studies, only minimal reactions were reported. A photopatch test demonstrated that a nail enamel containing 3% *n*-Butyl Alcohol resulted in no reactions. Workers complained of ocular irritation, disagreeable odor, slight headache and vertigo, slight irritation of nose and throat, and dermatitis of the fingers and hands when the air concentration of *n*-Butyl Alcohol was greater than 50 ppm, as compared to an odor threshold in air of 0.83 ppm. The available safety test data were considered adequate to support the safety of *n*-Butyl Alcohol in all cosmetic product categories in which it is currently used.

¹Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. This final amended report was prepared by Valerie C. McLain, CIR Scientific Analyst and Writer. Address correspondence to Ms. Valerie C. McLain, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) evaluated the safety of *n*-Butyl Alcohol (*n*-BuOH) in 1987, finding it safe in the practices of use and concentration in nail products (Elder 1987). This original safety assessment was specific in that the conclusion was issued only as regards the use of *n*-Butyl Alcohol in nail products.

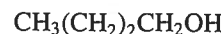
Recently, CIR undertook a re-review of this ingredient to determine what additional data relevant to the safety of *n*-Butyl Alcohol have appeared in the published literature. That re-review included information that *n*-Butyl Alcohol uses have expanded to include product categories in addition to nail products (FDA 2002).

The CIR Expert Panel considered that the safety test data in the original safety assessment, along with the additional data available since that time, were sufficient to support the safety of these other uses of *n*-Butyl Alcohol. This addendum describes current uses and available new safety test data. Summaries of data from the original safety assessment are summarized and introduced with a phrase such as “according to Elder (1987).” Details of the studies thus summarized are available in that original safety assessment.

CHEMISTRY

Definition and Structure

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), *n*-Butyl Alcohol (CAS No. 71-36-3) is the aliphatic alcohol that conforms to the formula:



and functions in cosmetic formulations as a denaturant, fragrance ingredient, and/or solvent.

Synonyms include

- butanol,
- 1-butanol,
- *n*-butanol,
- butyl alcohol,

TABLE 1
Physical and chemical properties of *n*-Butyl Alcohol.

Property	<i>n</i> -BuOH	Reference
Molecular weight	74.12	Elder 1987
Liquid density at 25°C	809.7 kg/m ³	Billig 1999
Specific gravity at 20/4°C	0.8096–0.810	Elder 1987; NIOSH 2005
Boiling point at 760 mm Hg	117–118°C 243°F	Elder 1987; Billig 1999 NIOSH 2005
Melting point	–90°C to –89.3°C	Elder 1987; Billig 1999
Freezing point	–129°F	NIOSH 2005
Flash point	36–38°C	Environmental Protection Agency 1989
Vapor pressure at 20°C	4.3 mm Hg	Elder 1987
25°C	6.5 mm Hg	Elder 1987
Refractive index at 20°C	1.39711–1.3993	Elder 1987
25°C	1.3971	Billig 1999
Autoignition temperature	367°C	Elder 1987
Solubility in water at 30°C by weight	7.85%	Billig 1999
Solubility of water in <i>n</i> -Butyl Alcohol at 30°C by weight	20.06	Billig 1999

- butyl hydroxide, and
- propyl carbinol.

Physical and Chemical Properties

As described in Elder (1987), *n*-Butyl Alcohol is a colorless liquid with a vinaceous odor. This odor is similar to that of fossil oil, only weaker. It is soluble in water, alcohol, ether, acetone, benzene, and other organic solvents. Ema et al. (2004) describes *n*-Butyl Alcohol as a flammable, colorless liquid with a rancid sweet odor. Table 1 lists physical and chemical properties available from the original safety assessment, the *Kirk-Othmer Concise Encyclopedia of Chemical Technology* (Billig 1999), and the National Institute for Occupational Safety and Health (NIOSH) Web site (NIOSH 2005).

Reactivity

As described in Elder (1987), *n*-Butyl Alcohol is a fire hazard when exposed to heat, flame, or oxidizers. When heated to decomposition, it emits toxic fumes, and can react with oxidizing materials. Under typical cosmetic use conditions, however, *n*-Butyl Alcohol is stable. It was noted that *n*-Butyl Alcohol is not recommended for use in suspension-type nail lacquers containing various modified montmorillonite clays. Billig (1999) recommended that *n*-Butyl Alcohol be stored in baked phenolic-lined steel tanks, but acknowledged that plain steel tanks can also be used under the condition that a fine-porosity filler is installed to remove any contaminating rust. Storage under dry nitrogen was also advised because it limits flammability hazards, as well as minimizes water pickup.

According to NIOSH (2005), *n*-Butyl Alcohol reacts with aluminum forming flammable gas (hydrogen). It is miscible with many organic solvents and reacts with strong oxidants, such as chromium trioxide, causing a fire hazard. In addition, it attacks some plastics and rubbers.

When the temperature of *n*-Butyl Alcohol is above 29°C, explosive vapor/air mixtures may be formed. Therefore, strong oxidizers, strong mineral acids, alkali metals, and halogens are incompatible with *n*-Butyl Alcohol (NIOSH 2005).

Method of Manufacture

According to Elder (1987), *n*-Butyl Alcohol can be produced by a synthetic process based on aldol condensation, the oxo process, selective bacterial fermentation of carbohydrate-containing materials, the Ziegler process, Reppe synthesis, as a by-product in the high-pressure oxidation of propane and butane, the reduction of butyraldehyde with sodium borohydride, from ethylene oxide and triethylammonium, and by oxidation of tributylaluminum. Billig (1999) reported that the general commercial source of *n*-Butyl Alcohol is *n*-butyraldehyde, obtained from the oxo reaction of propylene.

Analytical Methods

Elder (1987) listed the following qualitative and quantitative analytical approaches to *n*-Butyl Alcohol determinations: gas chromatography, gas chromatography–mass spectrometry, paper chromatography, thin-layer chromatography, x-ray diffraction, infrared spectrophotometry, high-performance liquid chromatography, and colorimetry.

Other approaches included titrimetry, a fluorophotometric method using alcohol dehydrogenase, activated carbon absorption, an odor reference method, use of an enzyme thermistor probe, an electronic identification method, and an electroadsorptive technique. A gas-liquid chromatographic procedure was described specifically for the determination of *n*-Butyl Alcohol in nail lacquer preparations (Elder 1987).

The *NIOSH Manual of Analytical Methods* (NIOSH 1994) gives a detailed procedure for the quantitative measurement of *n*-Butyl Alcohol among other analytes by varying gas chromatography conditions.

The odor threshold for *n*-Butyl Alcohol is reported to be 7.1 ppm in water and 0.83 ppm in air (Environmental Protection Agency 1989).

Impurities

In cosmetic products, *n*-Butyl Alcohol typically contains no more than 0.003% acidity (as acetic acid), no more than 0.1% moisture, or 0.005 g/100 ml nonvolatiles (Elder 1987).

USE

Cosmetic

Elder (1987) reported 112 uses of *n*-Butyl Alcohol in nail care products at concentrations ranging from $\leq 0.1\%$ to 10%. While Balsam and Sagarin (1974) had reported that *n*-Butyl Alcohol has been used as a clarifying agent in the manufacture of clear shampoos, no such uses were reported to the Food and Drug Administration (FDA) in 1981 (FDA 1981). Generally, *n*-Butyl Alcohol is used as a solvent in cosmetics, but the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004) includes two other functions: denaturant and fragrance ingredient.

In the most recent frequency of use data available, industry has reported only 29 uses to FDA (FDA 2002). A recent industry survey conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) identified use concentrations for *n*-Butyl Alcohol in a wide variety of product categories (CTFA 2005). These categories include bath products, eye makeup, personal hygiene products, and shaving products, in addition to nail care products. Current use concentrations range from a low of 0.000007% in bath soaps and detergents to a high of 4% in nail polishes and enamels. Table 2 includes all the available original and current frequency of use and use concentration data.

Noncosmetic

Elder (1987) reported that *n*-Butyl Alcohol is generally recognized as safe (GRAS) by FDA under conditions of intended use as a flavoring substance in food. It is permitted as a food additive for direct addition to food for human consumption; it may be safely used in food as a synthetic flavoring substance or adjuvant when used in the minimum quantity required to

produce the intended effect and otherwise in accordance with all the principles of good manufacturing practice.

n-Butyl Alcohol may be safely used as a diluent in color additive mixtures for food use exempt from certification; but no residue may be left in the food. These color additive mixtures may be used for marking food; the inks are used to mark food supplements in tablet form, gum, and confectionary. It is also permitted as an indirect food additive. It may be employed as a constituent of adhesives that may be safely used as components of articles intended for use in packaging, transporting, or holding food.

n-Butyl Alcohol may be used as an adjuvant in the manufacture of resinous and polymeric coatings for polyolefin films that may be safely used as a food-contact surface of articles intended for use in producing, manufacturing, packing, transporting, or holding food. It also may be used in the formulation of cellophane that may be safely used for packaging food; the *n*-Butyl Alcohol residue must be limited to 0.1% by weight of finished packaging cellophane. It may be used as a solvent in the formulation of polysulfide polymerpolyepoxy resins that may be safely used as the food-contact surface of articles intended for packaging, transporting, holding, or otherwise contacting dry food.

n-Butyl Alcohol is an inactive ingredient approved for prescription drug products.

n-Butyl Alcohol is a solvent and bactericide for veterinary use. It has been used in the treatment of frothy bloat in cattle.

n-Butyl Alcohol is a solvent for fats, waxes, resins and coatings, shellac, varnish, and gums. It is used in the manufacture of lacquers, rayon, detergents, and a variety of other butyl compounds.

n-Butyl Alcohol is used in plasticizers and in hydraulic fluids, as a dyeing assistant, dehydrating agent, and in chemical analyses. It also is used as a biological extractant, as well as a standard odor comparison substance to quantitate odorant concentrations (Elder 1987).

According to Rowe et al. (1982), *n*-Butyl Alcohol is widely used as a solvent for paints, lacquers, coatings, and a number of other applications. In addition to the noncosmetic uses already listed, a chemical industry Web site (Petrochemicals 2005) included uses as an intermediate in manufacturing herbicide pharmaceutical and veterinary medicine esters; to extract antibiotics, vitamins, and hormones; and in the synthesis of melamine formaldehyde resins.

GENERAL BIOLOGY

Biological Effects

Elder (1987) reported on the effects of *n*-Butyl Alcohol on enzymes and membranes. *n*-Butyl Alcohol was shown to affect the activity of a variety of enzymes and may stabilize or destabilize a variety of biological membranes. These are typical solvent effects and are dependent on the concentration of the alcohol and temperature, and may be due to perturbation of

TABLE 2
Historical and current cosmetic product uses and concentrations for *n*-Butyl Alcohol.

Product category	1981 uses (Elder 1984)	2002 uses (FDA 2002)	1981 concentrations (Elder 1984) (%)	2005 concentrations (CTFA 2005) (%)
Bath products				
Soaps and detergents	—	—	—	0.000007
Eye makeup				
Eyeliners	—	—	—	0.0003
Eye shadow	—	—	—	0.0004
Other eye makeup preparations	—	—	—	0.0001
Makeup				
Foundations	—	—	—	0.002
Lipsticks	—	—	—	0.0005
Nail care products				
Basecoats and undercoats	3	4	>0.1–5	0.5–2
Creams and lotions	—	—	—	1–3
Nail polishes and enamels	107	14	≤ 0.1 – 10	0.5–4
Nail polish and enamel removers	2	3	≤ 0.1	—
Other manicuring preparations	—	7	—	15
Personal hygiene products				
Underarm deodorants	—	—	—	0.00001
Shaving products				
Aftershave lotions	—	1	—	—
Total uses/ranges for <i>n</i>-Butyl Alcohol	112	29	≤0.1–10	0.000007–15

protein conformation, structural changes in membrane lipids, or disturbance of lipid-protein interactions.

n-Butyl Alcohol restrains rat liver mitochondrial perspiration and phosphorylation. At concentrations ranging from 35 to 700 mM, *n*-Butyl Alcohol inhibited by 50% of the activity of a variety of electron transport chain enzymes in submitochondrial particles from bovine heart and rat liver.

n-Butyl Alcohol is a hydroxyl radical scavenger. It has been asserted that this property of *n*-Butyl Alcohol may be responsible for the prevention of neurodegenerative actions of chemicals subsequently injected into mice. *n*-Butyl Alcohol has also been used as a biological tracer. It is freely permeable across the blood-brain barrier in rats and has been used to quantitate cerebral blood flow. It has also been used to quantitate regional myocardial perfusion in dogs (Elder 1987).

Chromosome Segregation

Crebelli et al. (1989) studied the activity of ethyl alcohol and acetaldehyde on mitotic chromosome segregation in *Aspergillus nidulans*. Ethyl alcohol (99.9% pure), methyl alcohol (99.9% pure), *n*-propanol (99.5% pure), *n*-Butyl Alcohol (99.8% pure), hydroquinone (99% pure), and acetaldehyde (99% pure) were used in this experiment.

Mitotic segregants were discovered as homozygous (yA2/yA2) or hemizygous (yA2/o) yellow sectors or patches

in heterozygous (yA2/yA2⁺) pale-green colonies growing on complete medium. Yellow segregants were isolated, analyzed for their nutritional requirements, and classified as mitotic cross-overs, nondysjunctional diploids or haploids. *A. nidulans* conidia underwent treatment with test chemicals during early germination. Monitored by light microscopy, conidia (10⁵/ml) were incubated at 37°C with agitation in liquid complete medium supplemented with test chemicals until the emergence of germ tubes.

A wide range of concentrations was applied to determine the lowest and highest effective doses, as well as the lowest concentration halting conidial germination. Treatments were ended by serial dilutions with sterile water. In order to determine the survival and detect mitotic segregants, conidia were plated on agarized complete medium. Plates having more than 15 to 20 colonies were discarded to prevent normal colonies from advancing to abnormal, slow-growing aneuploid colonies.

Cattle brain microtubule preparations (containing tubulin and tubulin-associated proteins) were prepared by three cycles of assembly and disassembly in the absence of glycerol and stored as pellets at –80°C. Assembly of tubulin was followed by measuring the increase in absorbency at 350 nm in an LKB spectrophotometer. The assembly mix, which was kept ice cold, contained 200 μl of microtubule preparation (2 mg of protein with bovine serum albumin as standard), 20 μl of 50 mM GTP, the test agent

and the polymerization buffer (0.1 M PIPES, pH 6.62, containing 0.1 mM Mg^{2+}) in a final volume of 1.0 ml. Polymerization began when the temperature was raised to 37°C by placing the cuvette in the water-heated cell holder of the spectrophotometer.

Ethanol effectively induced malsegregation in a narrow range of concentrations (4.5% to 5.5%, *v/v*) and was inactive at doses that arrested conidial germination (above 6%). The same bell-shaped dose-response curve was shown by the spindle poison chloral hydrate, which was active in the range 6 to 10 mM. Acetaldehyde displayed a biphasic dose-response curve. Analysis of induced segregants suggested that the disturbance of chromosome segregation is the primary genetic effect at low doses (0.025% to 0.037%), whereas at higher doses (above 0.1%), when growth was arrested, chromosome damage was primarily induced.

A similar pattern of segregants was produced by hydroquinone, a substance that indirectly affects chromosome segregation in *A. nidulans*. The differences in the genotoxic profiles of ethanol and acetaldehyde suggested that the effect exerted by ethanol on *A. nidulans* mitosis was not dependent on its conversion into acetaldehyde. In the absence of an effect of ethanol on in vitro polymerization of tubulin (actively inhibited by acetaldehyde at doses above 0.075%), a direct effect of ethanol on cell membranes was suggested as an hypothesis by the authors.

According to the authors, comparison of the inhibition of growth and the effectiveness in aneuploidy induction displayed by ethanol, methanol, *n*-propanol, and *n*-Butyl Alcohol demonstrated a fair correlation with $\log_p$, a descriptor of lipophilicity related to the partitioning of compounds in biological membranes (Crebelli et al. 1989).

Absorption, Distribution, Metabolism, and Excretion

According to Elder (1987), *n*-Butyl Alcohol can be absorbed through the lungs, the gastrointestinal tract, the cornea, and the skin. Dogs given intravenous *n*-Butyl Alcohol eliminated about 15% of the administered dose in the breath as CO_2 and eliminated about 2.7% of the administered dose in the urine; no unchanged *n*-Butyl Alcohol was detected in the breath. *n*-Butyl Alcohol is rapidly oxidized in vivo; it disappears from animal blood rapidly and oxidation products are not detected. *n*-Butyl Alcohol is a substrate for alcohol dehydrogenase, found primarily in mammalian liver, requires NAD^+ as a cosubstrate and catalyzes the oxidation of primary alcohols to aldehydes.

The International Programme on Chemical Safety/World Health Organization (IPCS/WHO) (1987) also reported that the butanols are readily absorbed through the lungs and gastrointestinal tract of animals. *n*-Butyl Alcohol, 2-butanol, and isobutanol are mainly metabolized by alcohol dehydrogenase and are eliminated rapidly from the blood.

Deisinger et al. (2001) described the pharmacokinetics of *n*-butyl acetate and its oxidative metabolites in rats following intravenous administration. *n*-Butyl Alcohol and acetate were produced in vivo by the hydrolysis of *n*-butyl acetate, followed

by oxidative metabolism of *n*-Butyl Alcohol to *n*-butyric acid, as expected with butyraldehyde occurring as an intermediate.

ANIMAL TOXICOLOGY

Acute Toxicity

As given by Elder (1987), the single oral dose LD_{50} of *n*-Butyl Alcohol for rats was 0.79 to 4.36 g/kg. The dermal LD_{50} for rabbits was reported as 4.2 g/kg.

Korsak et al. (1992) investigated the effects of acute combined exposure to *n*-Butyl Alcohol and *m*-xylene. The rotarod performance and motor activity were tested in rats and respiratory rate was measured in mice. Male Wistar rats, weighing 250 to 300 g were exposed to the vapors of *m*-xylene, *n*-Butyl Alcohol, and their mixture consisting of 50/50 (by volume) *m*-xylene and *n*-Butyl Alcohol in a 1.3- m^3 volume dynamic inhalation chamber. Vapors were generated by heating liquid solvents in washers. The desired concentrations were obtained by dilution with air. Concentrations of solvents vapor in the exposure chamber were measured every 30 min with a gas chromatograph with a flame ionization detector using a 1.5-m metal column, with 10% OV-17 on chromosorb WHP (80 to 100 mesh) as a stationary phase, at a column temperature of 100°C.

The animals were trained before rotarod performance testing, and only those rats that could perform normally for at least 10 consecutive days were used in the experiment. Rotarod performance was tested prior to exposure and directly following termination of exposure for 1 h. Spontaneous motor activity was measured by using a UMA-2-10 actometer for small laboratory animals immediately after 4 h of exposure. The respiratory rate was determined in Balb/C male mice (25 to 30 g) by using the plethysmographic method. Each animal was attached to a small dynamic inhalation chamber.

A Stattham pressure transducer was linked to each plethysmograph and the respiratory pattern was recorded using a Beckman plethysmograph. The respiratory rate was recorded constantly before the exposure solvents, during 6 min of exposure and 6 min after termination of exposure.

Exposure concentrations of *m*-xylene and *n*-Butyl Alcohol were expressed in ppm (1 ppm *m*-xylene = 4.35 mg/m^3 ; 1 ppm *n*-Butyl Alcohol = 3.08 mg/m^3). The rats exposed to the tested concentrations of *m*-xylene, *n*-Butyl Alcohol and their mixture for 4 h all survived the exposure.

Mice were exposed to vapors of single solvents and their mixtures at several concentrations. Each exposure group consisted of 8 to 10 mice.

Both solvents and their mixture caused concentration-dependent disturbances in the rotarod performance of rats. Throughout the experiment, all control animals performed normally. In the rotarod performance test, the effect of *m*-xylene was more noticeable than that of *n*-Butyl Alcohol. EC_{50} values for *n*-Butyl Alcohol, *m*-xylene, and their mixture are 6530, 1980, and 3080 ppm, respectively. The results of the rotarod performance test indicated the additive toxic effect of combined exposure.

TABLE 3

Spontaneous motor activity in rats exposed to *n*-Butyl Alcohol and *m*-xylene (Korsak et al. 1992).

<i>n</i> -Butyl Alcohol + <i>m</i> -xylene (1:1)	Experimental spontaneous motor activity	Expected spontaneous motor activity
968 ppm	+5%	+49%
1976 ppm	+20%	+104%
3041 ppm	+34%	+136%
3761 ppm	+16%	+172%

The spontaneous motor activity in the rats was changed by both solvents and their mixture. Table 3 shows the comparison of experimental values with those expected, assuming the summation of effects of individual solvents.

Significant decreases of spontaneous motor activity were caused by further increases in solvent concentration. Because of a two-phase effect, the concentration dependence of changes in spontaneous motor activity could not be defined. Comparison of combined exposure to *n*-Butyl Alcohol and *m*-xylene in spontaneous motor activity indicated that the solvents' mixture's effect is characteristic for antagonistic effects.

Both *m*-xylene and *n*-Butyl Alcohol caused a concentration-dependent decline in the respiratory rate of mice. The maximum decrease of respiratory rate was always observed in the 1st min of exposure. The effect of *m*-xylene was more distinct than that of *n*-Butyl Alcohol. The effect of the mixture of *m*-xylene and *n*-Butyl Alcohol was similar to that of *n*-Butyl Alcohol. The authors stated that the effect was lower than would be expected assuming the additive effects of individual solvents (Korsak et al. 1992).

Subchronic Toxicity

According to Elder (1987), a group of 30 male Wistar rats received drinking water containing 6.9% *n*-Butyl Alcohol and 25% sucrose for 13 weeks. Control rats received tap water. At 1 month, the hepatic mitochondria were often elongated, constricted, or cupshaped. The number of cristal membranes per mitochondrial profile was significantly decreased. In some hepatocytes, enlarged mitochondria were observed; these were pale and almost devoid of cristae. Similar observations were made at 2 months. In addition, some megamitochondria with diameters greater than 10 μm were observed. At 3 months, most of the hepatocyte mitochondria were enlarged, but coupling efficiencies were well preserved. The activities of mitochondrial monoamine oxidase and cytochrome oxidase in the treated rats were "moderately" decreased when compared to the control rats.

The rapid hydrolysis of butyl acetate to *n*-Butyl Alcohol and acetate in the blood suggested to Barton et al. (2000) that any hepatic effects of butyl acetate also might be caused by *n*-Butyl Alcohol. Butyl acetate was administered to rats via intravenous

(i.v.) injection or oral dosing. Measured blood levels of *n*-Butyl Alcohol in rats exposed to butyl acetate were about three times higher than blood levels of butyl acetate. A 500 mg/kg/day dose of butyl acetate for 13 weeks was predicted to result in a blood level of 4 to 6 μM *n*-Butyl Alcohol. These authors concluded that the blood level of *n*-Butyl Alcohol was not high enough to result in any hepatotoxicity.

Ocular Irritation

According to Elder (1987), *n*-Butyl Alcohol produced injury when 0.005 ml of test material was instilled in albino rabbit eyes as follows: *n*-Butyl Alcohol received a grade of 7 (on a scale of 0 to 20), a 40% solution had a score of over 5.0, and a 15% solution had a score of less than 5.0. A 5.0 score was representative of corneal necrosis, visible only after staining and covering about 75% of the surface of the cornea or a more severe necrosis covering a smaller area.

Inhalation Toxicity

Elder (1987) reported that irritation of the mucous membranes is one effect of exposure of laboratory animals to *n*-Butyl Alcohol; other effects include intoxication, restlessness, ataxia, prostration, and narcosis. High concentrations of *n*-Butyl Alcohol vapors can be fatal. Laboratory animals have been reported to adapt to low concentrations of *n*-Butyl Alcohol vapors during chronic exposure. Chronic and subchronic exposures can cause changes in various organs of animals and in enzyme activity.

Sensory irritation of the upper respiratory tract of mice by *n*-Butyl Alcohol vapors was accompanied by a reflex pause in the expiratory phase of respiration. A 1268-ppm concentration of *n*-Butyl Alcohol resulted in a 50% decrease in the respiratory rate of the mice. Rats exposed to 8000 ppm *n*-Butyl Alcohol for 4 h did not die. Male albino rats exposed to a saturated or concentrated *n*-Butyl Alcohol vapor for 8 h survived for 14 days; survival was reduced for exposure times longer than 8 h.

In another study, three guinea pigs were exposed to 100 ppm *n*-Butyl Alcohol vapor every day for 2 weeks (exposure periods unspecified) and then to 100 ppm *n*-Butyl Alcohol vapor for 4 h periods 6 days a week for about 2½ months. All three guinea pigs survived the 64 exposures. However, red blood cell counts decreased, and a relative and absolute lymphocytosis was observed. Two of the three animals had hemorrhagic areas in the lungs and a transient albuminuria. A second group of three guinea pigs was exposed to the same concentration of *n*-Butyl Alcohol.

After 30 exposures, all three developed a severe skin infection and, as a result, two of the three guinea pigs died at the 38th exposure. A decrease in red blood cell number and hemoglobin and an increase in leukocytes were observed. However, due to the skin infection, the polymorphonuclears dominated toward the end of the exposure period. The surviving guinea pig gained weight and had an improved blood picture by the end of the experiment.

The livers of the guinea pigs had early toxic degeneration, and there was "considerable evidence" of renal degeneration; these were probably both attenuated by the infection.

Another group of guinea pigs was exposed to the same concentration of *n*-Butyl Alcohol vapor for 28 exposure periods; early hepatic cell degeneration and more marked renal degeneration were observed. There was an increase in red blood cells and an absolute and relative lymphocytosis. A skin infection resulted in the deaths of one of three control guinea pigs placed in the gassing chamber daily with no exposure to *n*-Butyl Alcohol and of one of three untreated controls that remained in cages throughout the experiments. The control guinea pigs appeared clinically normal (Elder 1987).

Ototoxicity

Crofton et al. (1994) investigated solvent-induced ototoxicity in rats. Male Long Evans hooded rats (60 to 70 days of age) were exposed via inhalation in flow-through chambers. The animals came in contact with the air or vapors of styrene (1600 ppm), 1,1,2-trichloroethylene (3500 ppm), toluene (2500 ppm), or mixed xylene (1800 ppm) for 8 h per day for 5 days ($N = 7-8/\text{group}$). *n*-Butyl Alcohol exposures (4000 ppm) were limited to 6 h per day for 5 days due to cost restraints ($N = 10/\text{group}$). Testing was conducted 5 to 8 weeks after exposure using reflex modification audiometry (RMA). RMA thresholds were determined for frequencies of 0.5 to 40 kHz.

All solvents except *n*-Butyl Alcohol caused hearing defects in the mid-frequency range. *n*-Butyl Alcohol did not affect hearing thresholds in rats (Crofton et al. 1994).

Neurological Effects

Schulze (1988) described a study of 2,4-dichlorophenoxy-acetic acid (2,4-D-) esters and related alcohols were administered to rats and tested for their ability to increase landing foot splay, a measure of ataxia. Five adult male albino Wistar rats (approximately 200 days old) were used in this study. 2,4-D-*n*-butyl ester (99% pure); a 50:50 mixture consisting of 2,4-D-*n*-butyl ester and 2,4-D-isobutyl ester (99% pure); 2,4-D alone, *n*-Butyl Alcohol; 2-butanol; and a 50:50 mixture of *n*-Butyl Alcohol and 2-butanol were used.

Each test compound or mixture was emulsified into a vehicle of 20% Emulphor® in sterile distilled bacteriostatic (0.9% benzyl alcohol) water and administered via subcutaneous (s.c.) injection in volumes of 1 ml/kg. 2,4-D was diluted into a 3:2:5 mixture of Emulphor®, ethanol, bacteriostatic water and administered via subcutaneous injection in a volume of 1 ml/kg.

The behavioral endpoints measured were landing foot splay or photocell monitored locomotor activity. Motor activity was measured by placing rats in a PAC-001 photobeam activity chamber located in a sound attenuated room for 5 min per day. Landing foot splay was measured by placing colored ink on all four paws and then dropping the animal from a height of

30 cm onto a sheet of absorbent paper. The distance (cm) between each hind-limb was measured.

When administered for 3 to 4 straight days, 2,4-D-*n*-butyl ester (150 mg/kg/day s.c.) produced significant increases in landing foot splay whereas 2,4-D (120 mg/kg/day s.c.) and 2,4-D mixed butyl esters (150 mg/kg/day s.c.) did not. The ability of acute *n*-Butyl Alcohol, 2-butanol, and a 50:50 mixture of both (2.13 mM/kg s.c.) to increase landing foot splay was then assessed. Only *n*-Butyl Alcohol significantly increased landing foot splay.

When *n*-Butyl Alcohol was administered daily, at doses corresponding to 150 mg/kg/day of the 2,4-D-*n*-butyl ester, significant increases in landing foot splay were evident. The pattern of splay increases was similar to that of 2,4-D-*n*-butyl ester.

When locomotor activity was the dependent variable, daily *n*-Butyl Alcohol had no effect. The authors suggested that the *in vivo* formation of *n*-Butyl Alcohol following administration of 2,4-D-*n*-butyl ester is responsible for the motor incoordination, but not the depression of locomotor activity observed following 2,4-D-*n*-butyl ester administration (Schulze 1988).

David et al. (1998) evaluated the subchronic neurotoxicity of *n*-butyl acetate vapor (note: *n*-butyl acetate is metabolized to acetate and *n*-Butyl Alcohol) in male and female Sprague-Dawley rats using a functional observational battery, motor activity, neurohistopathology, and schedule-controlled operant behavior (SCOB) as indicators of neurotoxicity. Animals were exposed to concentrations of 0, 500, 1500, or 3000 ppm of *n*-butyl acetate for 6 h per day for 65 exposures over a period of 14 weeks. Functional observational battery and motor activity values for ad libitum fed male and female rats were measured during weeks 1, 4, 8, and 13. SCOB testing of food-restricted animals, using a multiple fixed ratio/fixed interval schedule, was conducted daily before each exposure to maintain the operant behavior. The data from weeks 1, 4, 8, and 13 were evaluated for evidence of neurotoxicity.

Short-term signs of sedation and hypoactivity were observed only during exposure to the 1500 and 3000 ppm concentrations. The only signs of systemic toxicity were decreased body weights for the 3000 ppm ad libitum fed groups and occasionally for the female 1500 ppm ad libitum fed group. There was no evidence of neurotoxicity during the functional observational battery examinations.

Motor activity for the 3000 ppm male group was significantly higher than the control group only during week 4 ($p \leq .05$). No significant differences were observed among groups for weeks 8 and 13. No significant differences in motor activity values were observed for female rats. No significant differences were seen in operant behavior at any test vapor concentration.

Microscopic evaluations of sections from the brain, spinal cord (cervical and lumbar regions), dorsal and ventral spinal roots, dorsal root ganglia, sciatic nerve, and tibial nerve of animals in the control and 3000 ppm groups did not show any treatment-related effects. The authors concluded that there was no evidence of cumulative neurotoxicity based on the functional

observational battery, motor activity, neurohistopathology, and schedule-controlled operant behavior end points. The authors suggested that the data are relevant to the neurotoxicity risk assessment of *n*-Butyl Alcohol due to the rapid hydrolysis of *n*-butyl acetate in vivo (David et al. 1998).

According to Deisinger (2001), *n*-butyl acetate, *n*-Butyl Alcohol, and *n*-butylaldehyde are known to cause central nervous system depression in experimental animals after oral and inhalation exposures at high concentrations. In a dose-selection study, the maximum tolerated dose was defined as that which resulted in no observable acute toxicity or respiratory depression persisting for greater than 15 s. The no-effect level for i.v. administration of *n*-Butyl Alcohol was 120 mg/kg.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Nelson et al. (1988a) assessed the teratology of *n*-Butyl Alcohol, 2-butanol, and *t*-butanol administered by inhalation to rats. Groups of about 15 Sprague-Dawley rats were used in this study. Virgin females (200 to 300 g) were individually placed with breeder males. Day 1 was established when spermatozoa were found in vaginal smears after mating. Bred females were individually placed into cages. Weekly food and water intake, as well as maternal weights, were measured on gestation days 0, 7, 14, and 20. Females were also weighed each morning during the first week of exposure.

On gestation days 1 to 19, females were placed into separate compartments within the exposure chambers. The control animals were placed in similar cages within an adjacent exposure chamber for the same hours as the exposed animals. The animals were exposed at 8000, 6000, 3500, or 0 ppm *n*-Butyl Alcohol, 7000, 5000, 3500, or 0 ppm 2-butanol, or 5000, 3500, 2000, or 0 ppm *t*-butanol on gestation days 1 to 19 (sperm = 0). Exposures occurred 7 h per day, and the animals were left in the chamber for degassing for about 1/2 h after vapor generation was terminated.

On day 20 of gestation, pregnant females were weighed individually and killed by CO₂ asphyxiation. One half of the fetuses were selected at random, placed into 80% ethanol, eviscerated, macerated in 1.5% KOH, stained in alizarin red S, and examined for skeletal malfunctions and variations. The remaining fetuses were placed in Bouin's solution and examined for visceral malformations and variations using a razor blade cross-sectioning technique.

For each butanol isomer considered, the highest concentration (and the intermediate in some instances) was maternally toxic, as manifest by reduced weight gain and feed intake. Even at a maternally toxic dose, and without being affected by a dose-dependent reduction in fetal weights for each isomer, the only developmental toxicity detected was a slight increase in skeletal malformations (primarily rudimentary cervical ribs), seen with the highest concentration of *n*-Butyl Alcohol. The authors stated that concentrations 50 times the current permissible

exposure limits for these three butyl isomers do not produce developmental toxicity in rats (Nelson et al. 1988a).

Nelson et al. (1989b) investigated behavioral teratology of *n*-Butyl Alcohol in rats. A concentration of 6000 ppm was selected as the high concentration due to slight maternal toxicity and 3000 ppm was the low concentration evaluated. These two concentrations were administered via inhalation to separate groups of 15 pregnant Sprague-Dawley rats for 7 h per day throughout gestation; 18 male rats were exposed to the same concentrations of *n*-Butyl Alcohol for 7 h per day for 6 weeks, and mated to unexposed females.

On the day of birth (day 0), litters were culled to 4 females and 4 males (± 1) and fostered to untreated controls. Offspring were weighed weekly through 5 weeks of age. On postnatal day 10, one female and one male per litter were randomly assigned to one of the four test groups. The animals were tested on days 10 to 90 using ascent on a wiremesh screen; rotorod; open field, photoelectrically monitored activity; running wheel; avoidance conditioning; and operant conditioning.

Additionally, on day 21, brains from 10 offspring per treatment group (1 male and 1 female/litter) were collected and after microwave fixation, were dissected into four general brain regions (cerebrum, cerebellum, brainstem, and midbrain), and analyzed for steady-state levels of protein and the neurotransmitters acetylcholine, dopamine, norepinephrine, serotonin or 5-hydroxytryptamine, substance P, β -endorphin, and met-enkephalin.

Concentrations measured in the exposure chambers approximated the target concentrations of 3000 and 6000 ppm. Mean *n*-Butyl Alcohol concentrations were 3010 (± 50) and 6000 (± 80) ppm, and results of periodic confirmatory charcoal tube samples were 3000 (± 90) and 5960 (± 110) ppm, respectively.

Inhalation of these concentrations of *n*-Butyl Alcohol had no effect on pregnancy rate after maternal or paternal exposure. Results from behavioral testing of the offspring indicated that there were no significant effects on the ascent test, rotorod, open field performance, or operant conditioning. In the photoelectric activity monitor, the counts were significantly lower than controls in the female offspring from paternal animals exposed to 3000 ppm *n*-Butyl Alcohol, $F(2, 39) = 6.01$, $p = .01$.

In avoidance conditioning, there were no effects in the animals tested beginning on day 34; in the animals tested beginning on day 60, both the time receiving shock (the escape period; $F(2, 43) = 39.37$, $p < .01$) and the total number of times the rats crossed one side of the cage to the other (escape and avoidance responses plus random side changes during session; $F(2, 43) = 8.58$, $p < .01$) were elevated from controls in the offspring whose male parent was exposed to 6000 ppm *n*-Butyl Alcohol. At 3000 ppm *n*-Butyl Alcohol, the older male offspring from the paternal exposure group required fewer trials to reach criterion in avoidance conditioning, $F(2, 38) = 6.81$, $p < .01$, than the other groups.

Neurochemical analysis revealed few differences in offspring from exposure and control groups (4 out of 64 [32 measures

times the two exposure groups]), and no treatment-related patterns were discernible. The multivariate analysis of variance for the main effect of group at the higher concentration of *n*-Butyl Alcohol was significant, $F(6, 16) = 4.11$, $p < .045$, but for the lower concentration it was not, $F(6, 16) = 2.63$, $p = .12$.

At the high concentration, the significant analysis of variance, which tested for significant differences between means, were determined for serotonin (the overall mean $\pm$ SEM from offspring of paternal exposure was 14.48 ± 2.38 versus the control value of 7.802 ± 1.48 , $p < .005$, with both brainstem and midbrain means being over twice as high as the control level) and dopamine (the overall mean $\pm$ SEM from offspring of paternal exposure was 0.715 ± 0.127 versus the control value of 0.515 ± 0.095 , $p < 0.046$, with all brain regions being 20% to 40% higher than controls). For norepinephrine and met-enkephalin, the individual comparisons of offspring from maternal or paternal groups were not significant.

Overall, the authors concluded there were few behavioral or neurochemical alterations detected in the offspring following maternal or paternal exposure to either 3000 or 6000 ppm *n*-Butyl Alcohol (Nelson et al. 1989b).

Barilyak et al. (1991) compared embryotoxic effects of methyl alcohol, ethyl alcohol, *n*-Butyl Alcohol, nonanol, and decanol (alcohols with increasing chain length) using rats, as well as the activity of alcohol dehydrogenase in rat hepatocytes. The experiment was performed on random bred white rats weighing 160 to 180 g. Alcohols as 40% water solutions were administered by gavage in a volume of 1 ml from days 1 to 15 of pregnancy; water was used as the control. The day when spermatozoa were found after mating was considered to be day 1 of pregnancy.

The rats were killed by cervical dislocation on day 20 of pregnancy. Following laparotomy, the number of yellow bodies was counted in the ovaries and the numbers of dead and live fetuses were counted in the uterus. The live (normal and abnormal) fetuses were examined; in some embryos (one to two from each female) the liver was excised and the activity of alcohol dehydrogenase (ADH) (EC 1.1.1.1) was determined. Protein was determined by the xanthoprotein reaction. To track changes in the ADH activity in embryonic hepatocytes, these measurements were carried out in fetuses from day 16 until day 21 of antenatal development, as well as on days 1, 3, and 20 of postnatal life. There were 534 live fetuses obtained from these rats, including 194 in the control. Historical control data also were provided.

All tested alcohols produced embryotoxicity as shown in Table 4. Fetal death at both the preimplantation and postimplantation stages were noted. The fertility index was reduced compared to the control. The authors suggested that the embryotoxic effect decreased with increasing alcohol chain length.

The ADH activity was maximal in 20-day-old embryos, but 16.4% lower than that of intact rats and 84.5% lower than in pregnant rats. In the newborn rats, the ADH activity increased by day 20 of postnatal life and was 35.2% greater than in intact

rats, but remained 74.8% lower than in pregnant rats. Following administration of monoatomic alcohols to pregnant rats, the ADH activity decreased in the liver of 20 day old embryos. Methyl alcohol decreased the ADH activity by 52.2%, ethyl alcohol by 38%, butyl alcohol by 77.6%, nonanol by 17.2%, and decanol by 69.6% (Barilyak et al. 1991).

Sitarek et al. (1994) assessed the effect of *n*-Butyl Alcohol on the sexual cycle and fertility of female rats and on the development of their offspring. Female rats, approximately 10 weeks old (180 to 200 g), that had never given birth were used. Three treatment groups consisting of 11 to 17 females were given aqueous solutions containing 0.24%, 0.8%, and 4% *n*-Butyl Alcohol (0.3, 1.0, and 5.0 g/kg/day, respectively) for 8 weeks before and during gestation. The 16 control animals were given tap water. The experiment was divided into two stages: (1) assessment of estrus cycle and (2) effect on fertility and fetal development.

Vaginal smears to determine the estrus cycle were taken daily between 8 and 10 AM in all animals for 14 consecutive days prior to exposure, and then during the 4th, 5th, 7th, and 8th weeks of exposure. Eight weeks following treatment, all the females were mated with untreated 17-week-old male rats for a maximum of 3 weeks. The day of detection of spermatozoa in the vaginal smears was considered to be day 0 of gestation. Administration of *n*-Butyl Alcohol was continued throughout the mating and gestation period. The overall behavior of the animals was observed throughout the experiment. Weight increases and the daily food, water, or *n*-Butyl Alcohol solutions intake were monitored every week in the nonpregnant females and on days 3, 7, 10, and 17 of gestation in the pregnant animals. On day 20 of gestation, the female rats were killed.

Table 5 summarizes the findings on the effect of *n*-Butyl Alcohol on pregnant and fetal development in rats. Overall, the appearance and behavior, body weight gain, and food and liquid intake of the animals exposed to *n*-Butyl Alcohol given in drinking water during the 8 weeks were similar to that observed in the control animals. There were no mortalities in either group. There was a similar cycle duration of 4 days on average in the control rats and exposed female rats.

The duration of the individual stages of the estrus cycle was not dependent on exposure to *n*-Butyl Alcohol and was similar to that observed in the control animals. Body weight gain during gestation, food and liquid (water or *n*-Butyl Alcohol solutions) intake, absolute and relative organ weights, hemoglobin concentration, and hematocrit values did not differ between the exposed and control groups.

n-Butyl Alcohol given to the female rats in drinking water during the 8 weeks prior to fertilization and until day 20 of gestation did not adversely affect fetal body weight. The intrauterine mortality in the controls, which were given tap water, was similar to that in the animals exposed to *n*-Butyl Alcohol at 0.3 to 5.0 g/kg daily doses. Fetuses of the animals receiving *n*-Butyl Alcohol at a dose concentration of 5.0 g/kg were significantly smaller than those of the control animals.

TABLE 4
Embryotoxic effects of alcohols administered to rats (Barilyak et al. 1991).

Alcohol	Rats per group	Number of yellow bodies	Number of implantations	Death of fetuses, % ^a			Number of live fetuses	Index of fertility
				Before implantation	After implantation	Total		
Methanol (C ₁)	11	111	74	33.5 ± 4.5	25.7 ± 5.1	50.4 ± 4.7	55	5.0
Ethanol (C ₂)	16	163	114	29.4 ± 3.5	39.5 ± 4.6	57.1 ± 3.9	70	4.4
<i>n</i> -Butyl Alcohol (C ₄)	10	106	83	21.7 ± 4.0	21.7 ± 4.4	38.7 ± 4.7	65	6.5
Nonanol (C ₉)	10	101	88	12.9 ± 3.3	25.0 ± 4.6	34.6 ± 4.7	76	7.6
Decanol (C ₁₀)	10	106	90	15.1 ± 3.5	17.8 ± 4.0	30.2 ± 4.4	74	7.4
Control	20	207	203	2.0 ± 1.0	4.4 ± 1.4	6.3 ± 1.7	194	9.7
Historical Controls	362	3684	3668	5.6 ± 0.4	5.2 ± 0.4	10.5 ± 0.5	3476	9.6

^aAll indices of the embryotoxic activity in the experimental groups are reliably higher than in the control ($p < .001$). C₁₋₁₀, number of carbon atoms in the alcohol molecules.

TABLE 5
Effect of *n*-Butyl Alcohol on fetal development in rats (Sitarek et al. 1994).

Parameter	Findings			
	Control	<i>n</i> -Butyl Alcohol dose (g/kg/day)		
		0.3	1.0	5.0
Females examined	16	17	17	11
Females inseminated	16	16	15	11
Females pregnant	12	14	12	9
Females not pregnant	4	2	3	2
Live fetuses per litter ^a	10.5 ± 3.1	11.0 ± 1.4	12.2 ± 1.9	11.3 ± 2.2
Litters with resorptions	12	9	7	9
Litters with early resorptions	10	9	7	9
Litters with late resorptions	5	2	3	2
Early resorptions per litter ^a	0.8 ± 0.4	1.1 ± 1.0	1.2 ± 1.5	1.8 ± 1.3
Late resorptions per litter ^a	0.7 ± 1.2	0.1 ± 0.4	0.3 ± 0.5	0.2 ± 0.4
Corpora lutea ^a	14.8 ± 2.6	14.6 ± 1.8	14.5 ± 2.1	15.1 ± 2.6
Total implants ^a	12.0 ± 3.2	12.3 ± 2.1	13.6 ± 2.0	13.3 ± 2.3
Preimplantation losses ^a	2.8 ± 2.1	2.4 ± 0.9	1.5 ± 1.6	2.0 ± 1.9
Postimplantation losses ^a	1.5 ± 1.2	1.3 ± 1.3	1.4 ± 1.8	2.0 ± 1.6
Mean daily food intake (g) ^b	21.2 ± 5.4	19.4 ± 4.6	19.4 ± 3.4	18.8 ± 1.5
Mean daily water intake (ml) ^b	30.3 ± 7.9	30.5 ± 6.9	35.1 ± 9.3	27.7 ± 4.2
Body weight gain of dams (g) ^a	89.6 ± 18.9	90.0 ± 18.5	94.3 ± 16.9	93.9 ± 12.7
Fetal body weight (g) ^c	3.2 ± 0.2	3.2 ± 0.3	3.2 ± 0.2	3.2 ± 0.3
Fetal crown-rump length (cm) ^c	4.0 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.8 ± 0.1 ^d
Placental weight (g) ^c	0.55 ± 0.07	0.48 ± 0.07	0.53 ± 0.05	0.60 ± 0.13

^aMean ± SD.

^bTotal mean ± SD calculated through 20 days of gestation.

^cMean of litter mean ± SD.

^dSignificantly different from control ($p < .05$).

TABLE 6

Skeletal and visceral effects in fetuses of female rats exposed to *n*-Butyl Alcohol (Sitarek et al. 1994).

Parameter	Findings			
	Control	<i>n</i> -Butyl Alcohol dose (g/kg/day)		
		0.3	1.0	5.0
Visceral observations				
No. of fetuses (litters) examined	61 (12)	73 (14)	71 (12)	51 (9)
Percentage of fetuses (litters) with dilation of	2 (8)	25 ^a (64) ^a	32 ^a (83) ^a	41 ^a (100) ^a
Subarachnoid space	0	3 (14) ^a	10 ^a (25) ^a	20 ^a (78) ^a
Lateral ventricle and/ or third ventricle of the brain	2 (8)	23 ^a (57) ^a	17 ^a (67) ^a	25 ^a (78) ^a
Unilateral renal pelvis	0	0	7 ^a (42) ^a	0
Bilateral renal pelvis	0	0	4 (25) ^a	0
Percentage of fetuses (litters) with congenital defects	0	0	7 ^a (33) ^a	4 (22) ^a
External hydrocephalus	0	0	3 ^a (17) ^a	0
Internal hydrocephalus	0	0	7 ^a (25) ^a	4 (22) ^a
Skeletal observations				
No. of fetuses (litters) examined:	65 (2)	81 (14)	75 (12)	51 (9)
Percentage of fetuses (litters) with delayed ossification:	15 (67)	16 (50)	24 (58)	33 ^a (67)
Percentage of fetuses (litters) with congenital defect	0	1 (7) ^a	0	2 (11) ^a
14th rib (L ₁)	0	0	0	2 (11) ^a
Wavy ribs	0	1 (7) ^a	0	0

^aSignificantly different from the control ($p < .05$).

Table 6 summarizes the skeletal and visceral effects in fetuses of pregnant rats exposed to *n*-Butyl Alcohol, including a dilation of subarachnoid space, cerebral ventricles, and renal pelvis, and a retarded ossification of the sternum. The authors noted that these changes existed only in the animals exposed to high *n*-Butyl Alcohol doses.

When *n*-Butyl Alcohol was given to female rats before fertilization and during gestation at daily doses of 0.3 to 0.5 g/kg body weight, developmental anomalies in the fetal skeleton and central nervous system defects were observed. Internal hydrocephalus was the anomaly most frequently found in the fetuses of female rats exposed to *n*-Butyl Alcohol.

n-Butyl Alcohol given to female rats before fertilization and during gestation at daily doses of 0.3 to 5.0 g/kg body weight resulted in developmental anomalies in the fetal skeleton, including wavy rib in the 13th rib pair and the presence of an extra rib in the 14th pair and central nervous system defects. Internal hydrocephalus was the most frequent anomaly observed in the fetuses of treated female rats. Other changes include a dilation of subarachnoid space, cerebral ventricles, and renal pelvis, and a retarded ossification of the sternum. According to these authors, *n*-Butyl Alcohol administered to female rats at high doses of 1 and 5.0 mg/kg/day is considered to be a fetotoxic agent (Sitarek et al. 1994).

Ema et al. (2004) reported on a developmental toxicity study using Crj:CD (SD) rats. *n*-Butyl Alcohol used in this study was 99.9% pure and a special grade reagent (lot no. CER 65688;

Wako Pure Chemical Industries, Ltd., Osaka, Japan). Healthy male rats at 10 weeks of age and virgin female rats at 9 weeks of age were mated overnight. The day when sperm were detected in the vaginal smear was considered to be day 0 of pregnancy. Pregnant rats weighed 217 to 273 g and were 10 to 11 weeks of age when they were distributed into four groups of 20 rats each and housed individually. On days 0 to 20 of pregnancy, rats were given drinking water containing *n*-Butyl Alcohol at concentrations of 0%, 0.2%, 1.0%, or 5.0% (0, 316, 1454, or 5654 mg/kg/day). The dosage levels were determined based on the results of a range-finding study. Maternal body weight and water consumption were observed and recorded every 3 or 4 days.

All females of every group became pregnant and there was no death found in female rats of any group. At the highest dose level, significant decrease in maternal body weight accompanied by reduced food and water consumption was found; fetal weight was lowered; and there was an increase in the incidence of fetuses with skeletal variations and decreased degree of ossification. Maternal toxicity is described in Table 7.

However, there was no increase in the incidence of fetuses with external, skeletal, and internal abnormalities at any dose level, and there was no significant increase in the incidence of preimplantation and postimplantation embryonic loss at any dose level. Reproductive findings are described in Table 8. The authors concluded that *n*-Butyl Alcohol is a developmental

TABLE 7
Maternal toxicity in rats given *n*-Butyl Alcohol on days 0 to 20 of pregnancy (Ema et al. 2005).

Parameter	Dose (%)			
	0 (control)	0.2	1.0	5.0
No. of rats	20	20	20	20
No. of pregnant rats	20	20	20	20
No. of dead rats	0	0	0	0
Initial body weight	245 ± 14	247 ± 13	245 ± 11	244 ± 12
Body weight gain during pregnancy (g) ^a				
Days 0–7	44 ± 7	45 ± 7	40 ± 6	20 ± 28 ^c
Days 7–14	40 ± 6	41 ± 5	41 ± 7	42 ± 10
Days 14–20	78 ± 14	82 ± 8	84 ± 7	75 ± 11
Days 0–20	162 ± 19	168 ± 16	165 ± 15	146 ± 16 ^c
Food consumption during pregnancy (g) ^a				
Days 0–7	179 ± 12	180 ± 16	164 ± 12 ^b	138 ± 21 ^c
Days 7–14	40 ± 6	41 ± 5	41 ± 7	42 ± 10
Days 14–20	78 ± 14	82 ± 8	84 ± 7	75 ± 11
Days 0–20	162 ± 19	168 ± 16	165 ± 15	146 ± 16 ^c
Water consumption during pregnancy (ml) ^a				
Days 0–7	284 ± 28	305 ± 37	258 ± 29 ^b	175 ± 34 ^c
Days 7–14	318 ± 35	337 ± 48	299 ± 40	239 ± 80 ^c
Days 14–20	328 ± 47	342 ± 47	334 ± 46	256 ± 85 ^c
Days 0–20	930 ± 105	983 ± 126	890 ± 106	669 ± 182 ^c

^aValues are given as the mean ± SD.

^bSignificantly different from the control, $p < .05$.

^cSignificantly different from the control, $p < .01$.

toxicant only at maternally toxic doses. Based on the significant decreases in maternal body weight gain and fetal weight, authors reported no observed adverse effect levels (NOAELs) of *n*-Butyl Alcohol for both dams and fetuses are 1.0% (1454 mg/kg/day) in rats (Ema et al. 1994).

GENOTOXICITY

Elder (1987) reported that *n*-Butyl Alcohol was found to be nonmutagenic in the *Salmonella*/mammalian-microsome mutagenicity test. A 15% aqueous *n*-Butyl Alcohol solution did not induce sister chromatid exchanges or chromosome breakage in the “chick embryo cytogenetic test.” Treatment of Chinese hamster ovary cells for 7 days with 0.1% *n*-Butyl Alcohol (*v/v*) resulted in no increase in the number of sister-chromatid exchanges observed per mitosis. *n*-Butyl Alcohol did not induce micronuclei formation in V79 Chinese hamster ovary cells.

Muller et al. (1993) reported on *Salmonella typhimurium* TA102 as a screen for mutagenicity of 30 chemical compounds of various chemical classes, performed in three laboratories. Aromatic amines often produce poor results in standard Ames tests. *n*-Butyl Alcohol was not mutagenic in any of the tests.

Engelhardt et al. (1998) examined chromosome-damage and damage of the mitotic apparatus in NMRI mice after a single

oral administration of *n*-Butyl Alcohol using the micronucleus test method. The mice had mean weights of 26.9 g (with an age range of about 5 to 8 weeks). Olive oil was chosen as the vehicle because of the limited solubility of *n*-Butyl Alcohol in water. The test substance was dissolved in oil and administered once orally to male and female animals at dose levels of 500, 1000, and 2000 mg/kg body weight in a concentration of 10 ml/kg body weight in each case.

As a negative control, both male and female mice were orally administered just olive oil. Control frequencies of micronucleated polychromatic erythrocytes were within the historical control range. Both positive control chemicals (cyclophosphamide for chromosome aberrations and vincristine for mitotic spindle effects) led to the expected increase in the rate of polychromatic erythrocytes containing small or large micronuclei.

n-Butyl Alcohol did not lead to any increase in the rate of micronuclei. Animals that were given the vehicle or the positive control substances (cyclophosphamide or vincristine) did not show any clinical signs of toxicity, but there were signs of toxicity in the highest *n*-Butyl Alcohol dose group, including irregular respiration, abdominal position, piloerection and squatting posture after about 30 to 60 min; the general state of the animals was poor. Piloerection had been observed in the 1000 mg/kg dose group as well.

TABLE 8
Reproductive Findings in Rats Given *n*-Butyl Alcohol on Days 0–20 of Pregnancy (Ema et al. 2005).

Parameter	Dose (%)			
	0 (control)	0.2	1.0	5.0
No. of litters	20	20	20	20
No. of litters totally resorbed	0	0	0	0
No. of corpora lutea per litter ^a	16.4 ± 3.6	16.7 ± 3.0 ^d	16.1 ± 2.1	16.3 ± 2.6
No. of implantations per litter ^a	14.3 ± 2.8	15.1 ± 1.7	15.2 ± 1.2	14.7 ± 2.5
% preimplantation loss per litter ^b	9.0	9.0 ^d	4.4	9.2
% postimplantation loss per litter ^c	6.0	5.4	3.7	8.0
No. of live fetuses per litter ^a	13.4 ± 2.6	14.3 ± 1.4	14.7 ± 1.5	13.5 ± 2.5
Sex ratio of live fetuses (male/female)	128/139	145/140	149/144	131/139
Body weight of live fetuses (g) ^a				
Male	4.18 ± 0.27	4.00 ± 0.24	4.04 ± 0.25	3.83 ± 0.18 ^e
Female	3.97 ± 0.25	3.86 ± 0.20	3.83 ± 0.16	3.59 ± 0.17 ^e
Fetal crown-rump length (mm) ^a				
Male	40.5 ± 1.2	40.3 ± 1.4	40.2 ± 1.2	39.7 ± 1.3
Female	39.4 ± 1.2	39.4 ± 1.2	39.3 ± 1.1	38.5 ± 1.4
Placental weight (g)				
Male	0.50 ± 0.05	0.49 ± 0.05	0.48 ± 0.06	0.50 ± 0.06
Female	0.49 ± 0.05	0.48 ± 0.05	0.47 ± 0.05	0.49 ± 0.06

^aValues are given as the mean ± SD.

^b(No. of preimplantation embryonic loss/no. of corpora lutea) × 100.

^c(No. of resorptions and dead fetuses/no. implantations) × 100.

^dValue was obtained from 19 pregnant rats.

^eSignificantly different from the control, *p* < .01.

The authors concluded that the single oral administration of *n*-Butyl Alcohol did not lead to any increase in the number of polychromatic erythrocytes containing either small or large micronuclei, and no inhibition of erythropoiesis determined from the ratio of polychromatic to normochromatic erythrocytes was detected (Engelhardt et al. 1998).

CLINICAL ASSESSMENT OF SAFETY

According to Elder (1987), 105 dermatological patients were tested with *n*-Butyl Alcohol using a chamber test on the upper back for non-immunological contact urticaria. No redness was observed in any patient, but four patients were positive for edema.

A nail color containing 3% *n*-Butyl Alcohol was studied in repeat-insult patch tests (RIPTs). In one study, a moderately intense erythema, with or without infiltration and involving at least 25% of the test area, was observed at challenge in 182 female and 10 male subjects; this finding, however, was not attributed to *n*-Butyl Alcohol exposure. In a second study of 173 female and 37 male subjects, no clinical response was noted at challenge. In the third study, a moderately intense erythema was observed at the second challenge in 115 female and 41 male subjects. Overall, the nail color was not considered to be a significant irritant or sensitizer.

Two additional RIPTs were performed using a nail enamel containing 3% *n*-Butyl Alcohol. In the first, a strong, infiltrated erythema and accompanying vesicles were noted at challenge in 182 female and 34 male subjects, but on further testing, the positive reaction was attributed to residual solvent (not *n*-Butyl Alcohol “solvent”). In the other study, only a faint erythema was noted in 144 female and 59 male subjects during induction. Overall, the nail enamel was not considered to be a significant irritant or sensitizer.

A photopatch test was conducted with the nail enamel containing 3.0% *n*-Butyl Alcohol in 30 subjects. No reactions were observed in any of the subjects. Under these test conditions, the nail enamel product was not considered a phototoxin and photoallergen (Elder 1987).

Nasal Irritation

Wysocki et al. (1996) examined the odor and irritation thresholds for *n*-Butyl Alcohol in 64 human subjects (49 females). The average age of the subjects was 37.5 years with an age range from 25 to 65. A total of 36 subjects were smokers. The study consisted of two experiments: (1) olfactory and chemesthetic sensitivities to *n*-Butyl Alcohol were evaluated in 32 acetone-exposed workers in a cellulose acetate production facility and (2) 32 nonexposed residents from the Philadelphia metropolitan

area. One individual (36-year-old female) withdrew from the study after completing the olfactory thresholds, which remained in the data set. Quantitative and qualitative measurements were performed.

Analytical grade *n*-Butyl Alcohol (99.8% pure) was used in this study. Mineral oil served as the diluent. The *n*-Butyl Alcohol was diluted in a tertiary series (each step was 33.3% as concentrated as the previous) from neat. The dilution series was made up of 26 steps ranging from 100% to $1.1802 \times 10^{-10}\%$ v/v. Direct measurements of vapor-phase concentrations were made. Immediately after completion of detection trials, intranasal irritation thresholds were obtained by using a similar, two-alternative, forced-choice, modified, staircase method. Unlike the detection trials, each irritation trial required that subjects sniff only from a single pair of bottles; one bottle was a blank and the other contained either acetone or *n*-Butyl Alcohol.

Results of the threshold tests indicated that the median olfactory detection threshold for *n*-Butyl Alcohol was 0.17 ppm, significantly lower than the lateralization threshold of 2400 ppm. The average overall rated intensity increased with increasing concentrations of *n*-Butyl Alcohol. Responses to the categorical probes differed between acetone-exposed factory workers and nonexposed Philadelphia residents. Individuals in the two study groups experienced different perceptions of irritation at a concentration of *n*-Butyl Alcohol that was below the individual's irritation threshold but well above the individual's detection threshold. Overall, factory workers treated *n*-Butyl Alcohol as a non-irritating odorant, whereas the non-acetone-exposed population ascribed irritating properties to *n*-Butyl Alcohol.

These authors extended this work by performing the sensitivity portion of the testing on a group of 142 individuals ranging in age from 20 to 89 years of age to determine the effects of age. Each decade of age included at least 10 males and 10 females. The results indicated a reduced olfactory sensitivity to *n*-Butyl Alcohol and a reduction in intranasal chemesthesis with age (Wysocki et al. 1996).

Cometto-Muniz et al. (1998) reported a study of homologous alcohols of increasing chain length to track sensitivity for human nasal irritation using a detection procedure that required the subject to indicate whether a vapor has stimulated the right or left nostril. An anosmic group (having an impaired sense of smell) comprised five subjects: three men and two women. The normosmic group (normal sense of smell) comprised four subjects: three men and one woman. The homologous *n*-alcohols tested included 1-propanol, *n*-Butyl Alcohol, 1-hexanol, and 1-octanol.

Odor, nasal pungency, and eye irritation thresholds were measured using the two-alternative, forced-choice procedure with an ascending-concentration method of limits. The method required the participant to choose the stronger odor (odor, nasal pungency, or eye irritation) of the two stimuli. One stimulus was a blank, i.e., diluent, and the other was a certain dilution

step in a series. Testing began with the highest dilution step (i.e., the lowest concentration) and progressed to stronger levels whenever the subject chose incorrectly. The first step chosen correctly five times in a row was taken as the threshold.

The two-alternative forced-choice procedure with presentation of progressively higher concentrations was also used to measure thresholds for nasal localization in normosmics and anosmics. Five correct choices in a row for a given nostril was the criterion for the localization threshold.

The results indicated that the nasal pungency, the odor detection, nasal localization and ocular irritation thresholds decreased as chain length increased. Within the limits of resolution, the authors stated that detection thresholds and nasal localization thresholds yielded comparable indices of the potency of the volatile organic compounds to evoke nasal irritation (Cometto-Muniz et al. 1998).

Ocular Irritation

Hempel-Jorgenson (1999) reported the time course of sensory eye irritation in humans exposed to *n*-Butyl Alcohol and 1-octene. There were a total of 16 participants in the study (7 males, 9 females). All were healthy, did not wear contact lenses, and had not smoked for more than 6 months. The participants were all told not to wear any cosmetics on the days of the study.

The subjects were randomly exposed to *n*-Butyl Alcohol or 1-octene. The average ages of the groups exposed to *n*-Butyl Alcohol and 1-octene were 31.9 ± 16.3 and 33.5 ± 19.1 years, respectively. Target concentrations for *n*-Butyl Alcohol were 300, 950, and 3000 ppm. Measured values were 363 ± 26 , 1033 ± 20 , and 2731 ± 213 ppm. The authors concluded that the threshold for irritation was clearly exceeded for 1-octene exposures, but not *n*-Butyl Alcohol (Hempel-Jorgenson 1999).

Audiologic Impairment

Velazquez et al. (1969) reported audiologic impairment in workers in a small, noisy cellulose acetate ribbon factory, where *n*-Butyl Alcohol was the only solvent used. Twenty-three of the 47 individuals exposed to intense factory noise had audiologic impairment and the magnitude of the impairment was directly related to exposure duration. Nine of 11 individuals exposed to both noise and *n*-Butyl Alcohol had audiologic impairment and the magnitude of the impairment also was directly related to exposure duration. Absent any explanation of the high proportion of individuals with audiologic impairment among workers exposed to both noise and *n*-Butyl Alcohol, the authors hypothesized that *n*-Butyl Alcohol may be an etiologic agent.

In an unpublished review of this study, Royster (1993) was critical of these findings, noting among other factors that noise induced hearing loss is not seen in direct relationship to exposure time, but rather is more pronounced in the first 10 years of a working lifetime and incrementally changes less over the remainder of an individual's working lifetime.

Occupational Exposure

Elder (1987) reported that workers who used *n*-Butyl Alcohol alone or in combination with other solvents at six plants complained of ocular irritation, disagreeable odor, slight headache and vertigo, slight irritation of nose and throat, and dermatitis of the fingers and hands, when the air concentration of *n*-Butyl Alcohol was greater than 50 ppm. At several plants, the use of *n*-Butyl Alcohol was discontinued and the complaints ceased.

Corneal lesions have been described in workers exposed to *n*-Butyl Alcohol and diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) and denatured alcohol. Some workers complained of ocular irritation, foreign body sensation, epiphora, and burning of the eyes. Blurring of vision, itching and swelling of lids, and redness of the eyes were described less often.

A 10-year study was conducted on men exposed to *n*-Butyl Alcohol vapors in an industrial setting. An initial group of 16 workers was increased to 100. The initial 200 ppm *n*-Butyl Alcohol vapor concentration in the breathing zone was reduced so that the mean value for most of the 10 years was 10 ppm. No eye injuries or symptoms were observed in workers exposed to levels up to 100 ppm. Complaints were rare. There was only one transfer among several hundred workers; this single person disliked the odor of *n*-Butyl Alcohol. At 200 ppm, some workers described transient corneal inflammation with associated burning feeling, lacrimation, and photophobia. No systemic effects were observed (Elder 1987).

Exposure Limits

The American Conference of Governmental Industrial Hygienists (ACGIH 2007) gives a time-weighted average (TWA) allowable as 20 ppm for *n*-Butyl Alcohol stating that this concentration should not be exceeded even instantaneously. NIOSH (2007) gives a ceiling exposure of 50 ppm and lists OSHA's permitted exposure level (PEL) as a TWA of 100 ppm.

According to the European Agency for the Evaluation of Medicinal Products (EAEMP), *n*-Butyl Alcohol may be considered to be less toxic and of lower risk to human health than other solvents. Although there are no long-term toxicity or carcinogenicity studies for many of the solvents considered to have low toxic potential, many of the available data show that they are less toxic in acute or short-term studies and negative in genotoxicity studies. This source states that exposure to residual amounts of *n*-Butyl Alcohol of 50 mg/day or less (5000 ppm or 0.5%) would be acceptable (EAEMP 1997).

SUMMARY

n-Butyl Alcohol is a primary aliphatic alcohol generally used as a solvent in cosmetics. In 1981, *n*-Butyl Alcohol was reported as an ingredient in 112 cosmetic formulations at concentrations ranging from $\leq 0.1\%$ to 10% only in nail care products, but new concentration of use data indicate that *n*-Butyl Alcohol is also being used at low concentrations in eye makeup, personal hygiene, and shaving products. The highest current reported

concentration for 2005 is 4% in nail polish and enamel products; outside of this category, the highest use concentration is 0.002% in makeup foundations.

n-Butyl Alcohol has been generally recognized as safe for use as a flavoring substance in food and appears on the 1982 FDA list of inactive ingredients for approved prescription drug products.

n-Butyl Alcohol can be absorbed through the skin, lungs, and the gastrointestinal tract. Dogs given intravenous *n*-Butyl Alcohol eliminated about 15% of the administered dose in the breath as CO₂ and eliminated about 2.7% of the administered dose in the urine; no unchanged *n*-Butyl Alcohol was detected in the breath. It may be formed in vitro by hydrolysis of butyl acetate in the blood. In the blood, *n*-Butyl Alcohol is rapidly oxidized in vivo; it leaves animal blood quickly and oxidation products are undetectable. *n*-Butyl Alcohol is oxidized more rapidly than ethanol, probably due to the high substrate affinity of *n*-Butyl Alcohol to alcohol dehydrogenase. *n*-Butyl Alcohol is a hydroxyl radical scavenger. *n*-Butyl Alcohol can be oxidized nonenzymatically to *n*-butyraldehyde by ascorbic acid.

The single oral dose LD₅₀ of *n*-Butyl Alcohol for rats ranged from 0.79 to 4.36 g/kg. The dermal LD₅₀ for rabbits was reported as 4.2 g/kg.

Exposure to *n*-Butyl Alcohol can result in intoxication of laboratory animals, restlessness, irritation of mucous membranes, ataxia, prostration, and narcosis. High concentrations of *n*-Butyl Alcohol vapors can be fatal. At 1268 ppm, *n*-Butyl Alcohol caused a 50% decrease in the respiratory rate of mice.

Ocular irritation was observed for *n*-Butyl Alcohol at 0.005 ml of a 40% solution.

Inhalation toxicity studies in humans demonstrate sensory irritation of the upper respiratory tract, but only at levels above 3000 mg/m³. Animal studies demonstrate intoxication, restlessness, ataxia, prostration, and narcosis in animals, but exposures of rats to levels up to 4000 ppm failed to produce hearing defects. High concentrations of *n*-Butyl Alcohol vapors can be fatal. Laboratory animals have been reported to adapt to low concentrations of *n*-Butyl Alcohol vapors during chronic exposure.

The behavioral no-effect dose for *n*-Butyl Alcohol injected s.c. was 120 mg/kg.

Fetotoxicity has been demonstrated, but only at maternally toxic levels (1000 mg/kg). No significant behavioral or neurochemical effects were seen in offspring following either maternal or paternal exposure to 3000 or 6000 ppm.

n-Butyl Alcohol was not mutagenic in Ames tests, did not induce sister-chromatid exchange or chromosome breakage in chick embryos or Chinese hamster ovary cells, did not induce micronuclei formation in V79 Chinese hamster cells, did not have any chromosome-damaging effects in a mouse micronucleus test, and did not impair chromosome distribution in the course of mitosis.

Clinical testing of *n*-Butyl Alcohol for nonimmunological contact urticaria were negative in 105 subjects. RIPT studies of

nail colors and enamels containing 3% *n*-Butyl Alcohol in one study produced reactions on challenge, but further study linked significant positive reactions to another solvent. In other RIPT studies, only minimal reactions were reported. A photopatch test demonstrated that a nail enamel containing 3% *n*-Butyl Alcohol resulted in no reactions.

Workers complained of ocular irritation (when the air concentration of *n*-Butyl Alcohol was greater than 50 ppm) disagreeable odor, slight headache and vertigo, slight irritation of nose and throat, and dermatitis of the fingers and hands. At several plants, the use of *n*-Butyl Alcohol was discontinued, and the complaints ceased. One study of workers suggested hearing loss may be linked to *n*-Butyl Alcohol exposure, but the methodology may have been flawed.

The ACGIH TWA is 20 ppm, the NIOSH ceiling level is 50 ppm, and the OSHA TWA is 100 ppm.

DISCUSSION

When the CIR Expert Panel previously reviewed the safety of *n*-Butyl Alcohol, the only reported uses were in nail care products. The original safety assessment was specific in limiting the conclusion only to the use of *n*-Butyl Alcohol in nail products. Since then, additional cosmetic uses have been reported in bath soaps and detergents, eye makeup, foundations, lipstick, underarm deodorants, and aftershave lotions, all at low concentrations. Of these non-nail uses, the highest use concentration is 0.002% in makeup foundations.

The CIR Expert Panel recognizes that there are data gaps regarding use and concentration of this ingredient. However, the overall information available on the types of products in which this ingredient is used and at what concentration indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

Since the original safety assessment was completed, new safety test data have become available. The Panel noted that new studies including: in vitro inhibition of cell growth, behavioral toxicity and neurotoxicity in rats, inhalation toxicity, ototoxicity in animals, genotoxicity, reproductive and developmental toxicity, and one occupational study of hearing loss. An in vivo study in mice, for example, found no chromosome damage at dose levels up to 2 g/kg.

In reproductive and developmental toxicity studies, *n*-Butyl Alcohol was fetotoxic only at maternally toxic doses (~1 g/kg or higher) and no significant behavioral or neurochemical effects were seen in offspring following either maternal or paternal exposure to 3000 or 6000 ppm. The ototoxicity study failed to demonstrate an adverse effect of *n*-Butyl Alcohol and inhalation toxicity data were consistent with findings in the earlier safety assessment. Likewise, the new genotoxicity data did not suggest any risk, confirming the data in the earlier safety assessment.

The Panel did note that the summary of the original safety assessment describes RIPT studies of nail colors and enamels in such a way to suggest that virtually none of the subjects

studied had any reaction. In the text, it is correctly noted that reactions in subjects were seen widely on challenge, but that those reactions were either indicative of a minimal reaction or were subsequently linked to another component of the product tested, not *n*-Butyl Alcohol.

Taken together, neither the original safety assessment data nor the new data suggest any concern about the use of *n*-Butyl Alcohol in nail care products (at concentrations up to 15%) or in other product categories (at concentrations up to 0.002%). Although these other exposure categories do present routes of exposure not found with nail care products, the Panel noted that the uses outside of nail products have been reported at extremely low concentrations. And as noted above, there are no toxicity concerns at these use levels described for the several new uses.

CONCLUSION

The CIR Expert Panel concluded that *n*-Butyl Alcohol is safe as a cosmetic ingredient in the practices of use and concentration as described in this safety assessment.

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Final Report of the Cosmetic Ingredient Review Expert Panel

On the Safety Assessment of 1,2-Glycols as Used in Cosmetics

June 28, 2011

The 2011 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Manager/Lead Specialist.

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ABSTRACT: Caprylyl glycol and related 1,2-glycols are used mostly as skin and hair conditioning agents and viscosity agents in cosmetic products, and caprylyl glycol and pentylene glycol also function as cosmetic preservatives. The Expert Panel noted that these ingredients are dermally absorbed and that modeling data predict decreased skin penetration of longer-chain 1,2-glycols. The Panel concluded that negative oral toxicity data on shorter-chain 1,2-glycols and genotoxicity data support the safety of all of the 1,2-glycols reviewed in this safety assessment. Thus, it was concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This report assesses the safety of 1,2-glycols, as used in cosmetic products. The 1,2-glycols are used mostly as skin and hair conditioning agents and viscosity increasing agents in these products, and caprylyl glycol and pentylene glycol are also used as preservatives. This safety assessment includes the following 1,2-glycols :

- caprylyl glycol
- arachidyl glycol
- cetyl glycol
- hexacosyl glycol
- lauryl glycol
- myristyl glycol
- octacosanyl glycol
- stearyl glycol
- decylene glycol
- pentylene glycol
- 1,2-butanediol
- 1,2-hexanediol
- C14-18 glycol
- C15-18 glycol
- C18-30 glycol
- C20-30 glycol

Of the 16 ingredients that are being reviewed in this safety assessment, 5 are being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The remaining 12 ingredients are not reported to be in current use.

A CIR final safety assessment on propylene glycol (PG), short-chain 1,2-glycol, and polypropylene glycols was published in 1994.^{1,1} The CIR Expert Panel concluded that PG and polypropylene glycols are safe for use in cosmetic products at concentrations up to 50.0%. At its June 28-29, 2010 meeting, the Expert Panel issued an amended final safety assessment on propylene glycol, tripropylene glycol, and polypropylene glycols with the following conclusion: The CIR Expert Panel concluded that propylene glycol, tripropylene glycol, PPG-3, -7, -9, -12, -13, -15, -16, -17, -20, -26, -30, -33, -34, -51, -52, -69, and any PPG ≥ 3 , are safe as cosmetic ingredients in the present practices of use and concentration as described in this safety assessment when formulated to be non-irritating.²

In the absence of safety test data on many of the 1,2-glycols reviewed in this safety assessment, data on PG from both the CIR published final safety assessment and amended final safety assessment are included to support the safety of these ingredients in personal care products.

CHEMISTRY

Definition and Structure

Other chemical names and cosmetic ingredient functions for the ingredients reviewed in this safety assessment are included in Table 1.³ Caprylyl glycol and other 1,2-glycols are generally defined as the compounds that conform to a structure or formula. The fundamental carbon backbone contains a hydroxyl group at the 1 and 2 positions, and the length of the carbon backbone varies from one structure to another. Chemical structures for the 1,2-glycols that are being reviewed are included in Figure 1.

Chemical and Physical Properties

Available data on the properties of the following ingredients are included in Table 2: caprylyl glycol, arachidyl glycol, cetyl glycol, lauryl glycol, myristyl glycol, octacosanyl glycol, stearyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol. The solubility of these ingredients in water ranges from highly soluble (1,2-butanediol, octanol/water partition coefficient of -0.8) to poorly soluble (octacosanyl glycol, octanol/water partition coefficient of approximately 11.9).

No information on the chemical and physical properties of C14-18, C15-18, C18-30, and C20-30 glycols were found, but because these ingredients are mixtures of various length glycols, their chemical and physical properties are expected to reflect their individual components.

Methods of Production

The commercially practiced synthesis of ethylene glycol, the simplest of the 1,2-glycols, commonly occurs via a thermal oxidation of ethylene oxide with water.⁴ The commercial production of other 1,2-glycols, including those currently under review herein, are commonly synthesized via either catalytic oxidation of the corresponding alkene oxide, or reduction of the corresponding 2-hydroxy acid.

C15-18 glycol, for example, has been prepared via oxidation of the corresponding C15-C18 1,2-alkylene oxides (and the 1,2-alkylene oxides have been synthesized via epoxidation of the corresponding 1,2-alkenes).⁵

Stearyl glycol has been prepared via the reduction of 2-hydroxyoctadecanoic acid with lithium aluminum hydride.⁶ This reaction is followed by the quenching of any unchanged lithium aluminum hydride with excess ethyl acetate, filtering of salt, and subsequent drying of the resulting solution.

The production of 1,2-butanediol, much like the synthesis of ethylene glycol, is commonly carried out via a continuous reaction and distillation operation.⁷

Composition/Impurities

The heavy metals specification for > 98% caprylyl glycol (Dermosoft® Octiol) is 5 ppm max (as Pb).⁸ Decylene glycol (as SymClariol®) contains 98% to 100% decylene glycol.⁹ 1,2-Butanediol is ≥ 99% pure and also contains water, 1,4-butanediol, and 1-acetoxy-2-hydroxybutane.⁷

Analytical Methods

Cetyl glycol has been analyzed using silica gel thin-layer chromatography, and has been identified using IR and mass spectrometry.^{10,11} Decylene glycol has been analyzed via gas chromatography, and has been identified using mass, IR, and NMR spectroscopy.^{11,12} Gas chromatography-mass spectrometry (GC-MS) has been used in the analysis of stearyl glycol.⁶

Lauryl glycol, myristyl glycol, caprylyl glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol have been identified using mass spectrometry and IR or NMR spectroscopy.¹¹

UV absorption data on caprylyl glycol or any of the other 1,2-glycols reviewed in this safety assessment were not provided or found in the published literature. Based on the chemical formulas included in Figure 1, there is no reason to suspect that any UV absorption would be associated with these 1,2-glycols.

Reactivity

For 1,2-butanediol at temperatures above 90°C, explosive vapor/air mixtures may be formed.¹³ Additional information on the reactivity of 1,2-butanediol, in relation to the EPA-proposed national rule on the reduction of ozone formation, is included in the section on Noncosmetic Use later in the report text.

USE

Purpose In Cosmetics

Most of the ingredients reviewed in this safety assessment function as skin and hair conditioning agents and viscosity increasing agents in personal care products.³

Scope and Extent Of Use In Cosmetics

According to information supplied by industry as part of the Voluntary Cosmetic Registration Program (VCRP), obtained from the Food and Drug Administration (FDA) in 2011, the following ingredients were being used in personal care products: caprylyl glycol, decylene glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.¹⁴ These data are summarized in Table 3. Independent of these data, the results of a survey of ingredient use concentrations that was conducted by the Personal Care Products Council in 2010, also in Table 3, indicate that three 1,2-glycols were being used at the following concentrations: caprylyl glycol (0.00003 to 5%), pentylene glycol (0.001 to 5%), and 1,2-hexanediol (0.00005 to 10%).¹⁵ According to FDA's VCRP data, there was no indication that the following remaining ingredients in this safety assessment were being used in cosmetic products in 2011: arachidyl glycol, cetyl glycol, hexacosyl glycol, lauryl glycol, myristyl glycol, octacosanyl glycol, stearyl glycol, 1,2-butanediol, C14-18 glycol, C18-30 glycol, and C20-30 glycol.

Personal care products containing these ingredients may be applied to the skin, nails, or hair, or, incidentally, may come in contact with eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin, nails, or hair for variable periods following application. Daily or occasional use may extend over many years.

Noncosmetic Use

Caprylyl Glycol

Study results support the notion that treatment of glutaraldehyde-treated tissue with a short-chain alcohol (ethanolic buffered solution) and long-chain alcohol (caprylyl glycol) combination will reduce both extractable phospholipids and the propensity for *in vivo* calcification. The use of glutaraldehyde-treated biological tissue in heart valve substitutes is an important option in the treatment of heart valve disease; however, the durability of these devices is limited, in part, because of tissue calcification.¹⁶

1,2-Butanediol

The Environmental Protection Agency (EPA) lists 1,2-Butanediol as one of the reactive compounds in aerosol coatings (i.e., aerosol spray paints) that contributes to ozone (O₃) formation. It is listed as having a reactivity factor of 2.21 g O₃/g 1,2-butanediol. Reactivity factor is defined as a measure of the change in mass of ozone formed by adding a gram of a volatile organic compound (VOC) to the ambient atmosphere. This listing of compounds, such as 1,2-butanediol, is in keeping with the EPA proposal to amend the aerosol coatings reactivity rule by adding compounds and associated reactivity factors based on petitions that were received. The EPA has concluded that a national rule based on the relative reactivity approach achieves more reduction in ozone formation than would be achieved by a mass-based approach for this specific product category. States have previously promulgated rules for aerosol spray paints based upon reductions of VOC by mass.¹⁷

Cetyl Glycol

Some colloidal nanoparticles of Sm-Co alloys are made in octyl ether using samarium acetylacetonate and dicobalt octacarbonyl as precursors in a mixture of 1,2-hexadecanediol (cetyl glycol), oleic acid, and trioctylphosphine oxide.¹⁸

Stearyl Glycol

Stearyl Glycol has been used as a surfactant (in octanol/water microemulsion) in a transdermal delivery system for the drug, 8-methoxypsoralen.¹⁹

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Information on the metabolism, distribution, and excretion of 1,2-butanediol following i.v. dosing indicate that, in rabbits, this chemical is metabolized slowly and excreted in the urine either as the glucuronide or unchanged; there was no evidence of tissue accumulation. Metabolites were not identified in the urine of rabbits fed 1,2-butanediol in the diet. Based on metabolism modeling data on caprylyl glycol (1,2-octanediol), 1,2-hexanediol, decylene glycol (1,2-decanediol), and lauryl glycol (1,2-dodecanediol), it is likely that C-oxidation, C-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. C-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

Caprylyl Glycol, 1,2-Hexanediol, Decylene Glycol, and Lauryl Glycol

A metabolism assessment for the following 1,2-glycols (C6 – C12) was provided by the Personal Care Products Council: caprylyl glycol (1,2-octanediol, C8), 1,2-hexanediol (C6), decylene glycol (1,2-decanediol, C10), and lauryl glycol (1,2-dodecanediol, C12).²⁰ Because metabolism database searches did not yield information on these four compounds, the possible metabolic fates of each were determined based on structural features, a substructure search, and a MeteorTM (9.0) metabolism prediction. The results of this assessment indicated that it is likely that C-oxidation, C-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. Furthermore, C-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

1,2-Butanediol

1,2-Butanediol was infused i.v. into rabbits at a dose of 1 g/kg body weight. Metabolism was described as slow, and 1,2-butanediol was excreted in the urine either as the glucuronide or unchanged.²¹ Accumulation in the tissues was not observed. Metabolites were not isolated from the urine of rabbits fed 1,2-butanediol at a dose of 0.2 g/kg body weight.

Propylene Glycol

The original 1994 CIR final safety assessment reported that, in mammals, the pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Percutaneous Absorption

Dermal penetration of PG from a ternary cosolvent solution through hairless mouse skin was 57% over a 24 h period. Using thermal emission decay (TED)-Fourier transform infrared (FTIR) spectroscopy, it appeared that PG did not reach the dermis. After PG was applied dermally to the fingertip of a human subject, the concentration of PG remaining at the surface of the stratum corneum decreased over time. Following topical application of 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol in alcoholic solution) to female pig skin in vitro, approximately 97% of the test

solution was found in the skin within 24 h post-application. Based on dermal penetration modeling data on caprylyl glycol (1,2-octanediol), 1,2-hexanediol, decylene glycol (1,2-decanediol), and lauryl glycol (1,2-dodecanediol), the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol. Also, because of the limited percutaneous absorption data on 1,2-glycols, octanol/water partition coefficients ($\log P$ values) for most of the ingredients in this safety assessment are presented in a graph of $\log P$ versus 1,2-glycol chain length (Figure 2).

Caprylyl Glycol

The dermal absorption and skin penetration of 5% Dermosoft Octiol in alcoholic solution (5% caprylyl glycol in 70% ethanol/30% propylene glycol) *in vitro* was evaluated using skin from the backs of female pigs (~ 130 days old) in Franz diffusion cells. The partition coefficient of caprylyl glycol was estimated using an appropriate computer program (ACD logD-Suite) to be $\log P_{ow} \approx 1$ (pH 3 to 7.4). The solution was applied topically to excised pig skin for 24 h. The investigators used an analytical method that only measured the parent compound, caprylyl glycol, and the total recovery was only 55%.

Approximately 97% of the recovered material was found in the skin within 24 h post-application, and the following distribution (as % of dermal absorbed caprylyl glycol) was reported: ~10% in stratum corneum, ~9% in epidermis, and ~81% in dermis. Caprylyl glycol was not detected in the receptor fluid, and this was likely a result of metabolism in the skin. The authors noted that, normally, the metabolism of caprylyl glycol takes place mainly in the epidermis/dermis. Therefore, undetectable amounts of the unchanged substances (below the detection limit) may penetrate into the receptor fluid. Because size of the sample ($N = 2$; taken from same pig) was very small and considered non-representative, it was not possible to perform an inductive statistical analysis. Therefore, according to the authors, the descriptive results achieved in this study have to be considered as a trend and interpreted as such.²²

In addition to the dermal penetration study, a study in which caprylyl glycol was incubated with and without cut up pig skin for 24 h was completed.²² Compared to the sample without pig skin, 50% of the caprylyl glycol was lost in the presence of skin during the 24 h incubation. The investigators attributed this loss to chemical or metabolic degradation, and suggested that the poor recovery in the dermal penetration study was likely a result of the metabolism.

Caprylyl Glycol, 1,2-Hexanediol, Decylene Glycol, and Lauryl Glycol

Dermal penetration modeling information on the following 1,2-glycols (C6 – C12) was provided by the Personal Care Products Council: caprylyl glycol (1,2-octanediol, C8), 1,2-hexanediol (C6), decylene glycol (1,2-decanediol, C10), and lauryl glycol (1,2-dodecanediol, C12).²³ Dermal penetration predictions were made on the basis of J_{max} (maximal flux) values calculated from K_p estimations and calculated water solubility. Based on the calculated J_{max} values, assignment of default % absorption values was done, as described by Kroes et al.²⁴ Utilizing this approach, the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol.

Propylene Glycol

The dermal penetration of [^{14}C]PG through excised female hairless mouse skin from the ternary cosolvent containing 10 mol% oleic acid and 6 mol% dimethyl isosorbide in 84% PG was determined. Over a 24-h period, the cumulative penetration of PG was 57.1% of the applied amount.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

The dermal absorption of PG was determined in the outermost layers of skin (1 human subject), after application to the fingertip, using TED-FTIR spectroscopy.²⁵ The concentration of PG remaining at the surface of the stratum corneum decreased over time. The authors suggested that PG molecules diffuse into stratum corneum only to a depth of 6-7 μm , approximately, and do not reach the dermis.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Skin Penetration Enhancement

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated in vitro. Skin penetration of the following was enhanced: ^3H -corticosterone, ^3H -triethanolamine, and dihydrovenanthramide D. PG can act as a penetration enhancer for some chemicals and under some conditions. Often, it works synergistically with other enhancers. The mechanism by which PG enhances penetration has not been definitively identified.

Caprylyl Glycol, 1,2-Hexanediol, and Decylene Glycol

Warner et al.¹² studied ³H-corticosterone (CS) and ³H-triethanolamine flux (TEA) enhancement across full-thickness hairless mouse (SKH-HR1 strain) skin in the presence of 1,2-octanediol (caprylyl glycol), 1,2-decanediol (decylene glycol), and 1,2-hexanediol, each in phosphate buffered saline (PBS). Permeability experiments were performed using a two-chamber diffusion cell, and results are presented in Table 4. Each of the 3 chemicals enhanced the skin penetration of CS and TEA in a concentration-dependent manner.

1,2-Butanediol and Pentylene Glycol

In a study by Heuschkel et al.,²⁶ the influence of pentyleneglycol and 1,2-butanediol on the skin penetration of the drug dihydroxynaphthylanthranamide D (DHA_vD, 0.2% in hydrophilic cream) across full thickness human skin (from breast, females) was investigated using Franz-type diffusion cells. Relative amounts of DHA_vD in different skin compartments (stratum corneum, viable epidermis, and dermis) following penetration from a hydrophilic cream and from a hydrophilic cream containing a 4% pentyleneglycol/1,2-butanediol mixture were compared. Within 30 min, the amount of DHA_vD that penetrated into the viable skin layers doubled in the presence of the glycol mixture. After 300 min, 12% of the applied dose was detected in the viable epidermis and dermis after application of DHA_vD in hydrophilic cream, compared to 41% after application in the cream with the glycol mixture.

Propylene Glycol

PG has been described as a penetration enhancer. Proposed mechanisms of penetration enhancement by PG include alteration of barrier function by its effects on a keratin structure or a PG-induced increase in the solution capacity within the stratum corneum.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

ANIMAL TOXICOLOGY

Acute Inhalation Toxicity

1,2-Butanediol

According to a data summary available from Dow Chemical Company, there were no obvious toxic effects in rats exposed for 7 h to an atmosphere saturated with 1,2-butanediol.²¹ Further details relating to this study were not available.

Acute Oral Toxicity

Acute oral toxicity data on Caprylyl glycol, propylene glycol, and other 1,2-glycols for which data are available suggest that death (rats) would occur at relatively high doses (LD₅₀ range: 2200 to > 20,000 mg/kg). Reportedly, high (unspecified) oral doses of 1,2-butanediol caused narcosis, dilation of the blood vessels, and kidney damage in rats.

Caprylyl Glycol

The acute oral toxicity of caprylyl glycol was evaluated using male and female rats (number and strain not stated).²⁷ Doses of ≥ 464 mg/kg caused sedation and ataxia. Specifically, loss of muscle tone and dyspnea were observed at a dose of 1000 mg/kg, and lateral position, coma, and death were observed at a dose of 1470 mg/kg. Deaths occurred within 2 h post-administration; at necropsy, pale parenchymal organs were observed in 3160 and 4640 mg/kg dose groups. Surviving animals recovered within 24 h, and 215 mg/kg was the nontoxic dose in this study. LD₅₀ values of 2240 (males) and 2200 (females) were reported.

In another study (OECD 423 test procedure) involving rats, the LD₅₀ for caprylyl glycol was > 2500 mg/kg.^{28,28}

1,2-Butanediol

An acute oral LD50 of 4,192 mg/kg was reported for 1,2-butanediol in a study involving female Swiss albino mice/ICR.²⁹ Study details were not provided.

According to a data summary available from Dow Chemical Company, the acute oral LD50 for 1,2-butanediol in rats was 16 g/kg body weight.³⁰ Also, high (unspecified) doses caused narcosis in rats (often leading to death in a few hours), dilation of the blood vessels, and kidney damage.

1,2-Butanediol administered orally to rats (ethanol-dependent) at a dose of 2.74 g/kg did not induce any overt toxic effects.²¹

Pentylene Glycol (1,2-Pentanediol)

The following acute oral LD50 values have been reported for pentylene glycol: 1.2700 E + 04 mg/kg (rats); 7,400 mg/kg (mice); 3,700 mg/kg (rabbits); and 5,200 mg/kg (guinea pigs).³¹

Stearyl Glycol

An LD50 of > 5,000 mg/kg was reported for rats dosed orally with stearyl glycol.³¹

C15-18 Glycol

The acute oral toxicity of C15-18 glycol was evaluated using adult male Sprague-Dawley rats, and an LD50 of > 20.0 g/kg body weight was reported.⁵

Propylene Glycol

The 24 h oral LD50 for PG was 22.8 g/kg body weight in a study involving 5 female Fischer rats. Oral LD50 values (rats) of up to 27 g/kg body weight have been reported in other studies.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Acute Dermal Toxicity**1,2-Butanediol**

According to a data summary provided by Dow Chemical Company, prolonged application of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.²¹ Details relating to the test procedure were not provided; however, it was presumed that neat material was tested.

Decylene Glycol

In an acute dermal toxicity study involving rats, the LD50 for decylene glycol (SymClariol®) was > 2,000 mg/kg.²⁸

Propylene Glycol

The dermal LD50 for PG was > 11.2 g/kg in mice and was 13 g/kg in rats.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Acute Intraperitoneal Toxicity

The available data suggest that 1,2-Butanediol (LD50s up to 5990 mg/kg) and pentylene glycol (TDLo = 3,510 mg/kg) are not significant acute i.p. toxicants. However, muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg. In an i.p. dosing study in which ED₃ values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED₃ value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg).

Caprylyl Glycol, 1,2-Butanediol, and Pentylene Glycol

In a report by Shoemaker,³² the intoxicating potency of alcohols, some of which were straight-chain primary alcohols and straight-chain diols, was determined. Data on the following 3 diols reviewed in this safety assessment were included: caprylyl glycol (1,2-octanediol), pentyleneglycol (1,2-pentanediol), and 1,2-butanediol. Doses of each alcohol were injected (intraperitoneally [i.p.]) into male Sprague-Dawley rats, and intoxicating scores were recorded based on the following rating scale: 0 (normal) to 7 (death).

An ED₃ value for each chemical was determined. The ED₃ was defined as the dose (mmole/kg body weight) required to obtain a score of 3 (ataxia) on the intoxication rating scale (0 to 7 [death]). The following ED₃ values were reported: 1.5 mmole/kg (caprylyl glycol), 256.0 mmole/kg (pentyleneglycol), and 32.6 mmole/kg (1,2-butanediol).³²

Groups of 6 adult female, ICR Swiss albino mice were injected i.p. with increasing doses of 1,2-butanediol (geometric factor of 1.2) in distilled water (injection volume = 0.01 ml/g body weight). Mean LD50 values and 95% confidence limits were calculated from cumulative mortality curves at 24 h and 144 h. The following values were reported for 1,2-butanediol: 24 h LD50 of 66.5 mmol/kg (~5.99 g/kg) and 144 h LD50 of 46.5 mmol/kg (~4.19 mg/kg).³³

Muscle incoordination was observed in rats at an i.p. dose of ~2.94 g/kg 1,2-butanediol.²¹ An i.p. TDLo of 3,510 mg/kg has been reported for pentyleneglycol in rats.³¹

Propylene Glycol

Following i.p. dosing with PG (5 ml/kg), none of the 5 female C3H mice died, but peritonitis was observed at necropsy. In other studies, i.p. LD 50 values up to 13.7 ml/kg (rats) and 11.2 g/kg (mice) have been reported. From the Final Report on Propylene Glycol and Polypropylene Glycols¹

An acute study was performed in which female ICR mice were dosed i.p. with 2600, 5200, or 10400 mg/kg PG.³⁴ All except the high dose mice survived 6 days after dosing. Signs of toxicity, such as lethargy and ruffled hair coats, were not observed in the 2600 and 5200 groups.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Other Acute Parenteral Toxicity Studies

Propylene Glycol

Acute i.v. LD50's of 6.2 ml/kg (rats) and 6.4 ml/kg (mice) have been reported for PG. In other parenteral toxicity studies, acute i.m. LD50 (20 g/kg - rats) and acute s.c. LD50 (18.5 g/kg - mice) values have been reported.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Short-Term Oral and Parenteral Toxicity

A no-observed effect level (NOEL) of 50 mg/kg/day and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity in rats were reported in a 28-day oral toxicity study on > 98% caprylyl glycol (Dermosoft® Octiol). The NOAEL was based on findings of irritation on the pars non-glandularis and limiting ridge of the stomach; analogous structures do not exist in man. An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on 98% to 100% decylene glycol (SymClariol®); squamous epithelial hyperplasia of the forestomach was observed at higher doses. Short-term oral administration of 1,2-butanediol to rats (males [42 days]; females [day 14 before mating to day 3 of lactation] yielded an NOAEL of 200 mg/kg/day. In rats fed 1,2-butanediol at concentrations of 5% to 40% in the diet for 8 weeks, death was not noted at 5% in the diet (~2.9 g/kg/day), but dietary concentrations ≥ 10% were fatal. Large (unspecified) doses of 1,2-butanediol did not cause irritation of the gastrointestinal tract in rats. All mice survived in a short-term study in which 10% PG was administered in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG 3 times per day for 3 days. Similarly, cats survived dosing 12% PG in the diet for 5 weeks and 41% PG in the diet for 22 days. Intravenous dosing with PG over a 2-week period resulted in little toxicity in rats.

Caprylyl Glycol

In a 28-day oral toxicity study, > 98% caprylyl glycol (Dermosoft® Octiol) was administered to groups of Wistar rats at doses of 50, 300, and 1000 mg/kg/day, respectively, according to OECD guidelines.³⁵ The number of animals per group was not stated and the control group was not identified. The authors reported no test substance-related mortalities or toxicologically relevant clinical signs during weeks 1 through 3 or week 4 (functional observational battery). Additionally, there were no differences in feed consumption, body weight, hematological/clinical biochemistry parameters, or macroscopic findings that were considered toxicologically relevant. Test substance-related findings (males and females) included slightly reduced locomotor activity and increased mean absolute and relative kidney weights at the highest dose. Whether or not microscopic changes were observed in the kidneys was not stated.

Systemic effects were not observed at doses up to 300 mg/kg/day. Test substance-related microscopic changes were observed in the stomachs of rats in 300 and 1000 mg/kg/day dose groups. These findings were considered indicative of an irritative potential of the test substance on the pars non-glandularis and limiting ridge of the stomach. The authors noted that analogous structures do not exist in humans. Study results indicated a no-observed effect level (NOEL) of 50 mg/kg/day, and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity. The NOAEL was based on findings (irritation) in the stomach likely due to local irritation effects.³⁵

1,2-Butanediol

In an 8-week oral study, groups of rats were fed 1,2-butanediol at concentrations ranging from 5 to 40% in the basic diet (one dose level per group).²¹ A control group only received basic diet. There were no mortalities at the lowest dose (~ 2.9 g/kg body weight/day); however, doses $\geq 10\%$ were classified as fatal. The following signs of toxicity were noted at the highest dose of 22 g/kg/day: weight loss, fatigue, reduced responsiveness, diarrhea, and rapid, shallow breathing. No abnormalities were observed in tissues of major organs from 2 rats at each of the 5 dose levels.

The following study is actually a combined repeated dose/reproductive and developmental toxicity study, and results relating to reproductive and developmental toxicity appear in that section later in the report text.³⁶ Groups of Crj-CD(SD) rats (10 males, 10 females) were dosed orally, by gavage, with aqueous 1,2-butanediol at doses of 40, 200, or 1,000 mg/kg/day. Males were dosed daily for 42 days, and females were dosed from day 14 before mating to day 3 of lactation. Control rats (10 males, 10 females) were dosed with distilled water.

None of the animals died, and there were no differences in histopathological findings or the following parameters between test and control animals: body weights, feed consumption, hematology parameters, clinical chemistry parameters, and organ weights. However, transient hypolocomotion and hypopnea (slight clinical signs) were observed in females that received 1,000 mg/kg doses. No observable effect levels (NOELs) for repeat dose toxicity were 1,000 mg/kg/day (males) and 200 mg/kg/day (females). The no observable adverse effect level (NOAEL) was 200 mg/kg body weight/day in this study.³⁶

According to a summary of data provided by Dow Chemical Company, the administration of large (unspecified) doses of 1,2-butanediol to rats caused irritation of the gastrointestinal tract.²¹

Decylene Glycol

In a 28-day oral toxicity study, 98% to 100% decylene glycol (SymClariol®) was administered to groups of SPF-bred Wistar rats (5 males, 5 females/group) at doses of 100, 300, and 1000 mg/kg/day, respectively, according to OECD guidelines.³⁷ The vehicle control group received 2.5% ethanol in distilled water. Rats in each group were killed after day 28. Two additional groups (same composition) were untreated and dosed with 1000 mg/kg/day, respectively, for 28 days. The animals in these groups were killed after a 14-day non-treatment period. In all groups, a functional observational battery was performed (week 4) before animals were killed. All of the animals survived the 28-day dosing period, and there were no toxicologically-relevant clinical signs during the study. Mean locomotor activity was significantly reduced in males and females in the 1000 mg/kg/day dose group, and this finding was deemed test substance-related. Decreased feed consumption was also noted in females at this dose level. Mean body weights of males and females were similar to those of negative control animals.

There were no test-substance-related differences in hematological or clinical biochemical parameters that were of toxicological relevance. The presence of ketone in the urine of males and females of the 1000 mg/kg/day dose group was considered likely representative of metabolic adaptation to the test substance. Both absolute and relative organ weights of dosed animals were comparable to those of negative control rats. Toxicologically-relevant macroscopic findings were not observed. Squamous epithelial hyperplasia, ulceration, and inflammation of the forestomach were observed at doses of 1000 mg/kg/day, and squamous epithelial hyperplasia of the forestomach was less severe and occurred at a lower incidence in the of 300 mg/kg/day dose group. After a 14-day recovery period, squamous epithelial hyperplasia remained in the animals previously dosed with 1000 mg/kg/day, but the severity and incidence of this finding after the treatment period was largely reversible. Both the NOEL and the NOAEL in this study was 100 mg/kg body weight/day.³⁷

Propylene Glycol

No significant toxicity was observed in short-term oral tests on PG involving dogs and cats. Dogs received 3.0 ml/kg doses of undiluted PG over a 3- day period, and cats received 12% PG in the diet for 5 weeks and 41% PG in the diet for 22 days. Short-term i.v. dosing with PG resulted in little toxicity in rats. Groups of rats received i.v. infusions of PG/ethanol/water (5:1:4) over a 2-week period.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Groups of 8 male and 8 female CD-1 mice were given 0.5, 1.0, 2.5, 5.0, and 10.0% PG in the drinking water for 14 days. Body weight gains of test animals were similar to or greater than controls. No animals died during the study.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Subchronic Inhalation Toxicity

Subchronic inhalation data reported some effects due to PG administration, but these effects were inconsistent and without dose-response trends. Rats were exposed, nose-only, to PG (0.16 to 2.2 mg/liter of air) for 13 weeks.

Propylene Glycol

Male and female Sprague-Dawley rats (number per group not given) were exposed to 0.16, 1.0, or 2.2 mg PG/l air for 6 h/day, 5 days/wk, for 13 wks in a nose-only inhalation study. Relevant differences occurred in some hematological parameters, serum enzyme activities, and lung, spleen, liver, and kidney weights; however these differences were inconsistent and without dose-response trends.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Subchronic and Chronic Oral Toxicity

A TDLo of 2,450mg/kg was reported for pentylene glycol in rats dosed orally over a 28-week period. In subchronic oral toxicity studies involving rats, PG (50,000 ppm in diet) given in feed for 15 wks did not produce any lesions. The same was true for dogs that received 5% or 10% PG in drinking water in subchronic studies. Toxic effects were not observed in PG chronic feeding studies involving rats or dogs. In a 92- to 97-day oral toxicity study involving mice, rats, dogs, and monkeys dosed with a formulation containing 1000 mg/kg propylene glycol, there were no adverse effects on body weight, food consumption, clinical pathology, histopathology, or adverse clinical observations.

Pentylene Glycol

Pentylene glycol was administered orally to rats, intermittently over a 28-week period. A TDLo of 2,450mg/kg was reported.³¹

Propylene Glycol

A 92- to 97-day study was conducted to assess the safety and tolerability of propylene glycol as an alternative formulation vehicle in general toxicology studies in the mouse, rat, dog, and monkey.³⁸ In Sprague-Dawley (CrI:CD[SD]VAF/Plus) rats (10/sex; 6 ± 1 weeks old) and CD1 (CrI:CD1[Icr]VAF/Plus) mice (10/sex; 6 ± 1 weeks old), the vehicle was administered orally via gavage at dose volumes of 5 ml/kg (rats) and 10 ml/kg (mice) for 92 to 93 days. In Beagle dogs (4/sex; 7 to 17 months old) and cynomolgus monkeys (*Macaca fascicularis*, 4/sex; juvenile to young adult), the vehicle was administered orally by gavage (dose = 1,000 mg/kg; dose volume of 5 ml/kg) for 95–97 days. Effects on clinical observations, body weight and food consumption parameters, clinical pathology, and histopathology were evaluated across all species. The

suitability of formulations containing up to 1000 mg/kg propylene glycol for use in preclinical safety studies was confirmed by a lack of effects on all parameters examined.³⁸

There was no evidence of toxic effects in subchronic oral toxicity studies in which rats were fed 50,000 ppm PG in the diet for 15 weeks, and dogs received 5% PG in drinking water for 9 months and 10% PG in drinking water for 6 months. Toxic effects were not observed in rats that received up to 50,000 ppm PG in the diet for 104 weeks or in dogs that received 2 g/kg PG in the diet for 104 weeks.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Repeated Dose Dermal Toxicity

1,2-Butanediol

According to a data summary provided by Dow Chemical Company, repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.²¹ Details relating to the test procedure were not provided; however, it is presumed that neat material was tested.

Cytotoxicity

The cytotoxicity of cetyl glycol, lauryl glycol, and pentylene glycol has been demonstrated in vitro. Cetyl glycol (130 µg/ml) had a cytotoxic effect on Ehrlich ascites carcinoma cells, lauryl glycol (99 µM) had a hemolytic effect on human erythrocytes, and pentylene glycol (5%) induced apoptosis in a human promyelocytic leukemia cell line. Propylene glycol was moderately cytotoxic to human fibroblasts and keratinocytes in vitro.

Pentylene Glycol

Anselmi et al.³⁹ conducted an *in vitro* DNA fragmentation assay (human promyelocytic leukemia cell line [HL60]) to investigate the apoptosis- and necrosis-inducing potential of brief, 10 min applications of the preservative, pentylene glycol (between 0.01 and 5% [usual concentration as a preservative]). Cells treated with phosphate buffered saline served as controls. The percentage of apoptotic cells was quantified by analysis of DNA content. Pentylene glycol induced apoptosis only at a concentration of 5%. Externalization of phosphatidyl serine, a hallmark of apoptosis, was concomitant with the subdiploid DNA peak in HL60 cells treated with pentylene glycol.

Lauryl Glycol

Osorio e Castro et al.⁴⁰ studied hemolysis rates (at 37°C) of human erythrocytes induced by C₂ and C₈-C₁₄ straight chain 1-alkanols, 1,2-alkanediols, and the corresponding benzilidene derivatives (benzaldehyde acetals). The most active compound was 1-dodecanol (50% hemolysis at 15 µM), followed by 1,2-dodecanediol (lauryl glycol, 50% hemolysis at 99 µM) and the C₁₀ benzylidene acetal (50% hemolysis at 151 µM).

Cetyl Glycol

In an antitumor activity test, 1,2-hexadecanediol (cetyl glycol) was injected intraperitoneally (i.p.) into 8 inbred C57BL/6 mice in which Ehrlich ascites carcinoma (EAC) cells had been implanted. Doses of 80/mg/kg/day were injected for 10 consecutive days. The survival of mice was monitored over a 2-month period. Compared to control mice, dosing with cetyl glycol prolonged the lifespan of animals more than 2.7-fold. Antitumor effects were described as marked, in that 4 of 8 mice injected were alive, with scarce tumor proliferation, at 60 days. Cetyl glycol (130 µg/ml) was found to have a cytotoxic effect (irreversible cell degeneration) on cultured EAC cells.⁴¹

Propylene Glycol

PG was found to be cytotoxic in assays that measured inhibition of human foreskin fibroblasts and keratinocytes, inhibition of collagen contraction by fibroblasts, and changes in cell morphology of fibroblasts and keratinocytes. Changes in morphology included detachment of cells from the culture and changes in cell shape.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Ocular Irritation

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Undiluted 1,2-butanediol, but not 10% aqueous, induced ocular irritation in rabbits. Undiluted decylene glycol induced corrosion when instilled into the eyes of rabbits. In an in vitro ocular irritation assay (HET-CAM), 1% decylene glycol in neutral oil and caprylyl glycol (1% and 3%) in neutral oil were classified as non-irritants; however, a 50:50 (w/w) mixture of caprylyl glycol and 1,2-hexanediol was classified as a severe ocular irritant when evaluated at a concentration of 1% aqueous (effective concentration per ingredient = 0.5%) in the same assay. Together, the results of a neutral red release (NRR) assay, the HET-CAM assay, and the reconstituted human epithelial culture (REC) assay indicated that a lash gel serum containing 3% pentylene glycol might be a slight ocular irritant. In other studies, undiluted PG was, at most, a slight ocular irritant.

Caprylyl Glycol

In an *in vitro* assay (hen's egg test on the chorioallantoic membrane [HET-CAM]) for evaluating ocular irritation potential, caprylyl glycol was classified as a non-irritant at test concentrations of 1% and 3% in neutral oil.⁴²

Caprylyl Glycol and 1,2-Hexanediol

A 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68) was also tested in the HET-CAM assay. The mixture was classified as a severe eye irritant at a test concentration of 1% aqueous (effective concentration per ingredient = 0.5%).⁴³

1,2-Butanediol

According to a summary of data provided by Dow Chemical Company, undiluted 1,2-butanediol was irritating to the eyes of rabbits, but was a non-irritant when tested as a 10% aqueous solution.²¹

Pentylene Glycol

The ocular irritation potential of a lash gel serum containing 3% pentylene glycol was evaluated using the following in vitro assays: neutral red release (NRR) assay using rabbit cornea fibroblasts, HET-CAM, and the reconstituted human epithelial culture (REC) assay.⁴⁴ In the NPR assay, the undiluted product and dilutions (in hydrophilic or lipophilic substance) ranging from 0.1% to 60% were tested. Sodium dodecyl sulfate served as the positive control. The test product concentration that gave rise to the release of 50% neutral red dye (NR₅₀) was used as an endpoint to reflect cytotoxicity. Data were expressed as a percentage of cytotoxicity, compared to the negative control (dilution 0%), and the NR₅₀ was calculated by interpolation from the curve representing the percentage of viability versus the concentration of test product. An NR₅₀ of > 50% (slightly cytotoxic) was reported for the lash gel serum.

In the HET-CAM assay, the undiluted product (0.3 ml) was applied to the chorioallantoic membrane and classified as moderately irritating. In the REC assay, the product (neat or diluted) was applied to the apical surface of the epithelial culture. Hexadecylpyridinium bromide solution in saline and saline solution served as positive and negative controls, respectively. Results were expressed as a percentage of cytotoxicity, compared to the negative control. The product was classified as slightly cytotoxic. Together, the results for the 3 in vitro assays indicate that the lash gel serum might be a slight ocular irritant, with a Draize score that might range from 0 to 15. The conclusion for this study (slight ocular irritant) is from a global assessment conducted by the International Research and Development Center that was based on results of the 3 methods used, because no single alternative method can predict ocular irritation with a sufficient level of safety.⁴⁴

Decylene Glycol

In an ocular irritation study (OECD 405 protocol) involving rabbits, decylene glycol (SymClariol®) induced corrosion when tested at a concentration of 100%. Additionally, the ocular irritation potential of 1% SymClariol® in neutral oil was evaluated in the HET-CAM assay, and results were negative.²⁸

Lauryl Glycol

According to Worth and Cronin,⁴⁵ the European Union has classified 1,2-dodecanediol (lauryl glycol) as a severe ocular irritant. The European classification system has allowed 2 classes of acute eye toxicity, R36 for moderate irritants and R41 for severe irritants, and the Draize eye test has been used for the identification of R41 chemicals. Actual Draize test results for lauryl glycol were not included. This classification of lauryl glycol as a severe ocular irritant is included in a study by the preceding authors to explore the possibility of distinguishing between eye irritants and non-irritants by using *in vitro* endpoints of the HET-CAM assay and the neutral red uptake (NRU) test.

According to one of the prediction models for eye irritation potential, a chemical is more likely to be an eye irritant if its log (TH10) value is low (i.e., if a 10% solution of the chemical produces rapid hemorrhaging of the chorioallantoic membrane) and if its log (IC 50) value is low (i.e., if the chemical is cytotoxic to 3T3 cells). TH10 is defined as the mean detection time (units not stated) for hemorrhage in the vascularized chorioallantoic membrane of embryonated chicken eggs. The IC50 is defined as the concentration of test chemical (mg/ml) resulting in 50% inhibition of neutral red uptake in 3T3 cells. The TH10 and IC50 values for lauryl glycol were 171.0 and 0.02, respectively.⁴⁵ Using a logarithm calculator, $\log 0.02 = -1.70$ and $\log 171.0 = 2.23$.

Propylene Glycol

PG (0.1 ml, pH 8.8) was a slight ocular irritant in rabbits in one study, but PG (0.1 ml, pH unknown) did not induce ocular irritation in another study involving rabbits.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

The ocular irritation potential of PG was determined using groups of 6 male and female New Zealand white albino rabbits. Following instillation of a single drop and multiple instillations, slight to moderate conjunctival hyperemia was observed and all reactions had cleared by day 3.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Skin Irritation and Sensitization

In the guinea pig maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted decylene glycol (SymClariol®) was classified as a moderate skin irritant in rabbits, but did not induce sensitization in the guinea pig maximization test at challenge concentrations of 2% and 5% in arachis oil or in the mouse local lymph node assay at concentrations of 5% to 50% in acetone/olive oil (4:1). Repeated applications of 1,2-butanediol to the skin of rabbits did not result in skin irritation, and results were negative for 1,2-hexanediol (10% to 100%) in the mouse local lymph node assay for evaluating sensitization potential. Dermal irritation/sensitization studies on PG were reported in the 1994 CIR final safety assessment and the amended final safety assessment. Both mild and no skin irritation were observed following the application of undiluted PG in animal studies. The application of 50% PG resulted in skin irritation/dermal inflammation. PG induced reactions ranging from no sensitization to mild sensitization.

Caprylyl Glycol

The skin sensitization potential of caprylyl glycol was evaluated in the guinea pig maximization test (OECD 406 protocol) using 20 animals. During intradermal and topical induction, caprylyl glycol was applied at concentrations of 5% (in peanut oil) and 50% (in petrolatum). The challenge concentration was 50% in petrolatum. Sensitization was not observed in any of the animals tested.⁴²

1,2-Butanediol

According to a summary of data provided by Dow Chemical Company, 1,2-butanediol did not induce skin irritation in rabbits, following prolonged and repeated application.²¹ Details regarding the test procedure were not provided; however, it was presumed that neat material was used.

1,2-Hexanediol

The sensitization potential of 1,2-hexanediol was evaluated at concentrations of 10%, 50%, and 100% in acetone/olive (3:1) using the mouse local lymph node assay (OECD 429 protocol). Study results were negative for skin sensitization.⁴⁶

Decylene Glycol

In a skin irritation study (OECD 404 protocol) involving rabbits, 100% decylene glycol (SymClariol®) was classified as a moderate skin irritant (PII = 3.2). SymClariol® was evaluated at the following concentrations in the guinea pig maximization test: 1% in arachis oil (intradermal induction), 5% in arachis oil (topical induction), and 2% and 5% in arachis oil (challenge). Sensitization was not observed in any of the 19 guinea pigs tested.²⁸

The skin sensitization potential of SymClariol® was also evaluated at the following test concentrations in the mouse local lymph node assay: 5%, 10%, 25%, and 50% in acetone/olive oil (4:1). Sensitization was not recorded at any of the concentrations tested.²⁸

Propylene Glycol

PG (50%) may have caused skin irritation in nude mice, while, in another study, 100% PG was minimally irritating to hairless mouse skin. In nude mice, hypertrophy, dermal inflammation, and proliferation were observed with 50% PG. Undiluted PG was, at most, a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. PG (concentrations not given) was negative in a number of sensitization/allergenicity assays using guinea pigs, but, in another study, PG (0.5 ml) was a weak sensitizer in guinea pigs.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

The dermal irritation potential of 100% PG was evaluated using male hairless SKH1 *hr/hr* mice. PG was minimally irritating, with a total score of 7 (maximum score = 77).

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

An oral NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats. In a developmental toxicity study involving rats dosed with 1,2-hexanediol, an oral NOEL of 300 mg/kg was reported. In other studies, no significant adverse reproductive or developmental effects in oral studies when evaluated in mice at concentrations of ≤5.0% PG, rats at doses of ≤1600 mg/kg PG, rabbits at doses of ≤1230 mg/kg PG, or hamsters at doses of ≤1550 mg/kg PG. Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively. A study examining induction of cytogenetic aberrations in mice reported an increase in the frequency of premature centromere separation (PCS) with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

1,2-Butanediol

The test procedure for the combined repeated dose and reproductive/developmental toxicity study (Crj-CD(SD) rats) and results relating to oral toxicity are included in the Short-Term Oral Toxicity section earlier in the report text. All of the animals were killed on day 4 of lactation. Neither effects on reproduction (copulation, implantation, pregnancy, parturition, or lactation) nor developmental toxicity effects on offspring were observed. The NOAEL was 1,000 mg/kg for parental animals and the F₁ generation.³⁶ The estimated dose of low concern (EDCL) for this study was calculated as 10 mg/kg/day, using an NOAEL of 1,000 mg/kg/day and a reproductive toxicity uncertainty factor of 100.⁷

1,2-Hexanediol

The developmental toxicity of Hydrolite-6 (99% 1,2-hexanediol) was evaluated using groups of 24 mated Sprague-Dawley rats of the CrI:CD strain.⁴⁷ Three groups received oral doses (gavage) of 30, 100, and 300 mg/kg/day, respectively, between days 5 and 19 of gestation. The negative control group received vehicle (not stated) only. Pregnant females were killed on day 20 of gestation and subjected to macroscopic necropsy. Doses up to 300 mg/kg/day were well-tolerated, and did not induce any effects on clinical condition, body weight, body weight change, food intake, or necropsy observations. There were also no effects on embryo-fetal survival, growth, or development at doses up to 300 mg/kg/day. It was concluded that Hydrolite-6 at doses up to 300 mg/kg/day was not associated with any adverse effect on the pregnant rat or the developing conceptus. The Hydrolite-6 (1,2-hexanediol) NOEL for the pregnant female and for embryo-fetal survival, growth, and development was considered to be 300 mg/kg/day.

Propylene Glycol

A continuous breeding reproductive study was conducted using COBS CrI:CD-1 (ICR)BR outbred Swiss albino mice (6 weeks old). The 3 experimental groups received the following doses (in feed or water), respectively, during a 7-day pre-mating period: 1.0% propylene glycol (daily dose of 1.82 g/kg), 2.5% propylene glycol (daily dose of 4.80 g/kg), and 5.0% propylene glycol (daily dose of 10.10 g/kg). PG was not a reproductive toxicant in this study.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

The reproductive and developmental effects of PG were evaluated using mice, rats, rabbits, and hamsters. Groups of 25 or 28 female albino CD-1 outbred mice were mated and 22, 22, 22, 20, and 23 gravid mice were dosed by oral intubation with 0.0, 16.0, 74.3, 345.0, and 1600.0 mg/kg aq. PG on days 6-15 of gestation. Groups of 25-28 female albino Wistar rats were mated and 22, 23, 22, 20, and 24 were dosed as above, respectively. PG was not a reproductive or developmental toxicant in this study.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Groups of 11, 11, 12, 14, and 13 gravid female Dutch-belted rabbits were dosed by oral intubation with 0, 12.3, 57.1, 267.0, or 1230.0 mg/kg aq. PG on days 6-18 of gestation, respectively. Administration of PG did not cause reproductive or developmental toxicity.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Groups of 24-27 female golden hamsters were mated and 21, 24, 25, 22, and 22 gravid hamsters were dosed by oral intubation with 0.0, 15.5, 72.0, 334.5, and 1550.0 mg/kg aq. PG on days 6-10 of gestation, respectively. PG was not a reproductive or developmental toxicant in this study.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

PG was used as a vehicle in a reproductive and behavioral development study. It was administered to 15 gravid Sprague-Dawley rats orally by gavage on days 7-18 of gestation at a volume of 2 ml/kg. PG did not have any effects on reproductive or behavioral development parameters.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

A study was performed to determine whether PG induced cytogenetic aberrations in mouse metaphase II (MII) oocytes that predispose zygotes to aneuploidy. In the MII portion of the study, female ICR mice were dosed i.p. with 1300, 2600, or 5200 mg/kg PG in distilled water after dosing with hCG. A statistically significant change in hyperploidy, hypoploidy, or single chromatids was not observed. An increase in the frequency of PCS at each dose was statistically significant, and the incidence of premature anaphase was significantly greater in the 5200 mg/kg dose group as compared to controls.

In the zygote portion of the study, female mice were dosed i.p. with 1300, 2600, or 5200 mg/kg PG 3 h after hCG administration. There were 30, 40, 49, and 66 mice in the control, 1300, 2600, and 5200 mg/kg groups, respectively. The increase in hyperploidy was statistically significant in all test groups compared to controls. A statistically significant change was not seen for polyploidy or hypoploidy, and zygotes containing PCS, premature anaphase, or single chromatids were not found. There was not a statistically significant difference in the proportion of zygotes collected for each group compared to oocytes. However, the number of zygotes analyzed compared to the number placed on slides was significantly decreased in the test groups; a relatively large portion of these zygotes had clumped chromosomes.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

GENOTOXICITY

Caprylyl glycol (Dermosoft® Octiol) did not induce gene mutations in Chinese hamster V79 cells (test concentrations up to 1489 µg/ml) and >98% caprylyl glycol (ADEKA NOL OG) did not induce chromosomal aberrations in Chinese hamster lung cells in vitro with or without metabolic activation at concentrations up to 700 µg/ml. Decylene glycol (SymClariol®) was non-genotoxic in the Ames test. 1,2-Butanediol was not genotoxic in assays involving bacterial cells (doses up to 5,000 µg/plate) or mammalian cells (doses up to 0.9 mg/ml). In the 1994 CIR final safety assessment, PG was not mutagenic in bacterial assays, but positive and negative results were reported in assays involving mammalian cells.

Caprylyl Glycol

The genotoxicity of > 98% caprylyl glycol (Dermosoft® Octiol) was evaluated in a gene mutation assay involving Chinese hamster V79 cells *in vitro* according to OECD and European Commission guidelines.⁴⁸ Test concentrations up to 1480 µg/ml were evaluated. The first experiment (with and without metabolic activation) involved a 4-h treatment period, whereas, the second experiment involved 4-h and 24-h treatment periods (without activation). A substantial or reproducible dose-dependent increase in the mutation frequency was not observed in either of the 2 experiments. Appropriate reference mutagens (positive controls, unnamed) induced a distinct increase in mutant colonies. Negative control cultures were not described. Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations under the experimental conditions reported, and therefore, was considered non-mutagenic.

The genotoxicity of > 98% caprylyl glycol (ADEKA NOL OG) was evaluated in the chromosome aberrations assay using Chinese hamster lung (CHL/IU) cells *in vitro* according to Ministry of Health and Welfare (Japan) genotoxicity test guidelines.⁴⁹ Short-term treatment of cultures (with and without metabolic activation) involved concentrations up to 700 µg/ml and continuous treatment involved concentrations up to 180 µg/ml, both with and without metabolic activation. Negative and positive control cultures were not identified. In all test cultures, the number of structural and numerical chromosomal aberrations was not increased when compared to negative control cultures. The positive control was genotoxic. The test substance did not induce chromosomal aberrations with or without metabolic activation.

1,2-Butanediol

1,2-Butanediol was not mutagenic to *Salmonella typhimurium* strains TA100, TA98, TA97, and TA102 at doses up to 5,000 µg/plate with or without metabolic activation. The test substance also induced neither chromosomal aberrations nor polyploidy in Chinese hamster CHL cells at doses up to 0.9 mg/ml either with or without metabolic activation.⁵⁰

Decylene Glycol

In the Ames test (OECD 471 protocol), decylene glycol (SymClariol®) was classified as non-mutagenic. Test concentrations were not stated.

Propylene Glycol

PG (≤10,000 µg/plate) was not mutagenic in Ames tests with or without metabolic activation. PG, tested at concentrations of 3.8-22.8 mg/ml, was a weak, but potential, inducer of sister chromatid exchanges (SCEs), causing a dose-dependent increase in SCEs in a Chinese hamster cell line. However, in another SCE assay using human cultured fibroblasts and Chinese hamster cells with and without metabolic activation, PG was not mutagenic. PG, 32 mg/ml, induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells. PG was not mutagenic in mitotic recombination or basepair substitution assays, or in a micronucleus test or a hamster embryo cell transformation assay (concentration used not specified).

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

CARCINOGENICITY**Propylene Glycol**

PG was non-carcinogenic in a 2-year bioassay in which rats were given $\leq 50,000$ ppm PG in the diet (feeding schedule not included). The dermal application of undiluted PG (volume not stated) to Swiss mice in a lifetime study was non-carcinogenic. PG was non-carcinogenic in other oral, dermal, and subcutaneous studies.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

CLINICAL ASSESSMENT OF SAFETY**Skin Penetration Enhancement**

Combined exposure to PG and oleic acid synergistically enhanced the dermal penetration of both compounds.

Propylene Glycol

By evaluating transepidermal water loss (TEWL) and determining attenuated total reflectance (ATR)-FTIR, PG dermal penetration was found to be enhanced by the addition of fatty acids, such as oleic acid. TEWL was determined using 10 subjects (number of males and females not specified) with application of occlusive chambers containing nothing, 300 μ l PG, or 300 μ l 0.16 M oleic acid in PG, for 3 or 24 h. To determine ATR-FTIR, an occlusion system containing PG or oleic acid/PG was applied to the forearm of each subject for 3 h.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Predictive Testing - Irritation and Sensitization

A 1,2-hexanediol/caprylyl glycol preservative mixture tested at concentrations up to 15% did not induce sensitization. Decylene glycol (20%) did not induce skin irritation/sensitization when applied to intact skin; however, decylene glycol (1%) had low skin irritation potential when applied to scarified skin. Results were negative for skin irritation/sensitization in RIPTs on products containing 1,2-glycols at concentrations ranging from 0.112% pentylene glycol to 0.5% caprylyl glycol or 1,2-hexanediol. In an in-use test of a products containing 0.15% 1,2-hexanediol, neither skin irritation nor sensitization was observed. PG was a slight skin irritant, but not a sensitizer, in human subjects. Deodorants or antiperspirant products containing 35 to 86% PG have been tested in HRIPTs and use tests. Although irritation was reported in some subjects exposed to the PG-containing products, studies including a reference deodorant or antiperspirant product without PG found that the PG-containing product did not result in more irritation than the reference product.

Caprylyl Glycol and 1,2-Hexanediol

A lipstick containing 0.5% caprylyl glycol was evaluated in an RIPT using 105 healthy subjects (males and females). The product was applied to the upper back of each subject and application sites were covered with a semi-occlusive patch for 24 h. It was concluded that the product did not demonstrate a potential for eliciting skin irritation or sensitization.⁵¹

Levy et al.⁵² studied the potential for delayed type IV dermal sensitivity following exposure to a new preservative containing 1,2-hexanediol and caprylyl glycol. In a repeat insult patch test, a 15% mixture of 1,2-hexanediol and caprylyl glycol (equal parts of the 2 ingredients) in carbomer gel (total volume = 20 μ l) was applied to each of 205 subjects (163 females, 42 males; 18 to 70 years old). The mixture was applied under 48 h occlusive patches (Finn chambers) during induction and challenge phases. Challenge application involved a new test site and reactions were scored at 48 and 72 h post-application according to the following scale: + (definite erythema without edema) to +++ (definite erythema, edema, and vesiculation). One of the subjects had a D reaction (damage to the epidermis: oozing, crusting, and/or superficial erosions) to the mixture; however, no reactions were observed in a subsequent 4-day repeat open application test. The reaction observed was indicative of irritation.

A cosmetic formulation containing the same preservative (gel vehicle) at an actual use concentration (0.5%) was evaluated in an additional group of 224 subjects (176 females, 48 males; 19 to 70 years old) according to the same test procedure. None of the subjects had a delayed type IV dermal reaction.⁵²

A 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68) was evaluated in an RIPT involving 56 subjects. At a test concentration of 20% in gel (effective concentration per ingredient = 10%), the mixture did not induce skin sensitization in any of the subjects tested.⁴³

A leg and foot gel containing 0.5% 1,2-hexanediol was applied to the upper back of each of 101 healthy subjects (males and females) in an RIPT. Each site was covered with a semi-occlusive patch that remained in place for 24 h. The product did not induce skin irritation or sensitization in this study.⁵³

In an in-use safety evaluation for skin irritation and sensitization potential, 28 subjects (males and females) were instructed to use a body wash containing 0.15% 1,2-hexanediol for a minimum of 3 times per week over a 30-day period. There was no evidence of erythema, edema, or dryness of application sites in any of the subjects, and it was concluded that the product did not demonstrate a potential for eliciting skin irritation or sensitization.⁵⁴

Pentylene Glycol

A foundation containing 0.112% pentylene glycol was evaluated in an RIPT using 101 subjects (males and females). A 1" x 1" semi-occlusive patch containing 0.2 g of the product was applied repeatedly (24 h applications) to the upper back. It was concluded that the product did not have a potential for inducing skin irritation or allergic contact sensitization.⁵⁵

Decylene Glycol

The skin irritation potential of decylene glycol (SymClariol®) was evaluated using 52 subjects in a 48 h semi-occluded patch test. At a concentration of 20% in petrolatum, the test substance did not induce skin irritation. SymClariol® (1% in neutral oil) had low skin irritation potential when applied to scarified skin sites on 10 subjects. In an HRIPT, SymClariol® (20% in petrolatum) did not induce skin sensitization in any of the 55 subjects tested.²⁸

In a facial stinging test, SymClariol® was classified as having very slight stinging potential when applied at concentrations of 1% and 2% (in neutral oil) in a group of 10 subjects.²⁸

Propylene Glycol

PG induced skin irritation reactions in normal subjects. Reactions were observed at concentrations as low as 10% in predictive tests. Use studies of deodorants containing 35-73% PG did not report any potential for eliciting irritation or sensitization. PG generally did not induce sensitization reactions when tested at 12-86%. In a modified Draize sensitization study with 203 subjects, PG (0.2 ml; concentration not stated) induced 19 cutaneous reactions at challenge.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

The effect of the addition of PG to an isopropanol vehicle on the irritant reaction of benzoic acid was determined in a non-occlusive test using 15 subjects, 7 males and 8 females. Benzoic acid in isopropanol was tested at concentrations of 31, 62, 125, and 250 mM without PG as well as with the addition of 1, 2, 5, 10, and 25% PG. Visual appearance, laser Doppler flowmetry, and skin color (using a Minolta chromameter) were measured. PG enhanced the strength of the reactions to 125 and 250 mM benzoic acid, but not to 31 or 62 mM benzoic acid. Enhancement was observed with the addition of 1% PG, and maximal enhancement was attained with 5%.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

It has been reported that intradermal injection of 0.02 ml undiluted PG produces a wheal-and-flare reaction within minutes, while the same volume applied epidermally does not produce any reaction. It has also been stated that subjective or sensory irritation sometimes occurs in volunteers after application of various concentrations of PG.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

A 24-h single insult occlusive patch test (SIOPT) was performed on an undiluted deodorant formulation containing 69.15% PG using 20 subjects (gender not specified). Four subjects had a score of $\pm$ (minimal faint uniform or spotty erythema) and 3 subjects had a score of 1 (pink-red erythema visibly uniform in the entire contact area.) The primary irritation index (PII) was 0.25.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

In another SIOPT, a deodorant formulation containing 68.06% PG was tested undiluted using 20 subjects (gender not specified). Three subjects had a score of $\pm$ and 1 had a score of 1 to the test formulation. The PII was 0.13.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

The irritation index for PG and 0.16 M oleic acid/PG was determined using 12 subjects (number per gender not specified) by applying occlusive chambers containing these 2 test substance to the volar forearm for 3 or 24 h. Visually, the 24-h application of PG produced only slight erythema, while the 24-h application of oleic acid/PG produced clearly visible irritation.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Thirty-day use studies were completed with 26 male, 40 female, and 24 male subjects to evaluate the potential for deodorant sticks containing 35, 65.2, and 73% PG, respectively, to induce dermal irritation and/or sensitization. The subjects were instructed to apply the product to the underarm once daily for 30 days. None of the subjects had any irritation or sensitization reactions. In a 4-wk use study completed with 26 male subjects following the same procedure, a deodorant stick containing 65.8% PG also did not demonstrate a potential for eliciting dermal irritation or sensitization.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

A maximization test was completed with 25 subjects, 18 male and 7 female, to determine the sensitization potential of a deodorant containing 69.15% PG. Sensitization reactions were not observed.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

An RIPT was completed with 101 subjects, 30 male and 71 female, to determine the sensitization potential of a stick deodorant formulation containing 73% PG. Scores of + (barely perceptible or spotty erythema) to 2, with some dryness, were observed throughout the study. While the authors stated that a stick deodorant formulation containing 73% PG “did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization,” the Expert Panel questioned that conclusion since repeated reactions were observed.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Another RIPT was completed with 99 subjects to determine the sensitization potential of a stick antiperspirant formulation containing 86% PG. One “+” reaction was observed during the entire study, and there was no evidence of sensitization.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Provocative Testing – Irritation and Sensitization

PG induced skin irritation reactions in patients at concentrations as low as 2%. Patients with chronic venous insufficiency (CVI) had sensitization reactions to PG, whereas contact dermatitis patients did not.

Propylene Glycol

PG induced skin irritation reactions in patients. Reactions were observed at concentrations as low as 2% in provocative tests.

From the Final Report on Propylene Glycol and Polypropylene Glycols¹

Thirty-six patients with CVI were patch tested with 5% PG in petrolatum by application to the back for 2 days. Twelve patients were male; 2, 5, and 5, had 1st, 2nd, and 3rd degree CVI, respectively. Twenty-four patients were

female; 5 and 19 had 2nd and 3rd degree CVI, respectively. The sensitization rate as a percentage of all patients was 8.3%. The sensitization rate of patients with 2nd and 3rd degree CVI tested with PG was 10 and 8.3%, respectively.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

During the period 2000-2004, 308 patients, 111 males and 197 females, with contact dermatitis were patch-tested using the European standard series and some additional chemicals, including PG. PG, 5% in petrolatum, did not cause any positive reactions.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Photoallergenicity

PG did not produce a photoallergic response in a provocative photopatch test.

Propylene Glycol

Over a 2-yr period, 30 males and 52 females with photoallergic contact dermatitis were photopatch tested with a standard series of sunscreens as well as some additional chemicals, including PG (dose not given). The allergens were applied in duplicate on the back and covered with opaque tape for 24 h. One set of test sites was irradiated with a UVA (320-400 nm) dose of 5 J/cm². PG did not produce a photoallergic or contact allergy response.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Retrospective Analysis

Propylene Glycol

The NACDG performed a number of retrospective analyses on various dermatological conditions, and data on the relevance of positive reactions to PG were presented. These studies are summarized in Table 5.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

Case Reports

Positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

Pentylene Glycol (1,2-Pentanediol)

A 68-year-old, non-atopic female developed facial dermatitis after using an eye cream that contained pentylene glycol (1,2-pentanediol), and patch test results were positive. Positive patch test reactions (+1) to 0.5% and 5% aqueous pentylene glycol were also reported. Except for one control subject with a follicular reaction to 5% pentylene glycol, reactions to 0.5% and 5.0% aqueous pentylene glycol were negative in a control group of 29 subjects.⁵⁶

Propylene Glycol

A few case reports have been described concerning PG and hand dermatitis or atopic dermatitis. The cases generally had positive patch test reactions to PG. Improvement was seen with the avoidance of PG-containing products.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols²

SUMMARY

The sixteen 1,2-glycols included in this safety assessment function primarily as skin and hair conditioning agents and viscosity increasing agents in personal care products, although caprylyl glycol and pentylene glycol also function as preservatives. The following five 1,2-glycols were reported to FDA as being used: caprylyl glycol, decylene glycol,

pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The results of a Personal Care Products Council industry survey indicate that ingredient use concentrations have range from 0.00003% (caprylyl glycol) to 10% (1,2-hexanediol). Use concentrations of pentylene glycol (up to 5%) were also included in this survey. C15-18 glycol was included in this survey, but no uses or use concentrations were reported.

Safety test data from the CIR safety assessment on propylene glycol have been reviewed and are relevant to the safety assessment of other 1,2-glycols included in this report, based on structural similarities.

The Environmental Protection Agency (EPA) lists 1,2-butanediol as one of the reactive compounds in aerosol coatings (i.e., aerosol spray paints) that contributes to ozone (O₃) formation.

Stearyl glycol is prepared via the reaction of 2-hydroxyoctadecanoic acid with lithium aluminum hydride in dry tetrahydrofuran, and the production of 1,2-butanediol is via a continuous reaction and distillation operation. The available impurities data indicate that 1,2-butanediol is $\geq 99\%$ pure and also contains water, 1,4-butanediol, and 1-acetoxy-2-hydroxybutane.

Information on the metabolism, distribution, and excretion of 1,2-butanediol following i.v. dosing indicate that, in rabbits, this chemical is metabolized slowly and excreted in the urine either as the glucuronide or unchanged; there was no evidence of tissue accumulation. Metabolites were not isolated from the urine of rabbits fed 1,2-butanediol in the diet. Based on metabolism modeling information on caprylyl glycol, 1,2-hexanediol, decylene glycol, and lauryl glycol, it is likely that C-oxidation, C-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. C-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

Following topical application of 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol in alcoholic solution) to female pig skin *in vitro*, approximately 97% of the test solution was dermally absorbed within 24 h post-application. Based on dermal penetration modeling information on caprylyl glycol, 1,2-hexanediol, decylene glycol, and lauryl glycol, the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol.

A skin penetration enhancement effect for caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated *in vitro*.

There were no significant toxic effects in rats exposed for 7 h to an atmosphere saturated with 1,2-butanediol. Acute oral toxicity data on caprylyl glycol and other 1,2-glycols for which data are available suggest that death would occur at relatively high doses (LD₅₀ range: 2200 to > 20,000 mg/kg). Reportedly, high (unspecified) oral doses of 1,2-butanediol caused narcosis, dilation of the blood vessels, and kidney damage in rats. Overt toxic effects were not observed in ethanol-dependent rats dosed orally with 2.74 g/kg 1,2-butanediol.

The available data suggest that 1,2-butanediol (LD₅₀s up to 5.99 g/kg) and pentylene glycol (TDLo = 3.51 g/kg) are not significant acute i.p. toxicants. However, muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg. In an i.p. dosing study in which ED₃ values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED₃ value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest. In an acute dermal toxicity study involving rats, the LD₅₀ for decylene glycol (SymClariol®) was > 2,000 mg/kg. Prolonged application or repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.

A no-observed effect level (NOEL) of 50 mg/kg/day and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity in rats were reported in a 28-day oral toxicity study on > 98% caprylyl glycol (Dermosoft® Octiol). The NOAEL was based on findings of irritation on the pars non-glandularis and limiting ridge of the stomach; analogous structures do not exist in man. An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on decylene glycol (SymClariol®). Short-term oral administration of 1,2-butanediol to rats yielded an NOAEL of 200 mg/kg/day. Reportedly, in another repeated dose study, the administration of large (unspecified) doses of 1,2-butanediol to rats, caused irritation of the gastrointestinal tract. Signs of toxicity were noted at the highest dose of 22 g/kg/day in rats receiving 1,2-butanediol in the diet for up to 8 weeks; abnormalities were not observed in tissues from major organs.

Intermittent oral administration of pentyleneglycol to rats over a 28-week period yielded a TDLo of 2,450mg/kg. In a 92- to 97-day oral toxicity study involving mice, rats, dogs, and monkeys dosed with a formulation containing propylene glycol (dose = 1000 mg/kg), there were no adverse effects on body weight, feed consumption, clinical pathology, histopathology, or adverse clinical observations.

Cetyl glycol (130 µg/ml) had a cytotoxic effect on Ehrlich ascites carcinoma cells, lauryl glycol (99 µM) had a hemolytic effect on human erythrocytes, and pentyleneglycol (5%) induced apoptosis in a human promyelocytic leukemia cell line *in vitro*.

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Undiluted 1,2-butanediol, but not 10% aqueous, induced ocular irritation in rabbits. Undiluted decylene glycol (SymClariol®) induced corrosion when instilled into the eyes of rabbits. In an *in vitro* ocular irritation assay (HET-CAM), 1% SymClariol® in neutral oil and caprylyl glycol (1% and 3%) in neutral oil were classified as non-irritants; however, a 50:50 (w/w) mixture of caprylyl glycol and 1,2-hexanediol was classified as a severe ocular irritant when evaluated at a concentration of 1% aqueous (effective concentration per ingredient = 0.5%) in the same assay. Together, the results of a neutral red release (NRR) assay, the HET-CAM assay, and the reconstituted human epithelial culture (REC) assay indicated that a lash gel serum containing 3% pentyleneglycol might be a slight ocular irritant.

In the guinea pig maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted decylene glycol (SymClariol®) was classified as a moderate skin irritant in rabbits, but did not induce sensitization in the guinea pig maximization test at challenge concentrations of 2% and 5% in arachis oil or in the mouse local lymph node assay at concentrations of 5% to 50% in acetone/olive oil (4:1). Repeated applications of 1,2-butyleneglycol to the skin of rabbits did not result in skin irritation, and results were negative for 1,2-hexanediol (10% to 100%) in the mouse local lymph node assay for evaluating sensitization potential.

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally. In a prenatal developmental toxicity study involving rats, an NOEL of 300 mg/kg was reported for 1,2-hexanediol.

Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations in Chinese hamster V79 cells (concentrations up to 1480 µg/ml) and >98% caprylyl glycol (ADEKA NOL OG) did not induce chromosomal aberrations in Chinese hamster lung cells (concentrations up to 700 µg/ml) *in vitro*. Decylene glycol (SymClariol®) was non-genotoxic in the Ames test, and 1,2-Butanediol was not genotoxic in assays involving bacterial cells (doses up to 5,000µg/plate) or mammalian cells (doses up to 0.9 mg/ml). Marked antitumor effects of cetyl glycol were observed in mice *in vivo* following i.p. doses of 80 mg/kg/day. Cetyl glycol (130 µg/ml) was found to have a cytotoxic effect (irreversible cell degeneration) on cultured EAC cells.

Results were negative for skin irritation and sensitization potential in RIPTs in which 105 subjects were patch tested with a lipstick containing 0.5% caprylyl glycol and 101 subjects were patch tested with a leg and foot gel containing 0.5% 1,2-hexanediol. An in-use test of a body wash containing 0.15% 1,2-hexanediol did not result in skin irritation or sensitization reactions in 28 subjects. 1,2-hexanediol/caprylyl glycol mixture (in preservative system) was non-sensitizing at a concentration of 0.5% or 15% in an RIPT involving 205 human subjects. Skin sensitization also was not observed in another RIPT in which 56 subjects were tested with a 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68; effective concentration per ingredient = 10%). Decylene glycol (SymClariol®) did not induce skin irritation in 52 subjects or sensitization (RIPT) in 55 subjects patch tested at a concentration of 20% in petrolatum. However, SymClariol® (1% in neutral oil) had low skin irritation potential when applied to scarified skin in a group of 10 subject, and very slight stinging potential when tested at concentrations of 1% and 2% in neutral oil in 10 subjects. A foundation containing 0.112% pentyleneglycol did not induce skin irritation or sensitization in an RIPT involving 101 subjects. Positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentyleneglycol, but not in the control group.

Propylene Glycol

In mammals, the major pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner.

Dermal penetration of PG from a ternary cosolvent solution through hairless mouse skin was 57% over a 24 h period. Using thermal emission decay (TED)-Fourier transform infrared (FTIR) spectroscopy, it appeared that PG did not reach the dermis.

PG is a penetration enhancer for some chemicals and, under some conditions, in human subjects, and can act synergistically with other enhancers. The mechanism by which PG enhances penetration has not been identified.

Based on the 1994 safety assessment and more recent information, few toxic effects were seen in dosing with PG. The oral LD₅₀ of PG was >21 g/kg for rats. The dermal LD₅₀ of PG was >11.2 g/kg for mice and was 13 g/kg for rats. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg). All mice survived in a short-term study in which mice were given 10% PG in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG, 3 times per day, for 3 days. In a subchronic study, a dose of ≤50,000 ppm PG given in the feed for 15 wks did not produce any lesions. Subchronic inhalation data reported some effects in rats due to PG exposure of 2.2 mg/l air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends. In the 1994 safety assessment, no toxic effects were reported in chronic studies when rats or dogs were given feed containing 50 g/kg or 5 g/kg, respectively, PG.

Undiluted PG was, at most, a slight ocular irritant. Dermal irritation studies were reported in the 1994 CIR final safety assessment and in the amended final safety assessment. In one study using nude mice, 50% PG may have caused skin irritation, while in another study, 100% PG was minimally irritating to hairless mice. Hypertrophy, dermal inflammation, and proliferation were also observed with 50% PG in nude mice. These effects were not seen in hairless mice with undiluted PG. Undiluted PG was at most a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. PG (concentrations not given) was negative in a number of sensitization assays using guinea pigs. In a study using guinea pigs, 0.5 ml PG was a weak sensitizer.

Oral administration of PG did not have any adverse reproductive or developmental effects when evaluated in mice at concentrations of ≤5%, rats at doses of ≤1600 mg/kg, rabbits at doses of ≤1230 mg/kg, or hamsters at doses of ≤1550 mg/kg. Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively. A study examining induction of cytogenetic aberrations in mice reported an increase in the frequency of premature centrosphere separation with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

PG, ≤10,000 µg/plate, was not mutagenic in Ames tests with or without metabolic activation. PG, tested at concentrations of 3.8-22.8 mg/ml, was a weak but potential inducer of sister chromatid exchanges (SCEs), causing a dose-dependent increase in SCEs in a Chinese hamster cell line. However in another SCE assay using human cultured fibroblasts and Chinese hamster cells with and without metabolic activation, PG was not mutagenic. PG, 32 mg/ml, induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells. PG was not mutagenic in mitotic recombination or base pair substitution assays, or in a micronucleus test or a hamster embryo cell transformation assay.

PG was not carcinogenic in a 2-yr chronic study in which rats were given ≤50 000 ppm PG in the diet. Dermal application of undiluted PG to Swiss mice in a lifetime study produced no significant carcinogenic effects. PG was not carcinogenic in other oral, dermal, and subcutaneous studies.

Combined exposure to PG and oleic acid synergistically enhanced the dermal penetration of both compounds. Addition of PG to an isopropanol vehicle enhanced the irritant reactions of benzoic acid; maximal enhancement was seen with 5% PG.

PG induced skin irritation reactions in normal subjects and in patients. Reactions were observed at concentrations as low as 10% in predictive tests and 2% in provocative tests. Use studies of deodorants containing 35-73% PG did not report any potential for eliciting irritation or sensitization. PG generally did not induce sensitization reactions when tested at 12-86%, although results were questionable in a RIPT of a deodorant containing 73% PG. Additionally, in a modified Draize sensitization study with 203 subjects, PG (0.2 ml, concentration not stated) induced 19 cutaneous reactions at challenge. PG did not produce a photoallergic response in a provocative photopatch test. Retrospective analysis of pools of patient patch test data indicated that ≤6.0% of patients tested had positive reactions to 30% aq. PG. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

DISCUSSION

The available safety test data for 1,2-glycols indicate that they are not significant acute toxicants, are not significantly genotoxic, are non-carcinogenic, and are not significant dermal irritants, sensitizers or photosensitizers. Data on the following 1,2-glycols were reviewed: caprylyl glycol, lauryl glycol, stearyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, 1,2-hexanediol, C15-18 glycol, and propylene glycol. Many of the studies included in this safety assessment are on propylene glycol. However, because increasing the chain length of the carbon backbone likely will not increase the potential for toxicity of longer-chain 1,2-glycols, data on propylene glycol may be used to support the safety of all 1,2-glycols reviewed in this safety assessment.

Results from an *in vitro* skin penetration study on 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol) using female pig skin indicated significant percutaneous absorption of caprylyl glycol. Dermal penetration modeling data on caprylyl glycol (C8), 1,2-hexanediol (C6), decylene glycol (C10), and lauryl glycol (C12) predicted that skin penetration would decrease with increasing chain length. Acknowledging the dermal absorption of these compounds, the Expert Panel determined that evaluation of reproductive/developmental toxicity data would be key to determining a safe level. The results of oral reproductive/developmental toxicity studies on propylene glycol (C3), 1,2-butanediol (C4), and 1,2-hexanediol (C6) were negative, and there was no evidence of systemic toxicity in other oral repeated dose toxicity studies involving caprylyl glycol (C8), propylene glycol (C3), 1,2-butanediol (C4), pentylene glycol (C5), and decylene glycol (C10). Additionally, the available repeated dose toxicity data included some 28-day oral toxicity studies, but no 28-day dermal toxicity data, and dermal reproductive/developmental toxicity data also were not available. However, the Expert Panel agreed that these oral toxicity data could be used to evaluate the safety of 1,2-glycols in products applied to the skin in the absence of dermal studies, because 1,2-glycol blood levels following oral exposure would be higher when compared to dermal exposure and systemic toxicity was absent in the oral studies.

Dermal absorption modeling data predicted that skin penetration decreases with increasing chain length, significant dermal penetration of the longer chain 1,2 glycols may occur. Metabolism modeling data on caprylyl glycol, 1,2-hexanediol, decylene glycol and lauryl glycol predicted that C-oxidation, C-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. The Expert Panel agreed that the negative oral reproductive/developmental toxicity (up to C6) and other negative oral repeated dose toxicity data (up to C10) may be extrapolated to longer –chain 1,2-glycols. The negative results of bacterial/mammalian genotoxicity assays on caprylyl glycol, 1,2-butanediol, and decylene glycol were also considered, and the Expert Panel agreed that these data can also be extrapolated to longer-chain 1,2-glycols as well. Thus, the modeling data predictions of decreased skin penetration of longer-chain 1,2-glycols and those relating to their metabolic fate, together with the negative oral toxicity data on shorter-chain 1,2-glycols and genotoxicity data, support the safety of all of the 1,2-glycols reviewed in this safety assessment in products applied to the skin.

The Expert Panel noted the potential for caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol to be penetration enhancers. Some cosmetic ingredients have been regarded as safe based on the fact that they do not penetrate the skin. If caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol enhance the penetration of such ingredients, then industry is advised to consider the impact of the penetration enhancing activity of these ingredients on the safety of other ingredients in formulation.

CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

- caprylyl glycol
- arachidyl glycol*
- cetyl glycol*
- hexacosyl glycol*
- lauryl glycol*
- myristyl glycol*
- octacosanyl glycol*
- stearyl glycol*
- decylene glycol
- pentylene glycol
- 1,2-butanediol*
- 1,2-hexanediol

- C14-18 glycol*
- C15-18 glycol
- C18-30 glycol*
- C20-30 glycol*

*Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Table 1. Caprylyl Glycol and Other 1,2-Glycols³

Chemical Names/CAS Nos.	Functions in Cosmetics
Arachidyl Glycol 1,2-Eicosanediol; CAS No. 39825-93-9	Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
Cetyl Glycol 1,2-Dihydroxyhexadecane; 1,2-Hexadecanediol; 1,2-Hexadecylene Glycol; 2-Hydroxycetyl Alcohol; CAS No. 6920-24-7	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
Hexacosyl Glycol	Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Nonaqueous
Lauryl Glycol 1,2-Dihydroxydodecane; 1,2-Dodecanediol; 1,2-Dodecylene Glycol; CAS No. 1119-87-5	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient
Myristyl Glycol 1,2-Tetradecanediol; CAS No. 21129-09-9	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Octacosanyl glycol 1,2-Octacosanediol; CAS No. 97338-11-9	Emulsion Stabilizers; Viscosity Increasing Agents - Nonaqueous
Stearyl Glycol 1,2-Dihydroxyoctadecane; 1,2-Octadecanediol; CAS No. 20294-76-2	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Nonaqueous
Caprylyl Glycol Capryl Glycol; 1,2-Dihydroxyoctane; 1,2-Octanediol; 1,2-Octylene Glycol; CAS No. 1117-86-8	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; preservative
Decylene Glycol 1,2-Decanediol; CAS No. 1119-86-4	Skin-Conditioning Agents - Miscellaneous
Pentylene Glycol 1,2-Dihydroxypentane; 1,2-Pentanediol; CAS No. 5343-92-0	Skin-Conditioning Agents - Miscellaneous; Solvents; preservative
1,2-Butanediol 1,2-Butylene Glycol; 1,2-Dihydroxybutane; CAS No. 584-03-2	Skin-Conditioning Agents - Humectant; Solvents; Viscosity Decreasing Agents
1,2-Hexanediol 1,2-Dihydroxyhexane; CAS No. 6920-22-5	Solvents
C14-18 Glycol Ethylene Glycol Fatty Acid Ester (2)	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C15-18 Glycol Alkylene (15-18) Glycol; Cetyl Stearyl Vicinal Glycol; Glycols, C15-18; CAS Nos. 70750-40-2 and 92128-52-4	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C18-30 Glycol Ethylene Glycol Fatty Acid Ester (1)	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C20-30 Glycol Alkylene (20-30) Glycol	Emulsion Stabilizers; Skin-Conditioning Agents - Occlusive

Table 2. Chemical and Physical Properties

Property	Values	Reference
<i>Arachidyl Glycol</i>		
Molecular weight	314.55	ACD/Labs ⁵⁷
Molar volume	354.0 ± 3.0 cm ³ /mole (20°C, 760 Torr)	"
Density	0.888 ± 0.6 g/cm ³ (20°C, 760 Torr)	"
Mass intrinsic solubility	0.000000063 g/l (25°C)	"
Mass solubility	0.000000063 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.0000000020 mol/l (25°C)	"
Molar solubility	0.0000000020 mol/l (pH 7, 25°C)	"
Melting point	84.3 to 84.8°C	"
Boiling point	435.2 ± 18.0°C (760 Torr)	"
Flash point	183.7 ± 15.8°C	"
Enthalpy of vaporization	79.83 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	2.11E-09 Torr	"
pKA	14.19 ± 0.20 (25°C)	"
logP	7.692 ± 0.216 (25°C)	"
<i>Cetyl glycol</i>		
Molecular weight	258.44	ACD/Labs ⁵⁷
Molar volume	288.0 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.897 ± 0.06 g/cm ³ (20°C, 760 Torr)	"
Mass intrinsic solubility	0.000067 g/l (25°C)	"
Mass solubility	0.000067 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.00000026 mol/l (25°C)	"
Molar solubility	0.00000026 mol/l (pH 7, 25°C)	"
Melting point	75 to 76°C (not calculated)	Bryun ⁵⁸
Boiling point	356.1 ± 10.0°C (760 Torr)	ACD/Labs ⁵⁷
Flash point	151.9 ± 13.6°C	"
Enthalpy of vaporization	69.61 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	1.69E-06 Torr (25°C)	"
pKA	14.19 ± 0.20 (25°C)	"
logP	5.567 ± 0.216 (25°C)	"
<i>Lauryl glycol</i>		
Molecular weight	202.33	ACD/Labs ⁵⁷
Molar volume	222.0 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.911 ± 0.06 g/cm ³ (20°C, 760 Torr)	"
Refractive index	1.4558 (20°C, λ = 589.3 nm)	"
Mass intrinsic solubility	0.028 g/l (25°C)	"
Mass solubility	0.028 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.00014 mol/l (25°C)	"
Molar solubility	0.00014 mol/l (pH7, 25°C)	"
Melting point	60 to 61°C (not calculated)	Swern ⁵⁹
Boiling point	179 to 181°C (4 Torr) – not calculated; 304.3 ± 10°C (760 Torr)	"
Flash point	134.3 ± 13.6 °C	"
Enthalpy of vaporization	63.17 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	8.40E-05 Torr	"
pKA	14.19 ± 0.20 (25°C)	"
logP	3.441 ± 0.216 (25°C)	"
<i>Myristyl glycol</i>		
Molecular weight	230.39	ACD/Labs ⁵⁷
Molar volume	255.0 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.903 ± 0.06 g/cm ³ (20°C, 760 Torr)	"

Table 2. Chemical and Physical Properties

Property	Values	Reference
Mass intrinsic solubility	0.0015 g/l (25°C)	ACD/Labs ⁵⁷
Mass solubility	0.0015 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.0000067 mol/l (25°C)	"
Molar solubility	0.0000067 mol/l (pH 7, 25°C)	"
Melting point	68 to 68.5 °C	"
Boiling point	152 to 154 °C (0.2 Torr); 333.1 ± 10.0°C (760 Torr)	"
Flash point	143.8 ± 13.6 °C	"
Enthalpy of vaporization	66.48 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	1.16E-05 Torr (25°C)	"
pKA	14.19 ± 0.20 (25°C)	"
logP	0.4504 ± 0.216 (25°C)	"
<i>Octacosanyl Glycol</i>		
Molecular weight	426.76	ACD/Labs ⁵⁷
Molar volume	486.1 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.877 ± 0.06 g/cm ³ (20°C, 760 Torr)	"
Mass intrinsic solubility	0.0000032 g/l (25°C)	"
Mass solubility	0.0000032 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.000000076 mol/l (25°C)	"
Molar solubility	0.000000076 mol/l (pH 7, 25°C)	"
Boiling point	536.3 ± 23.0°C (760 Torr)	"
Flash point	210.9 ± 17.2°C	"
Enthalpy of vaporization	93.49 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	9.74E-14 Torr (25°C)	"
pKA	14.19 ± 0.20 (25°C)	"
logP	11.943 ± 0.217 (25°C)	"
<i>Stearyl Glycol</i>		
Molecular weight	286.49	ACD/Labs ⁵⁷
Molar volume	321.0 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.892 ± 0.06 g/cm ³ (20°C, 760 Torr)	"
Mass intrinsic solubility	0.0000023 g/l (25°C)	"
Mass solubility	0.0000023 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.000000080 mol/l (25°C)	"
Molar solubility	0.000000081 mol/l (pH 7, 25°C)	"
Melting point	79 to 79.5°C (not calculated)	Niemann ⁶⁰
Boiling point	377.2 ± 10.0°C (760 Torr)	ACD/Labs ⁵⁷
Flash point	157.6 ± 13.6°C	"
Enthalpy of vaporization	72.30 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	3.09E-07 Torr (25°C)	"
pKA	14.19 ± 0.20 (25°C)	"
logP	6.629 ± 0.216 (25°C)	"
<i>Caprylyl Glycol</i>		
Form	Specification: Colorless liquid with mild odor (as > 98% caprylyl glycol [Dermosoft® Octiol])	Straetmans ⁸
Molecular weight	146.23	ACD/Labs ⁵⁷
Molar volume	155.9 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.937 ± 0.06 g/cm ³ (20°C, 760 Torr)	"
Mass intrinsic solubility	4.2 g/l (25°C)	"
Mass solubility	4.4 g/l (pH 7, 25°C)	"
Molar intrinsic	0.029 mol/l (25°C)	"

Table 2. Chemical and Physical Properties

Property	Values	Reference
solubility		
Molar solubility	0.030 mol/l (pH 7, 25°C)	"
Glycol value	Specification: 740 to 770 (as Dermosoft® Octiol)	Straetmans ⁸
Melting point	36 to 37°C (not calculated)	Fringuelli ⁶¹
Boiling point	137 to 139°C (not calculated); 243.0 ± 8.0°C (760 Torr)	Mugdan ⁶²
Flash point	109.1 ± 13.0°C	ACD/Labs ⁵⁷
Enthalpy of vaporization	55.78 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	5.59E-03 Torr	"
pKA	14.31 ± 0.10 (25°C)	"
logP	1.316 ± 0.215 (25°C)	"
<i>Decylene Glycol</i>		
Form	Whitish to white waxy mass (as 98% to 100% decylene glycol [SymClariol®])	Symrise ⁹
Molecular weight	174.28	STN ¹¹
Molar volume	188.9 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.922 ± 0.06 g/cm ³ (20°C, 760 Torr)	"
Mass intrinsic solubility	0.40 g/l (25°C)	"
Mass solubility	0.40 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.0023 mol/l (25°C)	"
Molar solubility	0.0023 mol/l (pH 7, 25°C)	"
Melting point	48-49°C	Swern ⁵⁹
Melting point	42 to 52°C	Symrise ⁹
Boiling point	93 to 96°C (0.5 Torr) - not calculated; 255.0 ± 0.0°C (760 Torr)	Orito ⁶³
Flash point	122.4 ± 13.0°C	ACD/Labs ⁵⁷
Flash point	>100°C (as SymClariol®)	Symrise ⁹
Enthalpy of vaporization	57.21 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	2.54E-03 Torr (25°C)	"
pKA	14.21 ± 0.20 (25°C)	"
logP	2.378 ± 0.216 (25°C)	"
<i>Pentylene Glycol</i>		
Molecular weight	104.15	ACD/Labs ⁵⁷
Molar volume	106.4 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.9723 g/cm ³ (20°C) – not calculated; 0.978 ± 0.06 g/cm ³ (20°C, 760 Torr)	Clendenning ⁶⁴
Refractive index	1.4400 (20°C, λ = 589.3 nm) – not calculated	Emmons ⁶⁵
Mass intrinsic solubility	95 g/l (25°C)	ACD/Labs ⁵⁷
Mass solubility	95 g/l (pH 7, 25°C)	"
Molar intrinsic solubility	0.91 mol/l (25°C)	"
Molar solubility	0.91 mol/l (25°C)	"
Boiling point	78 to 80°C (0.3 Torr) – not calculated ; 206.0 ± 0.0°C (760 Torr)	Clendenning ⁶⁴ ; Emmons ⁶⁵
Flash point	104.4 ± 0.0°C	ACD/Labs ⁵⁷
Enthalpy of vaporization	51.45 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	5.75E-02 Torr (25°C)	"
pKA	14.22 ± 0.20 (25°C)	"
logP	-0.278 ± 0.215 (25°C)	"
<i>1,2-Butanediol</i>		
Molecular weight	90.12	ACD/Labs ⁵⁷
Molar volume	89.9 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"

Table 2. Chemical and Physical Properties

Property	Values	Reference
Density	1.0205 g/cm ³ (20°C) – not calculated; 1.001 ± 0.06 g/cm ³ (20°C)	Mamedov ⁶⁶ , Tishchenko ⁶⁷
Refractive index	1.4380 (20°C, λ = 589.3 nm)	ACD/Labs ⁵⁷
Mass intrinsic solubility	230 g/l (25°C)	"
Solubility	Very soluble in water	NIOSH ¹³
Mass solubility	230 g/l (pH 7, 25°C)	ACD/Labs ⁵⁷
Molar intrinsic solubility	2.55 mol/l (25°C)	"
Molar solubility	2.55 mol/l (pH 7, 25°C)	"
Melting point	-50°C and -114°C (not calculated)	STN ¹¹
Boiling point	132 to 133°C (760 Torr) – not calculated; 190.3 ± 8.0°C (760 Torr)	Clendenning ⁶⁴ , Hill ⁶⁸
Flash point	93.3 ± 0.0°C	ACD/Labs ⁵⁷
Enthalpy of vaporization	49.64 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	1.48E-01 Torr 10 (20°C)	" NIOSH ¹³
pKA	14.27 ± 0.20 (25°C)	STN ¹¹
logP	-0.810 ± 0.215 (25°C)	"
Stability	Stable in neutral, acidic, or alkaline solutions	OECD ⁷
Half life	≥ 1 year (25°C; pH: 4, 7, and 9)	"
1,2-Hexanediol		
Form	Colorless to light yellow liquid with a characteristic odor (as Hydrolite-6, 99% 1,2-hexanediol)	Symrise ⁶⁹
Molecular weight	118.17	ACD/Labs ⁵⁷
Molar volume	122.9 ± 3.0 cm ³ /mol (20°C, 760 Torr)	"
Density	0.961 ± 0.06 g/cm ³ (20°C)	"
Relative density (D20/4)	0.9490 to 0.9540 (as Hydrolite-6)	Symrise ⁶⁹
Refractive index	1.4518 (25°C, λ = 589.3 nm) – not calculated	Zelinski ⁷⁰
Refractive index (n20/D)	1.4400 (as Hydrolite-6)	Symrise ⁶⁹
Solubility	Readily soluble in water and oil	
Mass intrinsic solubility	37 g/l (25°C)	ACD/Labs ⁵⁷
Mass solubility	37 g/l (pH7, 25°C)	"
Molar intrinsic solubility	0.31 mol/l (25°C)	"
Molar solubility	0.31 mol/l (pH 7, 25°C)	"
Melting point		"
Boiling point	112 to 113°C (12 Torr) – not calculated; 223.5 ± 0.0°C (760 Torr)	Laporte ⁷¹
Flash point	95.8 ± 13.0°C	"
Flash point	>100°C (as Hydrolite-6)	Symrise ⁶⁹
Enthalpy of vaporization	53.48 ± 6.0 kJ/mol (760 Torr)	"
Vapor pressure	1.94E-02 Torr	"
pKA	14.22 ± 0.20 (25°C)	"
logP	0.253 ± 0.215 (25°C)	"

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure^{14,15}

	Caprylyl Glycol		Decylene Glycol		Pentylene Glycol	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	269	0.3 to 5	NR	NR	114	0.005 to 4
Possible Ingestion	NR	NR	NR	NR	6	NR
Inhalation	27	0.2 to 0.5	NR	NR	6	1
Dermal Contact	1843	0.0003 to 5	1	NR	775	0.001 to 5

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<i>Deodorant (underarm)</i>	36	0.03 to 2	NR	NR	3	0.2
<i>Hair - Non-Coloring</i>	101	0.0002 to 2	NR	NR	8	0.001
<i>Hair-Coloring</i>	1	0.002 to 5	NR	NR	NR	NR
<i>Nail</i>	8	0.0004 to 0.5	NR	NR	1	4 to 5
<i>Mucous Membrane</i>	NR	NR	NR	NR	6	0.001 to 5
<i>Bath Products</i>	63	0.0004 to 1	NR	NR	1	NR
<i>Baby Products</i>	11	0.6	NR	NR	NR	NR
Duration of Use						
<i>Leave-On</i>	1721	0.00003 to 5	1	NR	713	0.005 to 5
<i>Rinse off</i>	416	0.0004 to 2	NR	NR	105	0.001 to 5
Totals/Conc. Range	2137	0.00003 to 5	1	NR	818	0.001 to 5
	1,2-Hexanediol		C15-18 Glycol			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type						
<i>Eye Area</i>	35	0.3 to 0.7	NR	NR		
<i>Possible Ingestion</i>	39	0.3	NR	NR		
<i>Inhalation</i>	2	10	NR	NR		
<i>Dermal Contact</i>	215	0.00005 to 10	1	NR		
<i>Deodorant (underarm)</i>	3	NR	NR	NR		
<i>Hair - Non-Coloring</i>	4	0.0003 to 0.3	NR	NR		
<i>Hair-Coloring</i>	NR	NR	NR	NR		
<i>Nail</i>	1	0.4	NR	NR		
<i>Mucous Membrane</i>	14	0.3	NR	NR		
<i>Bath products</i>	2	0.2	NR	NR		
<i>Baby Products</i>	3	NR	NR	NR		
Duration of Use						
<i>Leave-On</i>	182	0.2 to 10	1	NR		
<i>Rinse off</i>	51	0.00005 to 0.8	NR	NR		
Totals/Conc. Range	233	0.00005 to 10	1	NR		

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Corticosterone and TEA Permeability Coefficients in the Presence of Permeation Enhancers¹²

Enhancer	Enhancer Concentration (M)	Permeability Coefficient of CS ^a (cm/s x 10 ⁷)	Permeability Coefficient of TEA ^a (cm/s x 10 ⁸)
PBS – control		2.2 ± 0.8	1.35 ± 0.65
1,2-octanediol	0.005	6.2 ± 1.1	
	0.0104	7.4 ± 1.4	4.2 ± 1.3
	0.02	30 ± 3	12 ± 8
	0.024	27 ± 9	20 ± 5

	0.035	110 ± 10	
1,2-decanediol	0.0006	5 ± 1	
	0.001	11 ± 3	4.7 ± 2.1
	0.00141	28 ± 7	
	0.00192	80 ± 20	7.1 ± 0.7
	0.0024	110 ± 1	63 ± 16
1,2-hexanediol	0.09	6.5 ± 2.7	
	0.145	13 ± 3	2 ± 1
	0.25	23 ± 5	
	0.35	65 ± 23	9.2 ± 4.1

^aMean ± SD (n = 3)

Figure 2. Octanol/Water Partitioning Coefficient (log P)

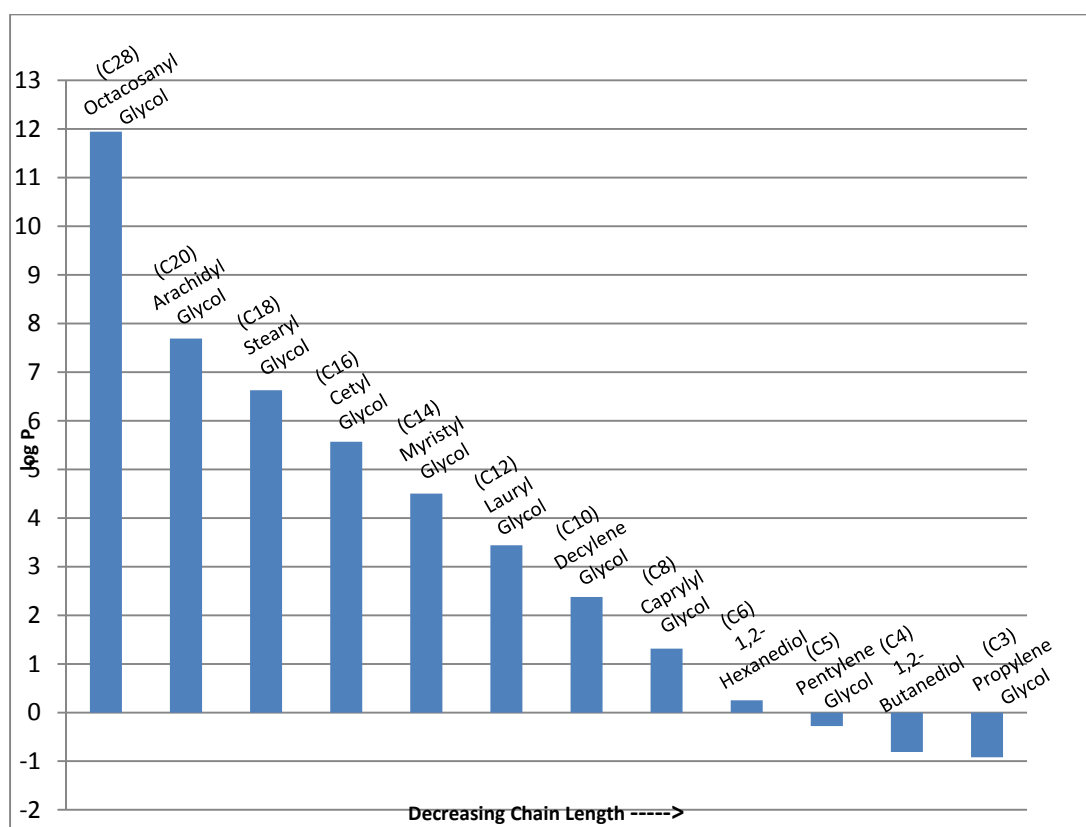


Table 5. Retrospective analyses with propylene glycol

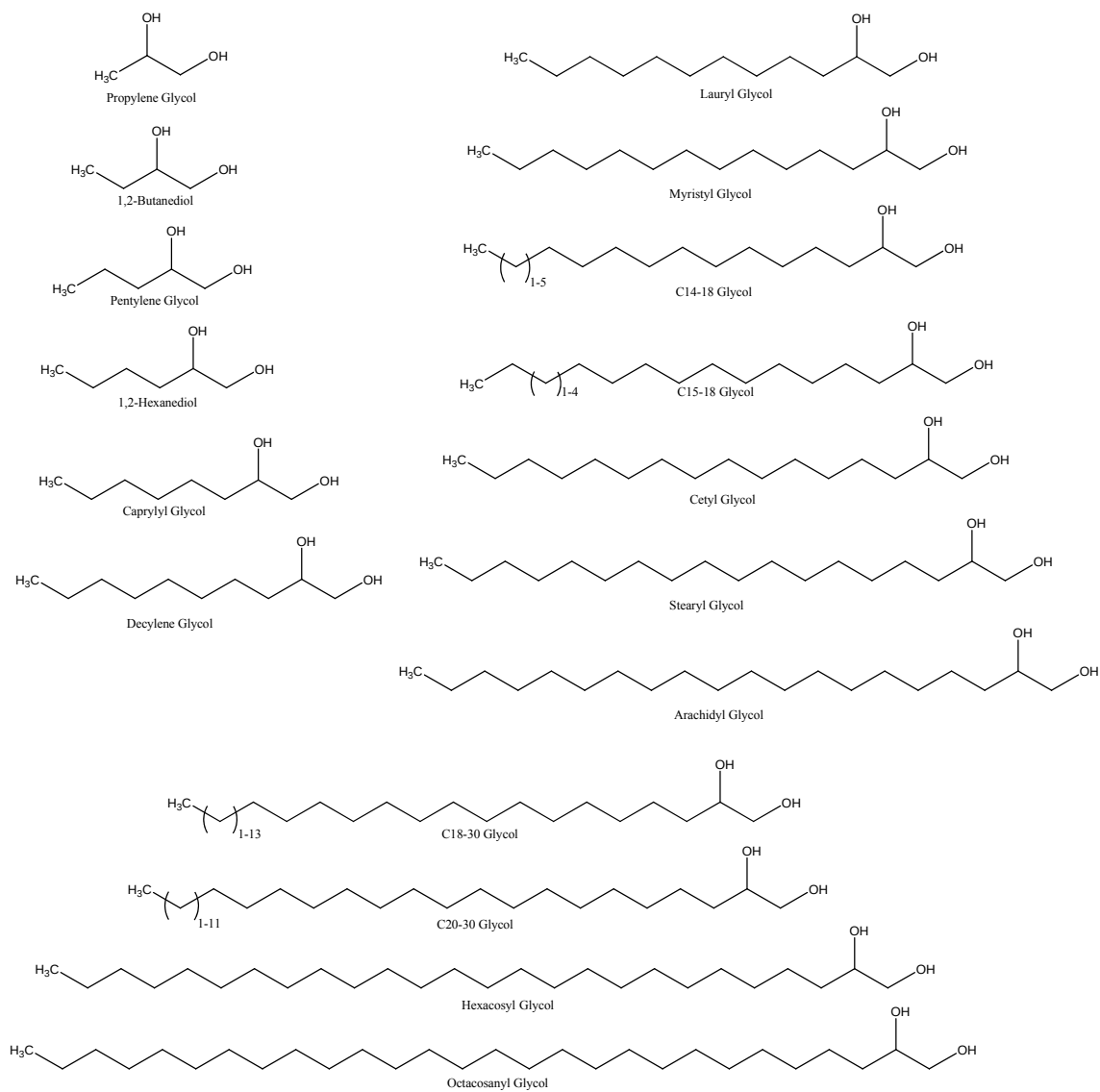
No. of patients	Years studied	% PG	Methods	Findings
not given	1984-1996	10 aq.	data were collected from NACDG-reported studies; the SPIN for each allergen was calculated as the proportion of the population allergic by the weighted clinician-assessed likelihood of relevance of the reaction	the SPIN rank for PG has changed over time: 23 in 1984-1985; 40 in 1992-1994; 41 in 1994-1996 ⁷²
45138 patients (16210 males; 28928 females)	1992-2002	20 aq.	analysis of a large pool of IVDK patch-test data, examining possible relevance of patient characteristics	- 1044 patients (2.3%), 412 males and 632 females, had positive reactions; 895, 129, and 20 patients had 1+, 2+, and 3+ reactions, respectively; of the 895 1+ reactions, 114 were to PG only - 1041 doubtful, 43 follicular, and 271 irritant reactions were observed - there were little difference between patients with positive and negative reactions to PG; the greatest difference was the high portion (27.2% vs. 13.1%) of patients with leg dermatitis – this was the only sig. risk factor - the most common concomitant reactions were with fragrance mix, balsam of Peru, lanolin alcohol, amerchol L-101, and nickel sulfate⁷³
23359 patients	1996-2006	30 aq.	retrospective cross-sectional analysis of NACDG patch-test data to evaluate the patient characteristics, clinical relevance (definite – positive reaction to a PG-containing item; probable – PG was present in the skin contactants; possible – skin contact with PG-containing material was likely), source of exposure, and occupational relationship	- 810 patients (3.5%) had reactions to PG; 12.8% of the reactions were definitely relevant, 88.3% were currently relative (definite, probable or possible relevance), 4.2% were occupation related - 135 patients were positive to only PG; in these patients, the face was the most commonly-affected area (25.9%), a scattered or generalized pattern was next (23.7%) - the most common concomitant reactions were with balsam of Peru, fragrance mix, formaldehyde, nickel sulfate, and bacitracin⁷⁴
1494 patients w/ SGD (patient pop. 10061)	2001-2004	30 aq.	retrospective analysis of cross-sectional NACDG data using only patients with SGD as the sole site affected	89 patients (6.0%) had positive reactions to PG 94% of the reactions were currently relative, with 30.3, 20.2, and 42.7% being of definite, probable, and possible relevance ⁷⁵
10061 patients	2001-2004	30 aq.	retrospective analysis of cross-sectional NACDG data to determine reactions to foods	109 patients (1.1%), 37 males and 72 females, had 122 reactions to foods; of those 122 reactions, 5 were to PG ⁷⁶

IVDK – Information Network of Departments of Dermatology

NACDG – North America Contact Dermatitis Group

SGD – scattered generalized distribution

SPIN – significance-prevalence index number, a parameter that assesses the relative importance of different allergens. SPIN for nickel (among the most clinically important allergens) = 894.⁷⁷

Figure 1. Formulas of 1,2-Glycols

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Final Report

Methyl Acetate, Simple Acetate Esters, Acetic Acid and Salts, and Related Alcohols as Used in Cosmetics

August 31, 2010

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Abstract

The main function of methyl acetate in cosmetic products is as a solvent in nail polish removers. However, the cosmetic functions of the alkyl acetate ingredients in this assessment vary considerably. The potential for these acetate ingredients to be metabolized to the parent alcohol and acetic acid is recognized and evaluated as part of this assessment. The currently available toxicity data support the conclusion of safe as used in current practices and concentrations for methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, myristyl acetate, cetyl acetate, stearyl acetate, isostearyl acetate, acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate, zinc acetate, propyl alcohol, and isopropyl alcohol, in cosmetics.

INTRODUCTION

This document presents a summary of the available safety information that pertains to methyl acetate, ten alkyl acetates, acetic acid, five acetate salts and two corresponding esterase metabolites, and their use in personal care products/cosmetics.

The ingredients included in this safety assessment are: methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, myristyl acetate, cetyl acetate, stearyl acetate, isostearyl acetate, acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate, zinc acetate, propyl alcohol, and isopropyl alcohol. The CIR Expert Panel has reviewed ethyl acetate,¹ butyl acetate,¹ ethyl alcohol (as "Alcohol Denat." with methyl alcohol),² and butyl alcohol³ and concluded that these ingredients are safe in the present practices of use and concentration.

The following ingredients are metabolites of the ingredients in this safety assessment and have been previously reviewed: methanol, *t*-butyl alcohol, butoxyethyl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, and isostearyl alcohol. Citations for the completed reports are provided, however, toxicity information on these previously reviewed ingredients has not been duplicated in this safety assessment, with the exception of excerpts from the clinical sections of each prior report.

The alkyl acetate ingredients are esters of acetic acid and the corresponding alcohols and can be metabolized via hydrolysis, by esterases present in skin, back to the parent alcohol and acetic acid (or a salt).

CIR does not review the safety of ingredients used as a fragrance, unless there are other reported functions, as is the case with a number of the ingredients in this report.

CHEMISTRY**Definition and Structure**

The registry numbers, definitions, functions, and CIR review history of the ingredients under consideration are presented in Table 1 and the structures are presented in Figure 1. The technical names for these ingredients are listed in Table 2. A map of how the structures and metabolic pathways of these ingredients are related is presented in Figure 2.

Physical and Chemical Properties

The shorter chain aliphatic esters are colorless and highly volatile liquids. Volatility decreases as the molecular mass (chain length) increases.⁴ The physical and chemical properties of the acetates are shown in Table 3. Experimental boiling point, density, vapor pressure, solubility, and log K_{ow} values were available for the shorter alkyl esters while only estimated log K_{ow} values were available for the longer alkyl esters. The shorter alkyl esters (methyl acetate to butoxyethyl acetate) have log K_{ow} values ranging from 0.18 – 1.78 (values for isopropyl acetate and butoxyethyl acetate were estimated using EPI Suite v. 4.0) while the longer alkyl esters (nonyl acetate to isostearyl acetate) have estimated log K_{ow} values > 4.

Acetic acid and the metal acetate salts dissociate readily in water and therefore have negative log octanol/water partitioning coefficients, and high solubilities in water. Propyl alcohol and isopropyl alcohol are volatile liquids. The physical and chemical properties of acetic acid, the acetate salts, and alcohols are shown in Table 4.

Manufacture and Production

In general, the alkyl acetates can be produced industrially via esterification of acetic acid.⁴ The manufacture of methyl acetate, for example, is traditionally accomplished via a reactive distillation process between acetic acid and methanol.⁵ Methanol and ethanol are normally obtained via fermentation of natural sources. However, some sources of alcohols with chains longer than ethanol are often produced synthetically. An important process for producing C₃-C₂₀ industrial alcohols involves a process known as oxo-synthesis (a process for the production of aldehydes which occurs by the reaction of olefins (which can be natural or petroleum sourced) with carbon monoxide, hydrogen and a catalyst (typically cobalt based)), followed by hydrogenation of the aldehyde products, to form the alcohols.⁶ More recently, a green, biocatalytic process developed specifically for the manufacture of esters for use in the formulation of cosmetic and personal care ingredients (i.e. for producing cosmetic grade esters) has been used.⁷

Acetic acid is most commonly manufactured by metal (e.g., rhodium or iridium) catalyzed carbonylation of methanol (via addition of carbon monoxide), or oxidation of ethylene (through an acetaldehyde intermediate and in the presence of manganese acetate, cobalt acetate, or copper acetate), also known as the Wacker process.⁸

Impurities

The manufacturing processes of the alkyl esters are typically high yielding ($\geq 90\%$) and easily purified (e.g., by distillation). Therefore, the starting materials and water, at least, may be expected to be present in preparations of these esters as the major impurities.⁴ For example, methyl acetate is available with a minimum of 96% purity, wherein the major contaminants are methanol ($\leq 2.5\%$) and water ($\leq 1.5\%$).⁹ In the case of isopropyl acetate, which is available at 99.6% purity, the major impurities are isopropanol ($\leq 0.2\%$), water ($\leq 0.05\%$), and acetic acid ($\leq 0.005\%$).⁹

Propyl alcohol and isopropyl alcohol can be obtained as 99.8% pure.⁹

Acetic acid can be obtained as glacial acetic acid (99.85% acetic acid, 0.15% water).⁹

Analytical Methods

The esters, acids, and alcohols can be analyzed using gas chromatography/mass spectroscopy (GCMS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, and infrared (IR) spectroscopy.^{4,6,10}

UV Absorption

The ingredients included in this review would not be expected to have any meaningful ultraviolet (UV) absorption. Except for the acid and ester functional groups, these ingredients do not possess any π -bonds or non-bonding electrons. The π -bonds and non-bonding electrons in the acid and ester functional groups are not part of any conjugated systems. Accordingly, the likelihood of any of these ingredients to absorb light within the UVA-UVB spectrum, at a detectable molar absorptivity, is extremely low. As such, no UVA-UVB absorption data were found.

USE

Cosmetic

The Voluntary Cosmetic Registration Program (VCRP) administered by the FDA indicates total number of uses in cosmetic formulations in 2010 for methyl acetate (7), propyl acetate (46), isopropyl acetate (6), isobutyl acetate (4), cetyl acetate (264), stearyl acetate (1), acetic acid (11), sodium acetate (88), calcium acetate (7), zinc acetate (1), propyl alcohol (1) and isopropyl alcohol (1748) (Table 5).¹¹ Use information was not available for *t*-butyl acetate, nonyl acetate, butoxyethyl acetate, or isostearyl acetate.

The main use of methyl acetate is in nail polisher removers. Concentration of use surveys conducted in 2007, 2009 and 2010 by the Personal Care Products Council reported use percent ranges for methyl acetate (10-60), propyl acetate (0.005-39), isopropyl acetate (0.5-), *t*-butyl acetate (10), isobutyl acetate (6-45), nonyl acetate (0.0004), cetyl acetate (0.01-17), stearyl acetate (0.02-0.5), isostearyl acetate (0.002-5), propyl alcohol (0.0001-0.5), isopropyl alcohol (0.002-100), acetic acid (0.0003-0.3), sodium acetate (0.0002-0.5), potassium acetate (3), magnesium acetate (0.02-0.03), and zinc acetate

(0.4%).^{12,13} Concentration of use survey results for calcium acetate resulted in no reported uses. Neither use nor concentration information was available for butoxyethyl acetate or myristyl acetate.

In the EU, methanol is allowed only as a denaturant for ethanol and isopropyl alcohol at a concentration of 5%, calculated as a % ethanol or % isopropyl alcohol.¹⁴ Additionally, the EU limits the amount of zinc acetate in cosmetics to 1% calculated as zinc.

Non-Cosmetic

The following ingredients in this report are permitted for direct addition to food for human consumption for flavoring purposes and are generally recognized as safe (GRAS) according to the USFDA: methyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, nonyl acetate, propyl alcohol, isopropyl alcohol, acetic acid, sodium acetate, potassium acetate, magnesium acetate, and calcium acetate.¹⁵ Zinc acetate is an approved ingredient for OTC skin protectant drug products.¹⁶

Additionally, esters are used as solvents in paints, lacquers and coatings, and as intermediates in various chemistry processes.⁴

Alcohols are commonly used as solvents and antiseptics.¹⁷

Isopropyl alcohol (rubbing alcohol) is an approved ingredient for topical antimicrobial OTC drug products.¹⁸

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Exposure to these ingredients is expected to occur mostly by inhalation and dermal routes, although some oral or ocular exposure could occur depending upon the product types in which these ingredients are used in. Shorter acetic esters, readily penetrate the skin and mucous membranes and are metabolized via esterases to the parent alcohol and acetic acid. The alcohols are further metabolized to the corresponding aldehyde or ketone and then to the corresponding acid.

ADME studies are reported by ingredient in the animal and in the human sections.

The alkyl acetate ingredients are esters of acetic acid and the corresponding alcohol, with the shorter chain alkyl acetates (methyl, propyl, isopropyl, t-butyl, isobutyl and butoxyethyl; MW range 74-160 g/mol) functioning in cosmetics as fragrance ingredients and solvents, and the longer chain alkyl acetates (nonyl, myristyl, cetyl, stearyl and isostearyl; MW range 186-312) functioning in cosmetics as skin conditioning agents.

These ingredients can be metabolized via hydrolysis, by esterases present in skin, to the parent alcohol and acetic acid (or a salt). The ability and efficiency of esterases in the skin is often species dependent and may even vary considerably

between individuals of the same species.¹⁹ Esterases found in the skin, such as human acetyl cholinesterase (hAChE), are capable of metabolizing branched substrates, including tertiary esters.²⁰

Shorter chain esters readily penetrate the skin and mucous membranes. Acetic acid esters can be metabolized by esterases (present in the respiratory tract, skin, blood and gastrointestinal tract^{21,22}) to the parent alcohols and acetic acid.⁴ As such, methyl acetate is metabolized to methyl alcohol, *t*-butyl acetate is metabolized to *t*-butyl alcohol, and so forth as illustrated in Figure 2.

The parent alcohols can be oxidized via alcohol dehydrogenases to produce the corresponding aldehydes or ketones. The aldehydes can then further be oxidized via aldehyde dehydrogenases to the corresponding acids.

Acetic acid is a principal metabolite of all of the above alkyl acetates, and in addition to its sodium, potassium, magnesium, calcium, and zinc acetate salts, is a cosmetic ingredient and has been included in this safety assessment.

Isobutyl alcohol and nonyl alcohol are principal metabolites of isobutyl acetate and nonyl acetate, respectively. They are not currently listed as cosmetic ingredients in the International Cosmetic Ingredient Dictionary and Handbook, but available data has been provided for the evaluation of the parent alkyl acetates.

t-Butyl alcohol is slowly metabolized by alcohol dehydrogenases and is eliminated in urine as a glucuronide conjugate and acetone. *t*-Butyl alcohol is also eliminated in exhaled air as acetone and carbon dioxide.^{10,23}

Propyl alcohol and isopropyl alcohol are principal metabolites of propyl acetate and isopropyl acetate, respectively. Propyl alcohol is metabolized to propanal and propanoic acid, which can be further metabolized to acetaldehyde and acetic acid.²⁴ Isopropyl alcohol is metabolized to acetone and then to acetate, formate and ultimately carbon dioxide.²⁵ The half-life of acetone in humans is 22.5 hours.

Bioavailability following inhalation, dermal or gavage exposure has been examined for acetic acid, propyl acetate, isopropyl acetate, *t*-butyl acetate, and isopropyl alcohol in animals and methyl alcohol bioavailability has been examined in humans.

Animal

Acetic Acid

Acetic acid is absorbed from the gastrointestinal tract and through the lungs and is readily, although not completely, oxidized.²⁶ As noted above, acetic acid can be metabolized and eliminated as carbon dioxide and water.

Propyl Acetate

Rats (strain/sex/number not specified) were exposed via inhalation to 2,000 ppm (8360 mg/m³) for 90 min.²⁷ Propyl acetate was rapidly hydrolyzed to propyl alcohol. During the 90 min exposure period, blood levels of propyl alcohol were between 2.6 and 7.7 fold greater than propyl acetate.

Isopropyl Acetate

Male Sprague-Dawley rats (n=6) were placed in a chamber charged with 2000 ppm isopropyl acetate and allowed to inhale for 90 min.²⁸ During this time, the concentration in the chamber decreased and correction for the amount of test compound lost to the chamber and on the surface of the animal was completed. Blood samples were taken at 0, 5, 10, 20, 25, 30, 40, 50, 60, and 90 min. Blood levels of isopropyl alcohol exceeded those of isopropyl acetate at 5 min into the exposure and at each time-point thereafter. At 90 min, 245 µM isopropyl alcohol and 24 µM isopropyl acetate were detected in the blood.

t-Butyl Acetate

Female Sprague-Dawley rats (n=5) were exposed via a tracheal cannula to 440 ppm (1900 mg/m³) *t*-butyl acetate in air for 5 h.²⁹ The concentrations of both the acetate and the alcohol increased continuously in the blood over the course of the exposure. By the end of the exposure, the concentration of *t*-butyl alcohol in the blood (~340 µmol/L) was greater than that of *t*-butyl acetate (285 µmol/L). In a second experiment, female Sprague-Dawley rats (n=5) were exposed via a tracheal cannula to 900 ppm (4275 mg/m³) *t*-butyl acetate in air for 255 min. A similar pattern was observed with concentrations in the blood at the end of the exposure of approximately 400 and 450 µmol/L blood for *t*-butyl acetate and *t*-butyl alcohol respectively.

Isopropyl Alcohol

Male rabbits (3/group; strain not specified) were treated by different routes of exposure to compare the absorption and metabolism of isopropyl alcohol.³⁰ Groups 1 and 2 were treated via gavage with the equivalent of 2 and 4 ml/kg absolute isopropyl alcohol, respectively, as a 35% isopropanol/water solution. Groups 3 and 4 were treated via whole-body inhalation for 4 h (towels soaked with isopropyl alcohol were placed in the inhalation chamber and replenished at ½ hour intervals to maintain a saturated environment; no exact concentration given), with Group 3 animals receiving an additional dermal exposure in the form of a towel soaked with 70% isopropyl alcohol applied to the animals' chests and Group 4 animals having plastic barriers on their chests and towels prepared the same way as in Group 3 applied on top of the plastic barriers. The alcohol on the towels was replenished at half hour intervals throughout the duration of the experiment. Blood samples were taken at 0, 1, 2, 3 and 4 h. Samples were analyzed for isopropyl alcohol and the metabolite acetone.

Following gavage exposure to 2 or 4 ml/kg, maximum blood levels of 147 and 282 mg/dl, respectively, of isopropyl alcohol were measured. Concentrations of acetone rose steadily over the 4 h period and were 74 and 73 mg/dl following exposure to 2 or 4 ml/kg, respectively. The authors stated that the maximum levels of isopropyl alcohol observed in this experiment, correlated with inebriation and near coma in the animals. Following inhalation and dermal exposure, the concentration of isopropyl alcohol in the blood continued to rise and was 112 mg/dl at 4 h while the concentration of acetone was 19 at 4 h. Inhalation exposure with a plastic barrier between the soaked towel and the chest resulted in isopropyl alcohol and acetone blood levels of < 10 mg/dl.

The researchers concluded that isopropyl alcohol is absorbed by the dermal route but that prolonged dermal exposure (i.e. repeated sponging or soaking for several hours) would be required to produce significant toxicity.

Butoxyethanol

The results of eight studies on the metabolism, distribution, and excretion of butoxyethanol were presented in the CIR expert panel review of butoxyethanol.³¹ These data show that butoxyacetic acid is the major metabolite (and toxicant) of butoxyethanol, that the first step of metabolism is mainly by alcohol dehydrogenase in the liver, and that excretion is mainly via urine.

ANIMAL TOXICOLOGY

With the exception of acetic acid which has an oral LD₅₀ of 3.31 g/kg, the oral LD₅₀ values, for those ingredients with acute toxicity data, are greater than 5 g/kg. With the exception of butoxyethyl acetate which has a dermal LD₅₀ of 1.5 g/kg and acetic acid which has a dermal LD₅₀ of 3.36 g/kg, all of the other ingredients with acute dermal toxicity data had LD₅₀ values greater than 5 g/kg. Central Nervous system depression has been documented in animals exposed to acetic acid and the smaller solvent acetates at high concentrations.

Acute Toxicity

Table 6 provides a summary of the available literature on the acute toxicity and LD₅₀ data for ingredients in this assessment.³²⁻³⁸ Narcotic-like effects have been associated with the inhalation of high concentrations of volatile esters (i.e. methyl, propyl, isopropyl, isobutyl, and t-butyl acetates).³⁹ Skin, eye and upper respiratory irritation are also associated with exposure to the volatile esters.³⁹

Acute Oral Toxicity

An oral LD₅₀ of 6.97 ml/kg (6500 mg/kg) was reported in rats for methyl acetate.³⁵

Oral LD₅₀ values of 9370 and 8300 mg/kg were reported in rats and mice respectively for propyl acetate.³³

Isopropyl acetate has a reported oral LD₅₀ of 6750 mg/kg while isobutyl acetate has a reported oral LD₅₀ of 15.4 ml/kg (13400 mg/kg).³⁴

Nonyl acetate has a reported oral LD₅₀ value greater than 5000 mg/kg in rats.³⁸

Cetyl acetate has a reported oral LD₅₀ value greater than 5000 mg/kg in rats and rabbits.³²

For butoxyethyl acetate, an oral LD₅₀ of 7.46 ml/kg (7000 mg/kg) was reported in rats.³⁵ Hemolysis was observed in acutely treated animals.

Oral LD₅₀ values of 3.15 ml/kg (3310 mg/kg) and 0.4-3.2 ml/kg (420-3400 mg/kg) were reported in rats for acetic acid.^{40,41} An oral LD₅₀ of 4280 mg/kg was reported in rats for calcium acetate.⁴² An oral LD₅₀ of 8610 mg/kg was reported in rats for magnesium acetate.⁴² An oral LD₅₀ of 3250 mg/kg was reported in rats for potassium acetate.⁴² An oral LD₅₀ of 3530 mg/kg in rats was observed with sodium acetate.⁴²

Inhalation Toxicity

No inhalation LC₅₀ was reported for methyl acetate, but exposure to 32000 ppm (96960 mg/m³) for 4 h caused 6/6 rats to die within 14 days.³⁵

10 mice were exposed to inhalation of isopropyl acetate, ranging from 1374 to 2000 ppm for 4 hours.⁴³ Neurobehavioral changes (i.e. duration of immobility during a three minute behavioral despair swimming test) were dose dependent and ranged from 19 to 81%, compared to controls.

An inhalation LC₅₀ of 5620 ppm was reported in mice for acetic acid.^{32,44} In rats, a 4 hour exposure to 16000 ppm killed 1 of six rats.

An inhalation LC₅₀ greater than 30 g/m³ in rats was observed with sodium acetate.⁴²

Dermal Toxicity

Nonyl acetate has a reported dermal LD₅₀ value greater than 5000 mg/kg in rats.³⁸

Cetyl acetate has a reported dermal LD₅₀ value greater than 5000 mg/kg in rats and rabbits.³²

Methyl acetate has a reported dermal LD₅₀ value greater than 5000mg/kg in rabbits.³⁸

Propyl acetate has a reported dermal LD₅₀ value greater than 5000mg/kg in rabbits.⁴⁵

In another report, the dermal LD₅₀ values for propyl, isopropyl, and isobutyl acetates are greater than 20 ml/kg (~17400 mg/kg).

For butoxyethyl acetate, a dermal LD₅₀ of 1.58 ml/kg (1500 mg/kg) was reported in rabbits.³⁷

A cutaneous LD₅₀ of greater than 3.2 ml/kg (3360 mg/kg) was reported for 28% acetic acid on guinea pigs.⁴⁰ A 5% solution of acetic acid (equivalent to vinegar) resulted in a cutaneous LD₅₀ of greater than 20 ml/kg (21000mg/kg). An

inhalation LC₅₀ of 5620 ppm was reported in mice for acetic acid. In rats, a 4 hour exposure to 16000 ppm killed 1 of six rats.

A subcutaneous LD₅₀ of 3200 mg in mice was observed with sodium acetate.⁴²

Additional reports were identified in reference texts that did not provide complete information.²⁶ These data have not been evaluated by CIR and are not included in the table.

SHORT-TERM TOXICITY

Butoxyethyl Acetate

Wistar rats (40 male and female rats divided into groups of 10 males or 10 females) and New Zealand rabbits (4/group) were exposed via inhalation to air-vapor mixtures of butoxyethyl acetate (approximately 400 ppm) 4 hr/day, 5 days/week for 1 month.³⁷ No effects were observed on body weight gain, as compared to controls. Red blood cell (RBC) counts and hemoglobin decreased slightly in 2 of 4 rabbits after 3 weeks of treatment. Hemoglobinuria and hematuria were observed in the rabbits, but were less pronounced in treated rats. Two rabbits died during the fourth week of treatment and blood filled kidneys and urinary bladders were observed at necropsy in these two animals. No other gross lesions were observed in the other animals killed at either the end of the study or after a 1-week recovery period.

Acetic Acid

Three out of five rats (sex and strain not specified) exposed via inhalation to 1300 µg/l of acetic acid showed slight red staining around the nose, with one animal showing staining around the mouth.⁴⁶ Very focal lesions in the respiratory epithelium of the dorsal meatus of level 1 of the nasal cavity in three out of five rats were observed. Acetic acid also increased spleen and kidney weights/damage at 23-31 mg/kg in rats, and induced hyperplasia in both organs at 60 mg/kg.⁴²

SUBCHRONIC TOXICITY

Acetic Acid

Rats (number, sex and strain not specified) were exposed to 0.01% to 0.25% solutions, via drinking water, of acetic acid (corresponding to 0.2 ml/kg) with no toxic effects over a period of two to four months. However, 0.5% solutions (corresponding to 0.33 ml/kg) immediately affected feed consumption and growth. A maximum toleration level of 30 mM (1.8 g/L) daily for two weeks was established for rats.²⁶

Sodium Acetate

In contrast to the maximum toleration level recited above for acetic acid, sodium acetate in drinking water was reported to have a maximum toleration level of 80 mM (4.2-4.8 g/L).²⁶

Isobutyl Alcohol

Isobutyl alcohol, the primary metabolite of isobutyl acetate, was evaluated for potential neurotoxicity in Sprague-Dawley rats. Rats (10/sex/group) were exposed via inhalation to isobutyl alcohol vapor concentrations of approximately 0, 770, 3100, or 7700 mg/m³, for 6 h/day, 5 days/week, for 14 weeks.¹⁰ The functional observational battery was conducted along with endpoints of motor activity, neuropathology, and scheduled-controlled operant behavior. A slight reduction in responsiveness to external stimuli was observed in all treated groups during exposure. This effect resolved upon cessation of exposure to isobutyl alcohol.

Isopropyl Alcohol

Fischer 344 rats and CD-1 mice (10/sex/group) were exposed via inhalation to 0, 100, 500, 1500, or 5000 ppm (0, 246, 1230, 3690, or 12,300 mg/m³) isopropyl alcohol for 6 h/day, 5 days/wk for 13 weeks.⁴⁷ To evaluate the neurobehavioral effects of isopropanol exposure, an additional 15 rats/sex were exposed (via inhalation) to 0, 500, 1500, or 5000 ppm (0, 1230, 3690, or 12,300 mg/m³) for 6 h/day, 5 days/wk for 13 weeks. Clinical signs, feed and water consumption, and body weights were recorded throughout the study. At 6 weeks, hematological and clinical chemistry evaluations were performed, and at the end of the study, necropsy, and hematological and clinical chemistry evaluations were performed on 10/rats/sex/group and 10/mice/sex/group.

Ataxia, narcosis, hypoactivity, and the lack of a startle reflex were observed during exposure at 5000 ppm. Hypoactivity was observed in animals exposed to 1500 ppm isopropyl alcohol. At 6 weeks, male rats had decreased platelet counts and female rats had decreased red blood cell counts at 1500 ppm. These effects were not observed at the 13-week hematological evaluation. At 13 weeks, no gross lesions were observed. Microscopic examination of control and 5000 ppm exposed animal tissues showed hyaline droplets within the kidneys of male rats only. The size and frequency of the droplets was increased in the treated group. The authors concluded that the NOAEL for this study was 500 ppm and the LOAEL was 1500 ppm based upon clinical signs and changes in hematology at 6 weeks. Isopropyl alcohol did not produce any changes to the parameters of the functional observations battery which was conducted at 1, 2, 4, 9, and 13 weeks.

Clinical signs observed in mice, during the exposure, included ataxia, narcosis, hypoactivity, and lack of a startle reflex at 5000 ppm. Narcosis, ataxia, and hypoactivity were observed in animals exposed to 1500 ppm isopropyl alcohol. At 5000 ppm, increased body weight and increased rate of weight gain were observed in female mice. Water consumption was increased in male and female mice. Hemoglobin, hematocrit, and mean corpuscular volume were increased in female mice.

Clinical chemistry changes were also noted in the 5000 ppm female mice group including increased total protein, albumin, globulin, total bilirubin, direct bilirubin, and inorganic phosphorus. No clinical chemistry changes were observed in male mice or in the other treated female mice groups. At 13 weeks, no gross lesions were observed and no treatment-related

microscopic changes were observed. A 10% and 21% increase in relative liver weight was observed in female mice at 1500 and 5000 ppm, respectively. The authors concluded that the NOAEL for this study was 500 ppm and the LOAEL was 1500 ppm based on clinical signs and increased liver weights.

CHRONIC TOXICITY

Butoxyethyl Acetate

Wistar rats (40 male and female rats divided into groups of 10 males or 10 females) and New Zealand rabbits (2/sex/group) were exposed via inhalation to 100 ppm butoxyethyl acetate (butylglycol acetate (BGA)) 4 h/day, 5 days/week for 10 months.³⁷ No effects on body weight gain, as compared to controls, and no hematological changes were observed. Upon necropsy, rabbits exhibited very discrete renal lesions including a few areas of tubular nephritis. Additionally, dilation of Henle's loop and the distal convoluted tubules was observed to a greater degree than in control animals. Treated and control rats also exhibited discrete renal lesions such as tubular enlargement in males and tubular nephrosis in females.

Additional chronic toxicity results are described in the CARCINOGENICITY section.

DERMAL IRRITATION

*Acetic acid and the alkyl acetate ingredients are minor skin irritants in animal studies. At high concentrations, acetic acid is an irritant.*²⁶

Propyl Acetate

Male and female rabbits (n=4; strain not specified) were tested for primary irritation on intact, abraded skin using the Draize method. Undiluted propyl acetate (0.5 ml) was applied to the skin without occlusion and produced only minor irritation with slight erythema in 1 of 4 animals. No edema was observed 72 h after application.²⁶

No irritation was observed in 5 rabbits (sex/strain not specified), following a 24-h non-occluded treatment with 0.01 ml of undiluted propyl acetate (no further experimental details provided).²⁶

Erythema and necrosis were observed in rabbits (sex/strain/number not specified) exposed to 20 ml/kg bw (17,756 mg/kg bw) undiluted propyl acetate.²⁶ Erythema and desquamation were observed in guinea pigs (sex/strain/number not specified) exposed to 10 ml/kg bw (8,880mg/kg bw), undiluted propyl acetate, for 24 h with occlusion. In the guinea pigs, the skin appeared normal after 14 days.

Butoxyethyl Acetate

New Zealand rabbits (6/group/1500 mg/kg) were tested for primary irritation on intact, abraded skin using the Draize method.³⁷ Butoxyethyl acetate (1500 mg/kg) produced slight erythema (Grade 1) in 4 of 6 rabbits at 24 h. At the 72 h reading, there was no perceptible irritation; the primary irritation index was reportedly 0.17.

Acetic Acid

Glacial acetic acid (equivalent to 95% acetic acid) caused complete destruction of the skin of guinea pigs on 24 h contact. 28% acetic acid, however, resulted in only moderate irritation after 24-hours.⁴⁰ At high concentrations, acetic acid is a irritant which can cause tissue destruction.²⁶

Zinc Acetate

The dermal irritancy of six zinc compounds was examined in three animal models. In open patch tests involving five daily applications, aqueous zinc acetate (20%) was severely irritant in rabbit, guinea-pig, and mouse tests, inducing epidermal hyperplasia and ulceration. Epidermal irritancy in these studies is related to the interaction of zinc ion with epidermal keratin.

t-Butyl Alcohol

Reniconen and Tier (1957) conducted an experiment to investigate the intradermal irritation of t-BuOH to rabbits. There were no vehicle controls. Eight rabbits were injected intradermally with t-BuOH (vehicle unspecified). The size of the local skin reaction after injection of 35 mg t-BuOH was 14 mm², and after 10 mg t-BuOH was 43 mm². No explanation of the significance of these results was provided.

Jacobs et al. (1987) tested skin irritation by hydrocarbons including 32 monoalcohols. A Teflon® exposure chamber containing a patch soaked with 0.5 ml of test substance was applied to shaved sites on New Zealand white rabbits (one per compound). The exposure time was 4 h, after which the patch was removed and the skin cleaned. The animals were examined for erythema and edema at 1, 24, 48, and 72 h. All the alcohols tested had calculated limit concentrations of 50% (w/w) including 1-Butanol, 1-Methylpropanol, and 2-Methylpropanol, which are structurally similar to t-BuOH. Results indicated that branching in alcohols had no effect on the limit concentrations for the aliphatic isomers. Although t-BuOH was not studied, the results demonstrated that the 50% limit concentration applied to all the alcohols with a molecular weight between that of Ethanol and 1-Undecanol.

In a study by Rhone-Poulenc Inc. (1992), six New Zealand white rabbits each received a single dermal application of 0.5 ml of a mixture of ethanol and t-BuOH (concentrations unspecified). Two 2.5 cm² test sites were used, one abraded and one intact. One rabbit exhibited moderate irritation at both the abraded and intact site. Three rabbits exhibited mild irritation at the abraded site, including one which also exhibited mild irritation at the intact site. None of the other four rabbits exhibited any irritation at the intact site. It was concluded that the test article was not a primary dermal irritant to rabbits under the conditions of the study.

Dow Chemical Company (1994) reported that t-BuOH (concentration unspecified) was found to have no irritating effect on the skin of shaved rabbits (strain unspecified) when observed for a period of one week.

*(Excerpted from CIR final report on t-butyl alcohol)*⁴⁸

OCULAR IRRITATION

The metal acetate ingredients have been labeled minor eye irritants in animal studies.²⁶ Acetic acid (5%) and isopropyl alcohol have been labeled severe ocular irritants in rabbit ocular irritation tests.

Propyl Acetate

Undiluted propyl acetate (0.5 ml) caused minor corneal injury described as Grade 2 on the Draize scale (0-10) in the rabbit eye (n/sex/strain not specified).²⁷

Butoxyethyl Acetate

New Zealand rabbits (6/group) were tested for eye irritation using the Draize method.³⁷ (Standard Draize method - 0.1 ml or 0.1 g solid or semisolid was instilled in the conjunctival sac of one eye for 24 h. Both eyes were examined at 1, 24, 48 and 72 h after treatment.) Butoxyethyl acetate produced slight conjunctival redness and discharge in 2 of 6 rabbits at 24 h. At 48 and 72 h observations, no irritation was observed.

Isopropyl Alcohol

Isopropyl alcohol has been labeled a severe ocular irritant based on rabbit ocular irritation tests involving application of 0.1 ml of a 70% solution in water.²⁵

Acetic Acid

Acetic acid at concentrations greater than 10% caused severe permanent eye injury in rabbits. In contrast, a 5% solution (equivalent to vinegar) caused severe, but reversible (two week recovery), eye injury.⁴⁰

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

For t-butyl acetate, NOAELs for maternal and embryo-fetal developmental toxicity in rats were 800 and 400 mg/kg, respectively. Exposure to 3500 ppm propyl alcohol resulted in significantly different fertility as compared to controls. For isopropyl alcohol, NOAELs for maternal and developmental toxicity of 400 mg/kg each were reported in rats. In rabbits, the corresponding NOAEL values were 240 and 480 mg/kg, respectively.

Oral

t-Butyl Acetate

Pregnant female Sprague-Dawley rats (22/group) were exposed to 0, 400, 800, or 1600 mg/kg/day *t*-butyl acetate via gavage on gestational days (GD) 6 through 19.⁴⁹ Dams were monitored for clinical effects, feed consumption, and changes in body weight, and the fetuses examined for body weight, sex and visceral and skeletal alterations at GD 20. Two dams died after treatment with 1600 mg/kg. Necropsy findings on these animals included liver hypertrophy, stomach expansion and congestion/hemorrhage of the small intestines. Clinical signs in the 1600 mg/kg group included piloerection, abnormal gait, decreased activity, loss of fur, reddish vaginal discharge, nasal hemorrhage, and coma. There were no deaths and no clinical signs in the 400 and 800 mg/kg groups. A dose-dependent decrease in gestational weight gain was observed during the treatment period, but this was not statistically significant as compared to controls. Feed consumption was significantly decreased on GD 6 and 9 in the 1600 mg/kg treatment group as compared to controls. No effects were observed on maternal reproductive health, including the number of corpora lutea, implantations, fetal deaths, litter size, and gender ratios. Male fetal body weight was significantly decreased in the 1600 mg/kg group as compared to controls. Female fetal body weight was also decreased at this exposure level, but the difference was not statistically significant. An increase in the incidence of skeletal variation and a delay in fetal ossification were observed in the 1600 and 800 mg/kg treatment groups, with the

changes in the 800 mg/kg treatment group described as minimal by the authors. No evidence of teratogenicity was observed at any tested exposure level. The authors concluded that the observed developmental effects were due to maternal toxicity and determined NOAEL's for both maternal and embryo-fetal developmental toxicity in rats of 800 and 400 mg/kg, respectively.

Isopropyl Alcohol

Female Sprague-Dawley rats (25/group) received 0, 400, 800, or 1200 mg/kg/day isopropyl alcohol via gavage on gestational days (GD) 6 through 15.⁵⁰ Female New Zealand white rabbits (15/group) were exposed to 0, 120, 240, or 480 mg/kg/day isopropyl alcohol via gavage on GD 6 through 18. Animals were observed for body weight, clinical effects and feed consumption and the fetuses examined for body weight, sex, and visceral and skeletal alterations at GD 20 for rats and GD 30 for rabbits. In rats, 2 dams died at the 1200 mg/kg dose and 1 dam died at the 800 mg/kg dose. Maternal gestational weight gain was reduced at the highest dose tested. No other effects were observed on maternal reproductive health. Fetal body weights at the two highest doses were decreased statistically. No evidence of teratogenicity was observed at any dose. In rabbits, four does died at the 480 mg/kg dose. Treatment related clinical signs of toxicity were observed at the 480 mg/kg dose and included, cyanosis, lethargy, labored respiration and diarrhea. No treatment related findings were observed at GD 30. Decreased feed consumption and maternal body weights, at 480 mg/kg, were statistically significant. No other effects were observed on maternal reproductive health. No evidence of teratogenicity was observed in the rabbits at any dose. The authors determined NOAEL's for both maternal and developmental toxicity of 400 mg/kg, each, in rats and 240 and 480 mg/kg, respectively, in rabbits.

Acetic Acid

No effects were observed on nidation or on maternal or fetal survival in mice, rats, and rabbits at oral doses (intubation/dosed day 6 of gestation) up to 1600 mg/kg bw/day of acetic acid.⁴² Protocol not stated.

Sodium Acetate

No maternal or neonatal effects were observed in mice exposed (gavage/dosed daily on days 8-12 of gestation) to 1000 mg/kg of sodium acetate.⁴² Sodium acetate was also determined to be nonteratogenic to chick embryos (10mg/egg).

Inhalation

Propyl Alcohol

The effects of propyl alcohol on fertility were investigated by exposing male Sprague-Dawley rats (18/group) to 0, 3500 or 7000 ppm (0, 8.61 or 17.2 mg/L) propyl alcohol vapor via inhalation 7 h/day, 7 days/week for 62 days, prior to mating with unexposed virgin females.⁵¹ Female Sprague-Dawley rats (15/group) were similarly exposed and mated with unexposed males. Following parturition, litters were culled to 4/sex and the pups fostered by unexposed dams. The pups

were weaned on post natal day (PND) 25 and weighed on PND's 7, 14, 21, 28, and 35. Male rats exposed to 7000 ppm exhibited a decrease in mating success with 2/16 producing a litter (1 male died as a result of a cage fight and 1 male did not mate). Mating success was not affected in 3500 ppm exposed males or in females. Six males from the 7000 ppm group were retained to determine if this effect was reversible. All 6 males successfully mated 15 weeks after exposure. The authors reported that weight gain was not affected in 7000 ppm exposed females (data not shown), but feed intake was decreased in this treatment group. Crooked tails were observed in 2-3 offspring in 2 of 15 litters from the 7000 ppm maternally exposed group. No other effects on female fertility were reported. No significant differences resulted between offspring of the 7000 ppm group and controls on several behavioral toxicology measures including the Ascent test, Rotorod test, Open Field test, activity test, running wheel activity, avoidance conditioning, and operant conditioning. Activity measures were significantly different between offspring of the 3500 ppm exposure group and controls.

GENOTOXICITY

Methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, propyl alcohol, and isopropyl alcohol have been tested in vitro and were not mutagenic. Acetic acid was also not mutagenic, when buffered to a physiological pH.

Methyl Acetate, Propyl Acetate, Isopropyl acetate, t-Butyl Acetate, Propyl Alcohol, and Isopropyl Alcohol

Methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, propyl alcohol, and isopropyl alcohol were not mutagenic in in vitro bacterial and mammalian cell assays.^{27,52-58} Isopropyl alcohol was not genotoxic in an in vivo micronuclei assay.⁵⁹ Details of these studies are provided in Table 7.

Acetic Acid

Acetic acid was reported to be slightly mutagenic to *E. coli* and mammalian cells, but, a more recent mammalian assay suggests that acetic acid is not mutagenic and that previous results were an aberration due strictly to low pH, and not the identity of the pH reducer.^{60,61}

CARCINOGENICITY

For isopropyl alcohol, no neoplastic lesions were observed in male or female mice exposed to 2800 or 5000 ppm for 78 weeks. For t-butyl alcohol, all orally treated females showed nephropathy and a dose-related (up to 650 mg/kg/day) increase in kidney weight, while males also demonstrated increased kidney weights (only at 420 mg/kg/day), they demonstrated increased incidence of combined adenoma and carcinoma after 24 months of exposure.

Inhalation

Isopropyl Alcohol

Fischer 344 rats and CD-1 mice (65/rats/sex/group; 55/mice/sex/group) were treated via inhalation with 0, 500, 2500, or 5000 ppm (0, 1230, 6150, or 12,300 mg/m³) isopropyl alcohol for 6 h/day, 5 days/wk for 104 weeks in rats and 78

weeks in mice.⁶² An additional 10/animals/sex/species were treated with these same concentrations of isopropyl alcohol for 6 h/day, 5 days/wk for 72 weeks in rats and 54 weeks in mice and underwent an interim evaluation. Another 10 mice/sex/group were treated according to the paradigm described above for 54 weeks and then allowed to recover before being killed at 78 weeks. Animals were observed and evaluated for body and organ weights, ophthalmology, and clinical and anatomic pathology.

In rats, increased mortality due to chronic renal disease was observed at 5000 ppm (both sexes) and at 2500 ppm (males only). Hypoactivity and lack of startle reflex were observed in 2500 ppm treated rats and hypoactivity, lack of startle reflex and narcosis were observed in 5000 ppm treated rats. With the exception of the ataxia, the clinical signs were transient and ceased when the exposure ended. Increases in body weight, body weight gain, and liver weights were observed in 2500 and 5000 ppm treated rats. Chronic renal disease was exacerbated in rats treated with isopropyl alcohol. Male rats had a concentration related increase in absolute and relative (B.W.) testes weights. At the interim euthanasia (after 72 weeks) male rats treated with 5000 ppm had an increased frequency of testicular seminiferous tubule atrophy upon microscopic evaluation. At the terminal euthanasia (104 weeks), male rats had a concentration dependent increase in the incidence of interstitial (Leydig) cell adenomas of the testes at all administered doses. No other tumor types were increased in rats under these treatment conditions as compared to controls.

In mice, no differences in mortality were observed between control and treated animals. Hypoactivity, lack of a startle reflex, narcosis, ataxia, and prostration were observed in 5000 ppm treated mice. Hypoactivity, lack of startle reflex and narcosis were observed in 2500 ppm treated mice. Increases in body weight, body weight gain, and liver weights were observed in 2500 and 5000 ppm treated mice. Male mice in all treatment groups had a decrease in relative testes weights, and female mice exposed to 5000 ppm isopropyl alcohol exhibited decreases in absolute and relative (B.W.) brain weights. At the terminal euthanasia (78 weeks) an increased incidence of minimal to mild renal tubular proteinosis was observed in males and females in all treatment groups. Male mice exposed to 2500 and 5000 ppm exhibited an increased incidence of dilation of the seminal vesicles. No neoplastic lesions were observed in male or female mice. The authors reported a NOAEL for toxic effects of 500 ppm for both rats and mice based on kidney and testicular effects.

IARC (International Agency for Research on Cancer) has determined that isopropyl alcohol is *not classifiable as to its carcinogenicity to humans* (Group 3).⁶³

Oral

t-Butyl Alcohol

F-344 rats (n=60/group, males and females) were exposed orally, via drinking water, to *t*-butyl alcohol at various doses for 15 months to 103 weeks. At 420 mg/kg/day in males and 650 mg/kg/day in females there was decreased survival.⁶⁴

Additionally, a dose related decrease in body weight gain was observed. All treated females had nephropathy and a dose-related increase in kidney weight. Males also demonstrated kidney weight gain, but not at all doses.⁶⁴

After 24 months of exposure, a combined incidence for adenoma and carcinoma of the renal tubules was found in 8/50, 13/50, 19/50 and 13/50 of the control, low-, mid-, and high-dose males (not females), respectively.⁶⁴

CLINICAL ASSESSMENT OF SAFETY

An LD₅₀ of 2-4 ml/kg of isopropyl alcohol has been reported in adults and 6 ml/kg was reported to induce coma in children. Individual susceptibilities to Methyl Alcohol varied, but typically, the ingestion of 80 to 150 ml of 80% methyl alcohol was fatal. 12.6% cetyl acetate caused no dermal sensitization. 2% propyl acetate in petrolatum caused no dermal irritation or sensitization. 10% methyl acetate in petrolatum caused no sensitization reactions. In multiple dermal occlusion studies, propyl alcohol caused no irritation. 10% acetic acid is reported to cause irritation.

Clinical data from previous CIR reports are interspersed below, and delineated by block quotations, to supplement metabolite profiles. Complete assessments of these metabolites may be found in the cited reports.

Absorption, Distribution, Metabolism, Excretion

Butoxyethyl Alcohol

The percutaneous absorption of butoxyethanol was evaluated using five healthy male volunteers (weights not stated) who had not been exposed to butoxyethanol in the workplace. Each subject placed four fingers of the left hand into a polyethylene jar (21°C) filled with undiluted butoxyethanol. Unexposed fingers served as controls. At the conclusion of the 2-h exposure, each subject washed the exposed hand with a mild soap and tap water. There was no evidence of skin irritation; however, exposed fingers appeared wrinkled and somewhat more rigid after exposure. These effects reached a maximum at 2-4 h post exposure and then gradually disappeared. The percutaneous uptake rate of butoxyethanol into the blood varied from 127 to 1891 μmol . These values corresponded to 7-96 nmol butoxyethanol/min/cm² of exposed area. During the decay phase, the half-time of butoxyethanol ranged from 0.6 to 4.8 h (geometric mean 1.3 h). A linear regression analysis for all of the experiments suggested that, on the average, 17% of the absorbed dose of butoxyethanol was excreted in the urine.

Two adult male subjects (between 30 and 45 years old) and one female subject (24 years old) breathed 200 ppm butoxyethanol during two 4-h periods, separated by a 30-min lunch. Blood pressure and pulse rate were determined three times, and erythrocyte fragility tests were conducted twice during the day of exposure. Urinalyses for glucose and albumin were conducted during the morning after exposure, and butoxyacetic acid concentrations were determined in 24-h urine samples that were collected at the end of the day of exposure. One male subject and the female subject excreted considerable amounts of butoxyacetic acid, while the other male subject excreted only trace amounts. All three subjects experienced immediate irritation of the nose and throat, followed by ocular irritation and disturbed taste. The female subject, who excreted the largest amount of butoxyacetic acid, reacted most adversely to the exposure. She acquired a headache that lasted for 24 h.

(Excerpted from CIR final report on butoxyethyl alcohol)⁶⁵

Methanol

Methyl acetate is metabolized to methanol and therefore, data on the effects in humans following inhalation exposure are applicable to this assessment. Metabolism of methyl acetate to methanol proceeds at a rate directly proportional to the exposure level. Methanol is further metabolized to formaldehyde and then to formic acid. The CIR Expert Panel concluded that Formic Acid is safe where used in cosmetic formulations as a pH adjustor with a 64 ppm limit for the free acid.⁶⁶ The main toxicological risks in humans are severe metabolic acidosis with increased anion gap, typically following oral exposure resulting in > 100 mg/L of formate in the urine.⁶⁷ The acidosis and the formic acid metabolite are believed to play a central role in both the central nervous system toxicity and the ocular toxicity.

A study to determine the formate levels that resulted from exposure of human volunteers to 200 ppm of methanol for 4 h was conducted. Human volunteers (n=27; age 20-55 y) were exposed to 200 ppm methanol (the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit) for 4 h and to water vapor for 4 h in a double-blind, random study.⁶⁸ Urine samples were collected at 0, 4, and 8 h and blood samples were collected from the subjects before they entered the chamber, every 15 min for the first hour, every 30 min from the first to the third hour and at 4 h. Urine and serum samples were analyzed for formate (LOD 0.5 mg/L). Twenty-six of 27 enrolled subjects completed the study (11 females and 15 males). One volunteer withdrew from the study due to blood drawing intolerance. Urine formate data were excluded for one subject due to their consumption of high levels of vitamin C which interfered with the formate assay. The researchers did not find any statistically significant differences in serum or urine formate levels between the two exposure conditions at any time point. At the end of the 4 h methanol exposure, formate concentrations of 14.28 ± 8.90 and 7.14 ± 5.17 mg/L were measured in serum and urine, respectively. Under control conditions, formate concentrations of 12.68 ± 6.43 (p=0.38; n=26) and 6.64 ± 4.26 (p=0.59; n=25) mg/L were measured in serum and urine respectively. After 8 h (4 h of no exposure) the serum concentrations were not statistically different with 12.38 ± 6.53 mg/L under methanol exposure conditions and 12.95 ± 8.01 (P=0.6; n=26) under control conditions. Urine formate concentrations after 8 h were 6.08 ± 3.49 and 5.64 ± 3.70 (p=0.6; n=25) in exposed and control conditions, respectively, and were not statistically significantly different.

Methyl Acetate

15 ml of methyl acetate was applied to the skin of the forearm with cotton dipped into the solvent and filled in a plastic vessel of 12.5 cm², which was fixed to the arm with a rubber band and covered with polyethylene film.⁶⁹ The amount of skin absorption was estimated by determining concentrations of the relevant solvents and their metabolites in blood, expired air, and urine. Blood samples were taken before and immediately after application. All the subjects were men and 1-4 subjects served in each experiment. The concentrations of solvents in blood were determined by gas chromatographic

method after separating them by gas-liquid equilibrium method. Blood concentration levels of methyl acetate ranged from 0.9 µg/ml at 1 hour post-application, to as great as 3.8 µg/ml at 2 hours

Toxicity

Isopropyl Alcohol

An LD₅₀ of 2-4 ml/kg of isopropyl alcohol has been reported in adults and 6 ml/kg (9 ml/kg 70% isopropyl alcohol) was reported to induce coma in children.²⁵

Methyl Alcohol

Clinical data show that methyl alcohol can cause severe metabolic acidosis, blindness, and death: toxicity was manifested earlier and at a lower dose compared to ethyl alcohol, but the comparative fatal dose was the same for both alcohols. All routes of exposure were toxicologically equivalent, as the alcohol distributed readily and uniformly throughout all tissues and organs. Individual susceptibilities to methyl alcohol varied, but typically, the ingestion of 80 to 150 ml of 80% methyl alcohol was fatal. Symptoms of methyl alcohol intoxication after ingestion were delayed for 12 to 18 hours; afterwards, the symptoms included headache, anorexia, weakness, fatigue, leg cramps, and/or pain and vertigo. Severe gastrointestinal pain, nausea, vomiting, diarrhea, mania, failed vision, and convulsions could occur. Chronic exposure to methyl alcohol could cause edema, granular degeneration, and necrosis of heart muscle fibers, as well as fatty degeneration of the heart muscle; sudden cardiac failure was associated with methyl alcohol intoxication. The liver and kidneys often had parenchymatous degeneration, and the liver had focal necrosis and fatty infiltration. Severe acidosis was necessary for the development of blindness. Similar symptoms were observed after percutaneous or inhalation exposure to methyl alcohol.

(Excerpted from CIR final report on methyl alcohol)⁷⁰

Irritation and Sensitization

Cetyl Acetate

According to unpublished data, a lipstick containing 12.6% cetyl acetate caused no dermal sensitization in 99 human test subjects.⁷¹ A formulation of 11.7% cetyl acetate did not cause sensitization in humans in another report.⁴⁵

Propyl Acetate

In a human maximization test pre-screen, 2% propyl acetate in petrolatum was applied to the backs of 25 healthy subjects for 48 hours under occlusion. No subject experienced any irritation or sensitization.⁴⁵

Methyl Acetate

Human maximization tests were carried out with 10% methyl acetate in petrolatum on various panels of volunteers. Application was under occlusion to the same site on the forearms or backs of all subjects for five alternate-day 48-hour periods.⁷² Patch sites were pre-treated for 24 hours with 2.5% aqueous sodium lauryl sulfate (SLS) under occlusion. Following a 10 – 14 day rest period, challenge patches were applied under occlusion to fresh sites for 48 hours. Challenge applications were preceded by a 60 minute SLS treatment. Reactions were read at patch removal and again at 24 hours thereafter. The following results were obtained: No sensitization reactions were observed in any of the 25 subjects tested.

Methyl Alcohol

Methyl alcohol caused primary irritation to the skin; prolonged and repeated contact with methyl alcohol resulted in defatting and dermatitis. In one occupational study, 3.2% of 274 metalworkers with dermatitis had positive results to a patch test of 30% methyl alcohol. Typical allergic responses observed after contact with alcohols were eczematous eruption and wheal and flare at the exposure sites. Eczema and erythema were reported after the consumption of alcoholic beverages by persons sensitized to ethyl alcohol. Five percent methyl alcohol caused a slight positive (+) reaction in a closed patch test for allergic contact dermatitis, and concentrations of 7% and 70% caused (+++) reactions.

*(Excerpted from CIR final report on methyl alcohol)*⁷⁰

Propyl Alcohol

A cumulative irritation study was conducted involving 20 male subjects, where the relative irritancy of free fatty acids of different chain lengths was evaluated.⁷³ Equimolar concentrations (0.5 M and 1.0 M) of even- and odd-numbered - straight chain saturated fatty acids were dissolved in propanol. Each Al-test® patch containing a fatty acid (0.5 M) was applied to the interscapular area of 10 subjects, and, similarly, each fatty acid was applied at a higher concentration (1.0 M) to the remaining 10 subjects. A control patch containing propanol was also applied to each subject. Patches remained in place for 24 h and reactions were scored 30 minutes after patch removal. This procedure was repeated daily for a total of 10 applications. In both groups of 10 subjects, there were no reactions to propanol.

In an irritation study, wherein 116 healthy male subjects (21 to 55 years old) were patch tested with pelargonic acid at concentrations of 5%, 10%, 20%, and 39.9% in propanol, a propanol-treated control patch was used.⁷⁴ Dose response curves were developed. Patches (Al-test® discs) were saturated with 0.04 ml of a test solution and applied to the upper back for 48 h. Reactions were scored at 48 h and 96 h post-application. There were no reactions to propanol.

In an another irritation study, wherein 16 volunteers (10 females, 6 males; median age of 29.5 years) were patch tested (closed patches, Finn chambers) with 20% pelargonic acid in propanol (pH of 4.3), propanol was one of the controls used.⁷⁵ Patches were applied to the anterolateral surface of both upper arms for 24 h. Reactions were scored at 24, 48, and 96 h post-application according to the following scale: 0 (no reaction) to 3 (strong positive reaction: marked erythema, infiltration, possibly vesicles, bullae, pustules and/or pronounced crusting). There were no reactions to propanol.

A skin irritation study was conducted using 42 healthy, non-atopic male volunteers (mean age = 34 years; skin types: II [20 subjects], III [17 subjects], and IV [5 subjects]).⁷⁶ Pelargonic acid was patch-tested (Finn chambers, volar forearm) at the following concentrations (in propanol): 40% (12 subjects), 60% (32 subjects), 70% (32 subjects), and 80% (28 subjects), and propanol was used as a control. Each subject received between 3 and 10 patch tests. The patches remained in place for 48 h, and reactions were scored 1 h later according to the following scale: - (no visible reaction) to 4+ (intense erythema with bullous formation). There were no reactions to propanol.

In an irritation study, wherein 16 healthy subjects (ages not stated) were patch tested with pelargonic acid (20% in propanol), propanol was used as a control.⁷⁷ Closed patches (Finn chambers) containing the test substance were applied to the anterolateral surface of both upper arms. The patches were removed at 24 h post-application and reactions were scored at 24 h and 96 h post-application. There were no reactions to propanol.

In study conducted to investigate a possible seasonal variation in the skin response to pelargonic acid during the winter and summer, propanol was used as a control.⁷⁸ The study was conducted using 17 healthy volunteers (10 males, 7 females; mean age = 27 years). The test substance was applied (closed patch, Finn chamber) to each arm for 24 h. Reactions were scored at 30 min post-removal. Reactions were not observed at sites treated with propanol, water, or to which an empty chamber was applied.

Isopropyl Alcohol

According to unpublished data, a 80.74% spray concentrate did not exhibit any potential for dermal sensitization in 9 human subjects.⁷⁹

According to unpublished HRIPT study on 109 test subjects, a 2.85% hair dye base formulation of isopropyl alcohol and 1.95% isopropyl acetate caused no dermal sensitization in humans.⁸⁰

The applicability of fluorescence confocal laser scanning microscopy for in situ imaging of irritant contact dermatitis caused by pelargonic acid using 12 healthy individuals (8 males, 4 females; 18 to 64 years old) was studied.⁸¹ Using Finn chambers (occlusive patches), the flexor side of the right and left forearm was exposed to 60 µl of 10% (w/v) pelargonic acid in isopropanol solution and isopropanol vehicle. Isopropanol was used as a control. The Finn chambers were removed at 24 h post-application and reactions were scored according to the following scale: 0 (no visible reaction) to 4+ (intense erythema with bullous formation). Reactions were not observed at sites treated with isopropanol.

Butoxyethyl Alcohol

The skin sensitization potential of 10.0% (vol/vol) aqueous butoxyethanol was evaluated using 214 male and female subjects between 18 and 76 years of age. A total of 201 subjects completed the study; withdrawal from the study was not related to administration of the test substance. Challenge reactions were observed in 14 subjects. Definite erythema, with no edema, was observed in one subject at 72 h and doubtful (barely perceptible erythema, only slightly different from surrounding skin) responses were observed in 13 subjects: 6 subjects at 48 and 72 h, 6 subjects at 72 h, and 1 subject at 48 h. Eleven of the 14 subjects with challenge reactions also had reactions ranging from doubtful to definite erythema, but with no edema, during the induction phase. Additionally, a total of 52 subjects had reactions only during the induction phase; 35 subjects had doubtful reactions and 17 subjects had reactions ranging from doubtful to definite erythema, but with no edema. The authors concluded that there was no evidence of sensitization to 10.0% aqueous butoxyethanol.

(Excerpted from CIR final report on butoxyethyl alcohol)⁶⁵

Cetyl Alcohol

A topical tolerance study involving an 11.5% cetyl alcohol cream base was conducted with 80 male subjects, ranging in age from 21 to 52 years and in weight from 120 to 220 pounds. The preparations were applied five times daily (every 3 hours) for 10 days. One subject had erythema, folliculitis, and pustule formation (forearm site).

A formulation containing 6.0% cetyl alcohol was tested for its skin irritation potential in 20 subjects according to the protocol stated above. The product did not induce skin irritation.

In another study, the skin irritation potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 12 female subjects (18-60 years old). The total irritation score (all panelists) for the 21 applications was 418, indicating mild cumulative irritation.

The skin irritation and sensitization potential of a product containing 8.4% Cetyl Alcohol was evaluated in 110 female subjects. Fourteen days after scoring of the tenth application site, a challenge patch was applied to each subject and removed after 48 h; sites were scored after patch removal. The product did not induce primary irritation or sensitization.

The sensitization potential of a cream containing 3.0% cetearyl alcohol was evaluated in 25 subjects (18-25 years old). Following a 10-day non-treatment period, occlusive challenge patches were applied to new sites and removed after 48 h. Sensitization reactions were not observed in any of the subjects.

(Excerpted from CIR final report on cetyl alcohol)⁶²

Myristyl Alcohol

A moisturizing lotion containing 0.80% myristyl alcohol was applied to the face of each of 53 subjects over a period of 4 weeks. None of the subjects had signs of skin irritation.

In another study, the irritation potential of a moisturizing lotion containing 0.25% myristyl alcohol was evaluated in 51 subjects, used daily during a 1-month period. A burning sensation was experienced by 1 of the subjects 1 day after initial use of the product. None of the subjects had signs of skin irritation.

A moisturizing lotion containing 0.25% myristyl alcohol was applied to the backs of 229 male and female subjects via occlusive patches for 24 h. The product was reapplied to the same sites following a 24-h non-treatment period and repeated for a total of 10 induction applications. None of the subjects had reactions to the product. The product was considered neither an irritant nor an allergen.

(Excerpted from CIR final report on myristyl alcohol)⁶²

Stearyl Alcohol

In 24-hour single insult occlusive patch tests, mild irritation was produced by 100 percent stearyl alcohol in 1 subject out of 80.⁸³

(Excerpted from CIR final report on stearyl alcohol)⁸³

Isostearyl Alcohol

The skin irritation potential of isostearyl alcohol was evaluated in 19 male and female subjects (18-65 years old) at a concentration of 25.0% in petrolatum. The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05). In three similar studies, three different lipstick products containing 25.0, 27.0, and 28.0% isostearyl alcohol, respectively, were tested according to the same protocol. The three products did not induce skin irritation.

The irritation and sensitization potential of isostearyl alcohol (25% v/v in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21-60 years old). Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch. Three of 12 subjects had slight erythema during induction, and there was no evidence of sensitization.

The sensitization potential of a pump spray antiperspirant containing 5.0% isostearyl alcohol was evaluated using 148 male and female subjects. The product was applied via an occlusive patch to the upper arm for a total of nine induction applications (3 times/week for 3 weeks). Each patch remained for 24 h, and sites were scored immediately before subsequent applications. During the challenge phase, a patch was applied to the induction site and to a new site on the opposite arm of each subject. Reactions were scored 48 and 96 h after application. Ten of the twelve subjects with reactions suggestive of sensitization were re-challenged with the product 2 months later. Patches remained for 24 h, and sites were scored at 48 and 96 h post-application. Six subjects had reactions during the re-challenge. Four of the six subjects were then tested with 5.0% Isostearyl Alcohol in solution with ethanol 6 weeks after scoring of the first rechallenge; all had positive responses. Negative responses were reported when the product (without isostearyl alcohol) and 100.0% ethanol each were tested. In a second study, the same product was applied to 60 male and female subjects (same protocol). Five of the subjects had positive responses after the first challenge. One of the five was re-challenged with 5.0% isostearyl alcohol in ethanol solution, and a positive reaction was observed.

(Excerpted from CIR final report on isostearyl alcohol)⁸²

Acetic Acid

Human volunteers (96/sex not provided) were tested for acetic acid dermal irritation via an interlaboratory 4-hour patch test.^{84,85} At a concentration of 10% acetic acid, 70-94% of volunteers, depending on the laboratory, reported irritation.

Photosensitization

Cetyl Alcohol

The photosensitization potential of a lipstick product containing 4.0% cetyl alcohol was evaluated in 52 subjects. The experimental procedure was not stated. Photosensitization reactions were not noted in any of the subjects. In another study, a skin care preparation containing 1.0% cetyl alcohol did not induce photosensitization in the 407 subjects tested. The experimental procedure was not stated.

(Excerpted from CIR final report on cetyl alcohol)⁸²

Myristyl Alcohol

A moisturizing lotion containing 0.10% myristyl alcohol was evaluated for its photosensitization potential in a study involving 52 subjects. The experimental procedure was not stated. The product did not induce photosensitization in any of the subjects.

(Excerpted from CIR final report on myristyl alcohol)⁸²

Case Reports

t-Butyl Alcohol

A woman who had a positive patch test reaction to ethanol was tested with 100% t-BuOH. The alcohol was applied for 48 h and the site was scored at 3, 24, and 48 h after removal of the test material. The woman did not react to t-BuOH. Four female patients were tested on the upper back with 1% and 10% t-BuOH in water. The patches were applied for 24 h and reactions were read 24 and 48 h after removal. None of the women had any reaction to t-BuOH.

Edwards and Edwards described a case of allergic contact dermatitis to the t-BuOH component of SD-40 alcohol in a commercial sunscreen preparation. A man who had a widespread, pruritic, red,

vesicular eruption of his face, neck, arms, and chest and who had used a variety of sunscreens was patch-tested with sunscreens and with the individual components of the product to which he reacted. A 70% concentration of t-BuOH was applied to the forearms. At 72 h, erythema was observed and at 96 h, vesiculation was observed. No reactions were observed in two controls who also had applied t-BuOH to their forearms.

(Excerpted from CIR final report on t-butyl alcohol)⁴⁸

Stearyl Alcohol

Contact sensitization to stearyl alcohol has been reported in 3 individuals: 2 had an urticarial-type reaction, and 1 of these reactions was thought to be due to impurities in the stearyl alcohol sample.

(Excerpted from CIR final report on myristyl alcohol)⁸³

SUMMARY

The ingredients methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, myristyl acetate, cetyl acetate, stearyl acetate, and isostearyl acetate are alkyl esters that function in cosmetics as fragrance ingredients, solvents, and skin conditioning agents. The ingredients acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate, and zinc acetate are also included because they represent the acetic metabolite of the above alkyl acetates and they function as one or more of the following agents: pH adjusters, buffering agents viscosity controllers, cosmetic astringents, cosmetic biocides, skin protectants and fragrance ingredients. The ingredients propyl alcohol and isopropyl alcohol are also included because they are metabolites of propyl acetate and isopropyl acetate, respectively and they function in cosmetics as antifoaming agents, fragrance ingredients, solvents, and viscosity decreasing agents.

Exposure to these ingredients is expected to occur mostly by the inhalation and dermal routes, although some oral or ocular exposure could occur depending on the types of products in which they are used. Shorter acetic esters readily penetrate the skin and mucous membranes and are metabolized via esterases to the parent alcohol and acetic acid. The alcohols are further metabolized to the corresponding aldehyde or ketone and then to the corresponding acid. The LD₅₀ values, for those ingredients in this assessment with acute toxicity data, are greater than 1 g/kg.

Alkyl acetates:

Central nervous system depression and narcotic-like effects have been documented in animals for the shorter alkyl chain acetates at doses much larger than can reasonably be attained from cosmetic product exposures.⁸⁶ The alkyl acetate ingredients have been labeled minor skin and eye irritants in animal studies. Those alkyl acetate ingredients that have been tested have been found negative for mutagenicity, *in vitro*.

A formulation of 1.95% isopropyl acetate did not cause sensitization in humans in one report. A formulation of 11.7% cetyl acetate did not cause sensitization in humans in one report, or in a formulation of 12.6% cetyl acetate in humans

in another report. A formulation of 10% methyl acetate did not cause sensitization in humans in one report. A formulation of 2% propyl acetate did not cause sensitization in humans in one report.

NOAELs for reproductive toxicity were greater than or equal to 400 mg/kg in rats for *t*-butyl acetate.

Ethyl acetate and butyl acetate have been found safe as used by the CIR Expert Panel.

Acetic acid/salts:

Central nervous system depression has been documented in animals for acetic acid. Acetic acid has been labeled a minor skin irritant, at low concentrations, in animal and human studies, and a severe ocular irritant in a rabbit ocular irritation test. The sodium salt of acetic acid has a more than two-fold higher toleration level than the pure free acid, and acetic acid is not mutagenic when buffered to physiological pH.

Alcohols:

The alcohol metabolites ethyl alcohol, butyl alcohol, *t*-butyl alcohol, butoxyethyl alcohol (with qualifications), myristyl alcohol, cetyl alcohol, stearyl alcohol, and isostearyl alcohol have been found safe as used by the CIR Expert Panel.

Isopropyl alcohol has been labeled a severe ocular irritant in a rabbit ocular irritation test. Isopropyl alcohol was negative in an in vivo micronuclei assay. A formulation of 2.85% isopropyl alcohol did not cause sensitization in humans, in one report, and a spray concentrate of 80.74% did not exhibit any potential for dermal sensitization in humans, in another report. Central nervous system depression behavioral effects have been documented in humans for isopropyl alcohol at relatively high concentrations unlikely to result from cosmetic product exposures. Reproductive toxicity NOAEL's for isopropyl alcohol were reported for maternal and developmental toxicity of 400 mg/kg each in rats and 240 and 480 mg/kg in rabbits, respectively. In an inhalation carcinogenicity study of isopropyl alcohol, rats exhibited an exacerbation of chronic renal disease and a concentration-dependent increase in interstitial cell adenomas of the testes. Male mice exhibited dilation of the seminal vesicles at 2500 ppm, but no neoplastic lesions were observed.

Exposure to 3500 ppm of *n*-propyl alcohol resulted in significantly different offspring behavioral toxicology measures as compared to controls.

Inhalation exposure to isobutyl alcohol induced a slight reduction in responsiveness to external stimuli in rats.

Long term oral exposure of *t*-butyl alcohol to rats, at relatively high concentrations unlikely to result from cosmetic product exposures, resulted in more combined adenoma and carcinoma of the renal tubules than in controls (13-19/50 versus 8/50).

Discussion

An unpublished maximization study of a lipstick formulation containing cetyl acetate showed no sensitization at the highest reported concentration of use (12.6%). Additionally, sensitization data was received that supported the lack of potential for human dermal sensitization to methyl acetate, propyl acetate and isopropyl acetate. The Panel determined that the ingredients assessed herein are safe in present practices of use and concentration.

The Panel recognized that butoxyethanol, a metabolite of butoxyethyl acetate, was previously determined to be safe as used with the qualification that it may be safely used up to 10% in hair and nail products and 50% in nail polish removers. However, the Panel determined that the concentration of butoxyethyl acetate that would be required to generate appreciable quantities of butoxyethanol through metabolic pathways is well above the present use concentrations of related alkyl acetates in cosmetics. (Butoxyethyl acetate is not currently being used in cosmetics.) Furthermore, the LD₅₀ values reported for butoxyethyl acetate are relatively high. Accordingly, the Panel has determined that butoxyethyl acetate should be included in the safe as used assessment of this report.

The CIR Expert Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

Conclusion

The CIR Expert Panel concluded that methyl acetate, propyl acetate, isopropyl acetate, *t*-butyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, myristyl acetate, cetyl acetate, stearyl acetate, isostearyl acetate, acetic acid, sodium acetate, potassium acetate, magnesium acetate, calcium acetate, zinc acetate, propyl alcohol, and isopropyl alcohol are safe in the present practices of use and concentration.^A

^A Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group (e.g., this assessment would apply to butoxyethyl acetate if used in product categories and at concentrations comparable to the alkyl acetates in this assessment; and to calcium acetate comparable to other acetate salts found in this assessment).

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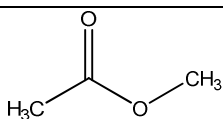
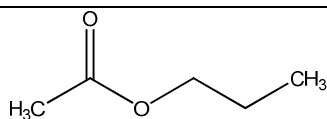
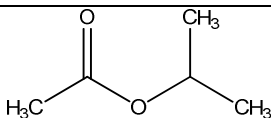
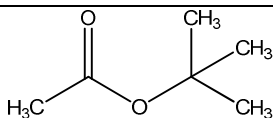
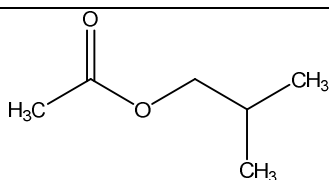
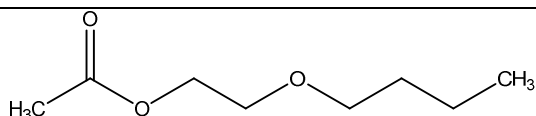
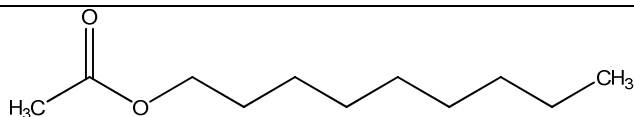
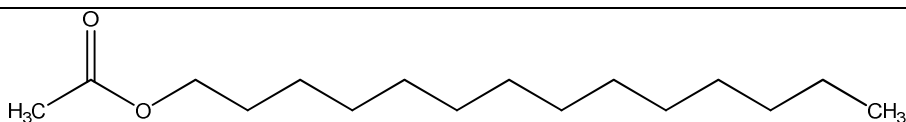
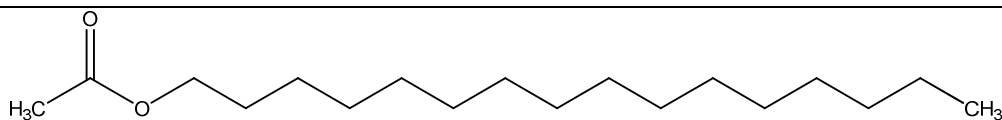
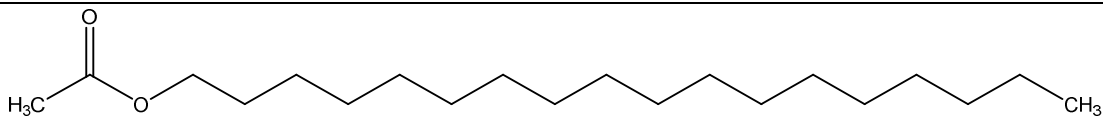
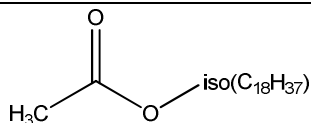
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Figure 1. Structures of the ingredients in this assessment.**Methyl Acetate****Propyl Acetate****Isopropyl Acetate****t-Butyl Acetate****Isobutyl Acetate****Butoxyethyl Acetate****Nonyl Acetate****Myristyl Acetate****Cetyl Acetate****Stearyl Acetate****Isostearyl Acetate**

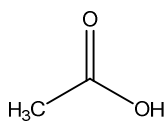
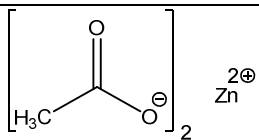
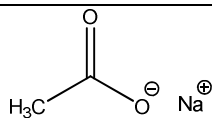
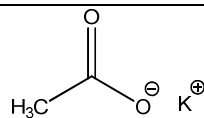
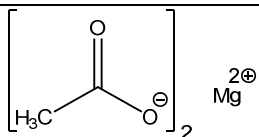
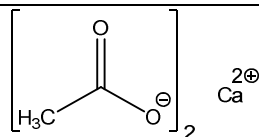
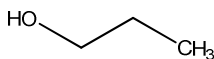
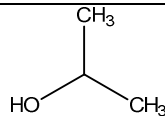
**Acetic Acid****Zinc Acetate****Sodium Acetate****Potassium Acetate****Magnesium Acetate****Calcium Acetate****Propyl Alcohol****Isopropyl Alcohol**

Figure 2. Map of the ingredients in this assessment, and associated esterase metabolites.

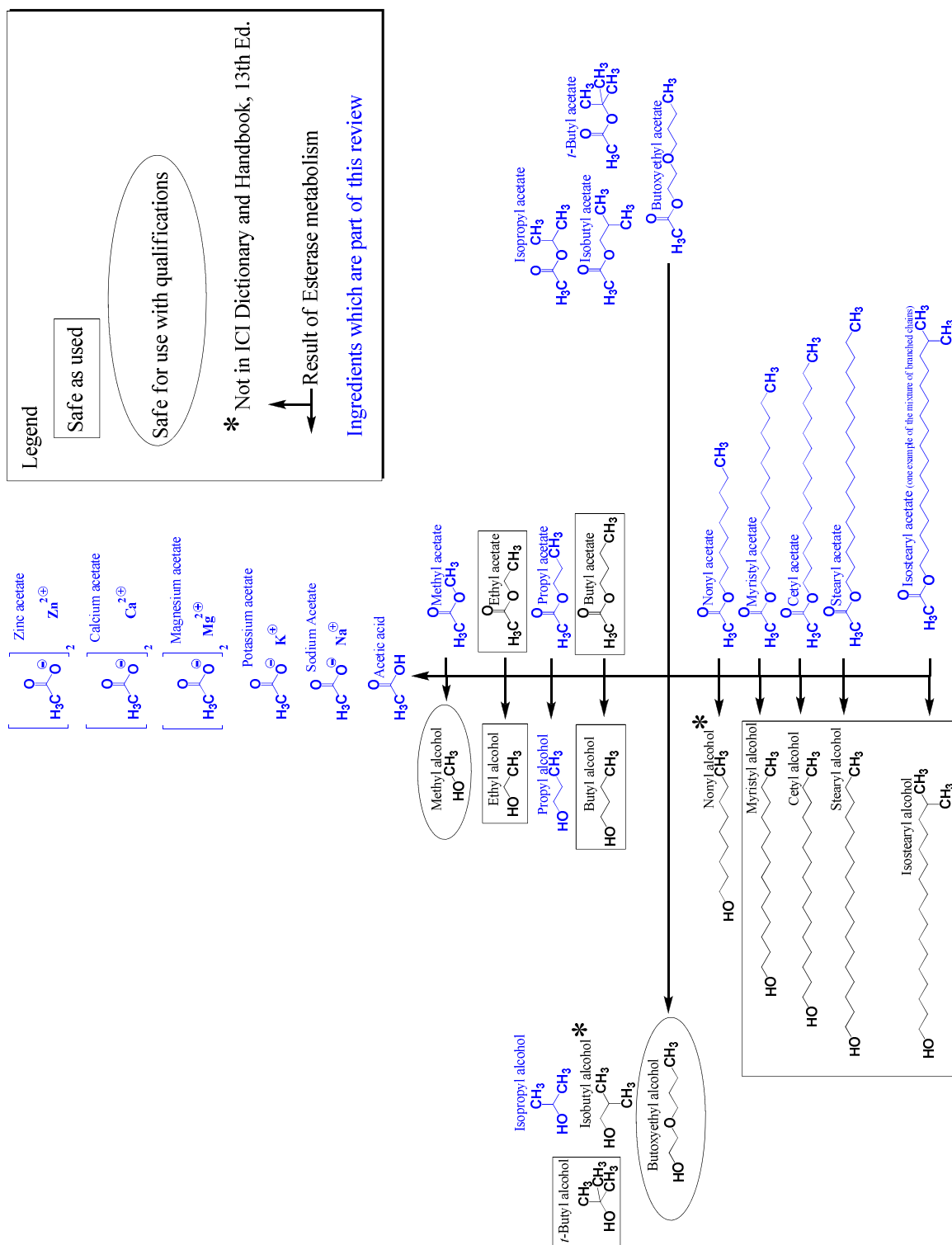


Table 1a. The name, CAS registry number, definition, function and CIR review history of metabolites of alkyl acetate ingredients in this assessment, which are also cosmetic ingredients.⁸⁷

Ingredient	Definition	Function	CIR Review History of Alcohol Metabolite
Methyl Acetate (CAS No. 79-20-9)	The ester of methyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Methyl Alcohol IJT 20 (S1):57-85, 2001 Safe for use as a denaturant in ethyl alcohol
Propyl Acetate (CAS No. 109-60-4)	The ester of propyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Propyl Alcohol Included in this Review
Isopropyl Acetate (CAS No. 108-21-4)	The ester of isopropyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Isopropyl Alcohol Included in this Review
<i>t</i> -Butyl Acetate (CAS No. 540-88-5)	Organic compound	Solvents	<i>t</i> -Butyl Alcohol IJT 24 (S2):1-20, 2005 Safe as used
Isobutyl Acetate (CAS No. 110-19-0)	The ester of isobutyl alcohol and acetic acid	Fragrance Ingredients; Solvents	Isobutyl Alcohol Not listed as a cosmetic ingredient
Butoxyethyl Acetate (CAS No. 112-07-2)	Organic compound	Fragrance Ingredients; Solvents	Butoxyethanol JACT 15(6):62-526, 1996 Safe for use in hair and nail products at concentrations up to 10%; Safe for use in nail polish removers at concentrations up to 50%
Nonyl Acetate (CAS No. 143-13-5)	The ester of nonyl alcohol and acetic acid	Fragrance Ingredients; Skin-Conditioning Agents-Emollient	Nonyl Alcohol Not listed as a cosmetic ingredient
Myristyl Acetate (CAS No. 638-59-5)	Organic compound	Skin-Conditioning Agents-Emollient	Myristyl Alcohol JACT 7(3):359-413, 1988 Safe as used
Cetyl Acetate (CAS No. 629-70-9)	The ester of cetyl alcohol and acetic acid	Fragrance Ingredients; Skin-Conditioning Agents-Emollient	Cetyl Alcohol JACT 7(3):359-413, 1988 Safe as used
Stearyl Acetate (CAS No. 822-23-1)	The ester of stearyl alcohol and acetic acid	Skin-Conditioning Agents-Emollient	Stearyl Alcohol JACT 4(5):1-29, 1985 Safe as used

Ingredient	Definition	Function	CIR Review History of Alcohol Metabolite
Isostearyl Acetate (CAS No. NL)	The ester of isostearyl alcohol and acetic acid	Skin-Conditioning Agents-Emollient	Isostearyl Alcohol JACT 7(3):359-413, 1988 Safe as used

Table 1b. The name, CAS registry number, definition, function and CIR review history of acid, metal salts, and alcohol ingredients in this assessment.⁸⁷

Ingredient	Definition	Function	CIR Review History of Metabolite
Acetic Acid (CAS No. 64-19-7)	A carboxylic acid	Fragrance Ingredients; pH Adjusters	Formic Acid IJT 16(3) 1997 Safe where used in cosmetic formulations as a pH adjustor with a 64 ppm limit for the free acid
Sodium Acetate (CAS No. 127-09-3)	The sodium salt of acetic acid	Buffering Agents; Fragrance Ingredients	
Potassium Acetate (CAS No. 127-08-2)	The potassium salt of acetic acid	Buffering Agents; Fragrance Ingredients	
Magnesium Acetate (CAS No. 142-72-3)	The magnesium salt of acetic acid	Buffering Agents	
Calcium Acetate (CAS No. 62-54-4)	The calcium salt of acetic acid	Fragrance Ingredients (Viscosity Controller – via EWG database)	
Zinc Acetate (CAS No. 557-34-6)	The zinc salt of acetic acid	Cosmetic Astringents; Cosmetic Biocides; Skin Protectants	
Propyl Alcohol (CAS No. 71-23-8)	An alkyl alcohol	Antifoaming Agents; Fragrance Ingredients; Solvents; Viscosity Decreasing Agents	
Isopropyl Alcohol (CAS No. 67-63-0)	An alkyl alcohol	Antifoaming Agents; Fragrance Ingredients; Solvents; Viscosity	

Ingredient	Definition	Function	CIR Review History of Alcohol Metabolite
Decreasing Agents			

Table 2. Nomenclature for the ingredients in this safety assessment.^{17,87}

Ingredient Name	Other Technical Names	IUPAC Name
Methyl Acetate	Acetic Acid, Methyl Ester	Methyl ethanoate
	Methyl Ethanoate	
Propyl Acetate	Acetic Acid, Propyl Ester	Propyl ethanoate
	<i>n</i> -Propyl Acetate	
	Propyl Ethanoate	
	1-acetoxyp propane	
Isopropyl Acetate	Acetic Acid, Isopropyl Ester	Methylethyl ethanoate
	Acetic Acid, 1-Methylethyl Ester	
	Isopropyl Ethanoate	
	1-Methylethyl Acetate	
<i>t</i> -Butyl Acetate	Acetic Acid, <i>t</i> -Butyl Ester	Dimethylethyl ethanoate
	Acetic acid 1,1-dimethylethyl ester	
Isobutyl Acetate	Acetic Acid, Isobutyl Ester	2-Methylpropyl ethanoate
	Acetic Acid, 2-Methylpropyl Ester	
	2-Methylpropyl Acetate	
Butoxyethyl Acetate	2-Butoxyethyl Acetate	2-Butoxyethyl ethanoate
	Butyl Glycol Acetate	
	Ethanol, 2-butoxy-, Acetate	
	Ethylene Glycol Monobutyl Ether Acetate	
	Glycol Monobutyl Ether Acetate	
Nonyl Acetate	Acetic Acid, Nonyl Ester	Nonyl ethanoate
	1-Acetoxynonane	
	<i>n</i> -Nonyl Ethanoate	
	Perlargonyl Acetate	
Myristyl Acetate	Acetic Acid, Tetradecyl Ester	Tetradecyl ethanoate
	Tetradecanol Acetate	
	Tetradecyl Acetate	
Cetyl Acetate	1-Acetoxylhexadecane	Hexadecyl ethanoate
	1-Hexadecanol, Acetate	
	Hexadecyl Acetate	
	Palmityl Acetate	
Stearyl Acetate	Acetic Acid, Octadecyl Ester	Octadecyl ethanoate
Isostearyl Acetate	Acetic Acid, Isostearyl Ester	16-Methylheptadecyl ethanoate
Acetic Acid	Acidum aceticum	Ethanoic acid
	Ethanoic Acid	
	Ethylic Acid	
	Glacial Acetic Acid	

Methanecarboxylic Acid		
Sodium Acetate	Acetic Acid, Sodium Salt	Sodium ethanoate
	Natrii acetas	
Ingredient Name	Other Technical Names	IUPAC Name
Potassium Acetate	Acetic Acid, Potassium Salt	Potassium ethanoate
	Kalii acetas	
	Potassium Ethanoate	
Magnesium Acetate	Acetic Acid, Magnesium Salt	Magnesium ethanoate
	Magnesium Diacetate	
Calcium Acetate	Acetic Acid, Calcium Salt	Calcium ethanoate
	Calcium Diacetate	
Zinc Acetate	Acetic Acid, Zinc Salt	Zinc (II) ethanoate
Propyl Alcohol	1-Propanol	Propanol
	<i>n</i> -Propanol	
	<i>n</i> -Propyl Alcohol	
	1-Hydroxypropane	
Isopropyl Alcohol	2-Propanol	Methylethanol
	Isopropanol	
	1-Methylethanol	
	2-Hydroxypropane	

Table 3. Physical and Chemical properties of the acetate ingredients.^{4,23,88-90}

	Methyl Acetate	Propyl Acetate	Isopropyl Acetate	t-Butyl Acetate	Isobutyl Acetate	Butoxyethyl Acetate
Cas No.	79-20-9	109-60-4	108-21-4	540-88-5	110-19-0	112-07-2
Molecular Weight (g/mol)	74.08	102.13	102.13	116.16	116.16	160.21
Boiling Point (°C)	56.9	101.6	85	97.8	118	187.8
Density (g/cm ³)	0.933	0.887	0.872	-	0.871	0.943
Vapor pressure (mm Hg @ 20°C)	170	25	60.8 (@25°C)	47(@25°C)	13.0	-
Solubility (g/100g water @ 20°C)	25	1.5 (@16°C)	9.6 (@25°C)	-	0.8	-
Log K _{ow}	0.18	1.24	1.28 (EST)	1.76	1.78	1.57(EST)
^a Conversion Factor	1ppm = 3.03 mg/m ³	1ppm = 4.18 mg/m ³	1ppm = 4.18 mg/m ³	1ppm = 4.75 mg/m ³	1ppm = 4.75 mg/m ³	1ppm = 6.55 mg/m ³
	Nonyl Acetate	Myristyl Acetate	Cetyl Acetate	Stearyl Acetate	Isostearyl Acetate	
Cas No.	143-13-5	638-59-5	629-70-9	822-23-1	NL	
Molecular Weight (g/mol)	186.29	256.43	284.48	312.54	312.54	
Boiling Point (°C)	208-212	-	-	-	-	
Density (g/cm ³)	-	-	-	-	-	
Vapor pressure (mm Hg @ 20°C)	-	-	-	-	-	
Solubility (g/100g water @ 20°C)	-	-	-	-	-	
Log K _{ow}	4.3(EST)	6.76(EST)	7.74(EST)	8.72(EST)	8.65(EST)	
^a Conversion Factor	-	-	-	-	-	

^a Conversion factors were obtained from the NIOSH Online Pocket Guide to Chemical Hazards
EST- Values were estimated using the EPI Suite, Version 4.0 program.

- Not found

Table 4. Physical and Chemical properties of the acid and alcohol ingredients.⁶

	Acetic Acid	Sodium Acetate	Potassium Acetate	Magnesium Acetate	Calcium Acetate	Zinc Acetate
Cas No.	64-19-7	127-09-3	127-08-2	142-72-3	62-54-4	557-34-6
Molecular Weight (g/mol)	60.05	82.03	98.14	142.39	158.17	183.50
Boiling Point (°C)	118	(melt at 58°C)	(melt at 292°C)	(melt at 80°C)	(decomp. above 160°C)	-
Density (g/cm ³)	1.05	-	-	-	-	-
Vapor pressure (mm Hg @ 20°C)	14.8 (@25°C)	7.08E-007 (EST)	1.37E-008 (EST)	1.79E-005 (EST)	0.00548 (EST)	6.57E-006 (EST)
Solubility (g/100g water @ 25°C)	100	100 (EST)	100 (EST)	100 (EST)	100 (EST)	30.3
Log K _{ow}	-0.17	-3.72 (EST)	-3.72 (EST)	-1.38 (EST)	-1.38 (EST)	-1.28 (EST)
^a Conversion Factor	1ppm = 2.46 mg/m ³					
	Propyl Alcohol	Isopropyl Alcohol				
Cas No.	71-23-8	67-63-0				
Molecular Weight (g/mol)	60.1	60.1				
Boiling Point (°C)	97.2	82.4				
Density (g/cm ³)	0.8035	0.7850				
Vapor pressure (mm Hg @ 20°C)	14.9	33.0				
Log K _{ow}	0.25	0.05				
^a Conversion Factor	1ppm = 2.46 mg/m ³	1ppm = 2.46 mg/m ³				

^a Conversion factors were obtained from the NIOSH Online Pocket Guide to Chemical Hazards

Table 5. Current cosmetic product uses and concentrations for methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, nonyl acetate, cetyl acetate, stearyl acetate, propyl alcohol and isopropyl alcohol.^{11-13,91}

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Methyl Acetate		
Noncoloring hair care products		
Sprays/aerosol fixatives	1 (312)	-
Nail care products		
Creams and lotions	- (14)	11
Polish and enamel removers	- (24)	45 - 60
Other	- (138)	10
Total uses/ranges for Ingredient	1	10 - 60
Propyl Acetate		
Eye products		
Lotion	- (254)	0.005
Nail care products		
Basecoats and undercoats	2 (79)	10
Polish and enamel	26 (333)	1-39
Polish and enamel removers	- (24)	10
Other ^a	6 (138)	7
Skin care products		
Body and hand sprays	- (-)	0.8
Paste mask/mud packs	- (441)	0.042
Total uses/ranges for Propyl Acetate	34	0.005-39
Isopropyl Acetate		
Noncoloring hair care products		
Tonics, dressings, etc.	2 (1205)	-
Hair coloring products		
Dyes and colors	5 (2393)	2
Nail care products		
Polish and enamel	- (333)	2
Polish and enamel removers	1(24)	0.5
Total uses/ranges for Isopropyl Acetate	8	0.5-2
t-Butyl Acetate		
Nail care products		
Polish and enamel removers	- (24)	10
Total uses/ranges for t-Butyl Acetate	-	10
Isobutyl Acetate		
Nail care products		
Basecoats and undercoats	1 (79)	6

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Creams and lotions	- (14)	34
Polish and enamel	3 (333)	45
Polish and enamel removers	- (24)	35
Total uses/ranges for Isobutyl Acetate	4	6-45
Nonyl Acetate		
Bath products		
Bubble baths	- (169)	0.0004
Total uses/ranges for Nonyl Acetate	-	0.0004
Cetyl Acetate		
Baby products		
Lotions, oils, powders, etc.	2 (137)	0.07
Bath products		
Soaps and detergents	3 (1665)	0.8-3
Other	1 (234)	-
Eye products		
Eyebrow pencil	- (144)	0.9
Eyeliner	2 (754)	3-4
Shadow	8 (1215)	3-8
Lotion	1 (254)	--
Mascara	- (499)	0.03
Other	4 (365)	-
Fragrance products		
Colognes and toilet waters	- (1377)	0.3
Perfumes	- (666)	2
Powders	1 (221)	-
Other	1 (566)	-
Noncoloring hair care products		
Conditioners	1 (1226)	0.3-0.9
Sprays/aerosol fixatives	1 (312)	2
Tonics, dressings, etc.	6 (1205)	2-7
Other	7 (807)	-
Hair Color Preparations		
Other hair coloring preparations ^b	- (168)	0.4
Makeup		
Blushers	7 (434)	0.3-9
Face powders	9 (661)	2-8
Foundations	2 (589)	12
Lipstick	101 (1883)	3-12.6

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Makeup bases	- (117)	2
Other	3 (485)	-
Nail care products		
Basecoats and undercoats	- (79)	0.2
Polish and enamel removers	- (24)	0.2
Personal hygiene products		
Underarm deodorants	- (580)	0.9
Shaving products		
Aftershave lotions	2 (367)	-
Shaving cream	1 (122)	0.01-0.9
Shaving soap	1 (10)	-
Skin care products		
Cleansing creams, lotions, liquids, and pads	4 (1446)	0.3
Face and neck creams, lotions, etc.	7 (1583)	0.5-2
Body and hand creams, lotions, etc.	33 (1744)	0.9-9
Foot powders and sprays	3 (47)	0.9
Moisturizers	51 (2508)	2
Night creams, lotions, powder and sprays	2 (353)	0.9
Paste masks/mud packs	2 (441)	-
Fresheners	1 (259)	-
Other	5 (1308)	-
Suntan products		
Suntan gels, creams, liquids and sprays	4 (107)	-
Indoor tanning preparations	1 (240)	-
Total uses/ranges for Cetyl Acetate	277	0.01-12.6
Stearyl Acetate		
Bath products		
Soaps and detergents	- (1665)	0.5
Makeup		
Face powders	- (661)	0.4
Nail care products		
Basecoats and undercoats	- (79)	0.02
Shaving products		
Shaving soap	1 (10)	-
Skin care products		
Face and neck creams, lotions, etc.	1 (1583)	-
Body and hand creams, lotions, etc.	- (1744)	0.3

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Total uses/ranges for Stearyl Acetate	2	0.02-0.5
Isostearyl Acetate		
Fragrance products		
Perfumes	- (666)	5
Noncoloring hair care products		
Shampoos	- (1361)	0.002
Total uses/ranges for Isostearyl Acetate	-	0.002-5
Acetic Acid		
Tonics, Dressings, and Other Hair Grooming Aids	1	
Colognes and toilet waters	-	0.0004
Hair conditioners	-	0.07
Hair dyes and colors	-	0.2
Other Hair Coloring Preparation	1	0.3
Nail polish and enamel	-	0.0003
Bath Soaps and Detergents	9	0.01
Total uses/ranges for Acetic Acid	11	-
Sodium Acetate		
Mascara	-	0.003
Hair conditioners	-	0.001-0.09
Shampoos	-	0.002-0.1
Tonics, Dressings, and Other Hair Grooming Aids	-	0.008-0.07
Hair dyes and colors	-	0.5
Hair rinses	-	0.07
Makeup bases	-	0.002
Nail polish and enamel	-	0.5
Other personal cleanliness products	-	0.005-0.2
Other shaving preparation	-	0.004
Skin cleansing	-	0.003-0.004
Face and neck creams, lotions and powders	-	0.0002-0.2
Body and hand creams, lotions and powders	-	0.002-0.008
Moisturizing creams, lotions and powders	-	0.05
Night creams, lotions and powders	-	0.0005

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Paste masks	-	0.0002
Total uses/ranges for Sodium Acetate	64	-
Potassium Acetate		
Nail creams and lotions	-	3
Total uses/ranges for Potassium Acetate	0	-
Magnesium Acetate		
Hair conditioners	-	0.03
Permanent waves	-	0.02
Shampoos	-	0.02
Tonics, Dressings, and Other Hair Grooming Aids	-	0.02
Hair rinses (coloring)	-	0.02
Total uses/ranges for Potassium Acetate	0	-
Calcium Acetate		
Cleansing	1	
Face and Neck (exc shave)	1	
Moisturizing	5	
Total uses/ranges for Potassium Acetate	7	-
Zinc Acetate		
Mouthwashes and Breath Fresheners	1	0.4
Total uses/ranges for Potassium Acetate	1	0.4
Propyl Alcohol		
Bath products		
Other	- (234)	0.0001
Makeup		
Lipstick	- (1883)	0.0001
Nail care products		
Cuticle softeners	- (27)	0.0001
Creams and lotions	- (14)	0.0001
Oral hygiene products		
Mouthwashes and breath fresheners	- (74)	0.5
Skin care products		
Body and hand creams, lotions, etc.	- (1744)	0.0001

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Total uses/ranges for Propyl Alcohol	-	0.0001-0.5
Isopropyl Alcohol		
Baby products		
Lotions, oils, powders, etc.	- (137)	0.2
Bath products		
Soaps and detergents	11(1665)	0.004-0.07
Oils, tablets, and salts	3 (314)	0.8
Bubble baths	1 (169)	-
Eye products		
Eyebrow pencil	2 (144)	3
Eyeliner	1 (754)	2
Shadow	1 (1215)	0.014
Mascara	12 (499)	0.3-3
Other ^c	5 (365)	14
Fragrance products		
Colognes and toilet waters	1 (1377)	0.2-2
Perfumes	- (666)	0.2-0.7
Other	2 (566)	0.02
Noncoloring hair care products		
Conditioners	184 (1226)	0.4-2
Sprays/aerosol fixatives	7 (312)	0.05-5
Hair straighteners	- (178)	0.6
Permanent waves	2 (69)	0.8-2
Rinses	3 (33)	0.8-1
Shampoos	13 (1361)	0.2-8
Tonics, dressings, etc.	45 (1205)	0.6-41
Wave sets	1 (51)	-
Other	50 (807)	2
Hair coloring products		
Dyes and colors	758 (2393)	3-16
Tints	15 (21)	3
Shampoos	7 (40)	-
Color sprays/aerosol	1 (7)	4
Hair lighteners with color	2 (21)	-
Hair bleaches	8 (149)	-
Other ^d	6 (168)	7
Makeup		

Product Category (FDA 2009)	2009 uses (total number of products in category; FDA 2009)	2007, 2009, 2010 concentrations (%) (PCPC 2007; 2009; 2010)
Blushers	1 (434)	0.05
Face powders	- (661)	0.2
Foundations	15 (589)	0.002-5
Leg and body paints	3 (29)	-
Lipstick	1 (1883)	0.009-1
Makeup bases	- (117)	0.02
Rouges	1 (102)	-
Makeup fixatives	2 (45)	-
Other	1 (485)	0.3
Manicuring preparations		
Basecoats and undercoats	71 (79)	5-25
Cuticle Softeners	1 (27)	0.04-17
Nail creams and lotions	1 (14)	5-23
Nail polish and enamel	292 (333)	6-18
Nail polish and enamel removers	4 (24)	8-35
Other ^e	40 (138)	15-100
Personal Cleanliness		
Other	3 (792)	0.3
Shaving preparations		
Aftershave lotion		1
Shaving cream	1 (122)	
Other ^f		10-76
Skin care preparations		
Cleansing creams, lotions, liquids, and pads	8 (1446)	0.3-26
Face and neck creams, lotions, etc.	6 (1583)	0.1-1
Body and hand creams, lotions, etc.	10 (1744)	1
Body and hand sprays	- (-)	0.08
Foot powders and sprays	- (47)	6
Moisturizers	25 (2508)	0.04-0.2
Paste masks/mud packs	2 (441)	0.02-4
Fresheners	7 (259)	0.07-7
Other	10 (1308)	14
Suntan products		
Suntan gels, creams and liquids	- (107)	0.06
Indoor tanning preparations	1 (240)	-
Total uses/ranges for Isopropyl Alcohol	1647	0.002-100

^a 7% in a nail mender

^b 0.4% in a gradual hair color

^c 14% in a eye lash tint

^d 7% in a hair color remover

^e 50% in a nail surface sanitizer; 100% in a nail degreaser

^f 76% in a razor burn/ingrown hair eliminator

- Not found

Table 6. LD₅₀/LC₅₀ values reported in the literature for methyl acetate, propyl acetate, isopropyl acetate, isobutyl acetate, butoxyethyl acetate, nonyl acetate, cetyl acetate, and isopropyl alcohol for various routes of exposure and test species.

Species/Strain	N	Route	LD ₅₀ or LC ₅₀ *	Signs of Toxicity	Reference
Methyl Acetate					
Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	6.97 ml/kg (6500 mg/kg)		35
Rats	10/group	Oral	>5000mg/kg		38
Albino rats	6/group (Male)	Inhalation	16000 ppm (48,480 mg/m ³) for 4 h did not cause mortality within 14 days. 32000 ppm (96,960 mg/m ³) for 4 h caused 6/6 animals to die within 14 days.		35
Rabbits	6/group	Dermal	>5000 mg/kg		38
Propyl Acetate					
Osborne-Mendel Rats	5/sex/group	Oral-Gavage	9370 mg/kg 95%CI 7670-11,430	Depression soon after treatment, rough fur, scrawny appearance	33
Mice/NR	NR	Oral-Gavage	8300 mg/kg 95% CI 7280-9460	Depression soon after treatment	33
Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	9.8 ml/kg (8692.6 mg/kg)		36
New Zealand giant albino rabbits	4/group (Male)	Dermal	>20 ml/kg (>17,740 mg/m ³)		36
Albino rats	6/group (Male)	Inhalation	8000 ppm (33,440 mg/m ³) for 4 h caused 4/6 animals to die within 14 days		36
Rabbits	10/group	Dermal	>5000 mg/kg		45
Isopropyl Acetate					
Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	6750 mg/kg		34
New Zealand giant albino rabbits	4/group (Male)	Dermal	>20 ml/kg (>17440 mg/kg)		34
Albino rats	6/group (Male)	Inhalation	32,000 ppm (133,700 mg/m ³) for 4 h caused 5/6 animals to die within 14 days		34
Isobutyl Acetate					
Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	15.4 ml/kg (13,400 mg/kg)		35
New Zealand giant albino rabbits	4/group (Male)	Dermal	>20 ml/kg (~17,400 mg/kg)		35
Albino rats	6/group (Male)	Inhalation	8000 ppm (38,000 mg/m ³) for 4 h caused 4/6 animals to die within 14 days		35

Species/Strain	N	Route	LD ₅₀ or LC ₅₀ *	Signs of Toxicity	Reference
Butoxyethyl Acetate					
Carworth-Wistar Rats	5/group (Male)	Oral-Gavage	7.46 ml/kg (7000 mg/kg)		35
New Zealand giant albino rabbits	4/group (Male)	Dermal	1.58 ml/kg (1500 mg/kg)		35
Wistar rats	10/group	Oral-Gavage	3000 mg/kg in males 2400 mg/kg in females	Kidney pathology; Hemoglobinuria and hematuria	37
New Zealand rabbits	6/group	Dermal	1500 mg/kg	Kidney pathology; Hemoglobinuria and hematuria	37
Wistar rats	10/group (Male and Female)	Inhalation	400 ppm (2,620 mg/m ³) for 4 h did not cause mortality.		37
New Zealand rabbits	2/sex/group	Inhalation	400 ppm (2,620 mg/m ³) for 4 h did not cause mortality.	Transient hemoglobinuria and hematuria in rabbits only.	37
Nonyl Acetate					
Rat/NR	NR	Oral	>5000 mg/kg		38
Rat/NR	NR	Dermal	>5000 mg/kg		38
Cetyl Acetate					
Rat/NR	NR	Oral-Gavage	>5000 mg/kg		32
Rabbit/NR	NR	Dermal	>5000 mg/kg		32
Acetic Acid					
Rat/NR	NR	Oral-Gavage	0.4-3.2 ml/kg	Kidney pathology; Hemoglobinuria and hematuria	32
Rat/NR	NR	Oral-Gavage	3310 mg/kg		41
Mouse/NR	NR	Oral	4960 mg/kg		42
Mice/NR	NR	Inhalation	5620 ppm for a 1 h exposure		32 / 44
Rat/NR	NR	Inhalation	11.4 mg/l for a 4h exposure		42
Rats/NR	6/group	Inhalation	16000 ppm for a 4 hour exposure caused 1/6 animals to die.	Pharyngeal edema and chronic bronchitis	32
Guinea pigs/NR	NR	Dermal	> 3.2 ml/kg of 28% acetic acid. > 20 ml/kg of a 5% acetic acid		40
Rabbit/NR	NR	Dermal	1060 mg/kg		92

Species/Strain	N	Route	LD ₅₀ or LC ₅₀ *	Signs of Toxicity	Reference
Mice/NR	NR	Intravenous	525 mg/kg of 10% acetic acid (buffered with sodium hydroxide to pH 7.3)		40
Sodium Acetate					
Rat/NR	NR	Oral	3530 mg/kg		42
Rat/NR	NR	Inhalation	>30 g/m ³		42
Mouse/NR	NR	Subcutaneous	3200 mg/kg		42
Mice/NR	NR	Intravenous	380 mg/kg		93
Calcium Acetate					
Rat/NR	NR	Oral	4,280 mg/kg		42
Mouse/NR	NR	Intravenous	52 mg/kg		42
Magnesium Acetate					
Rat/NR	NR	Oral	8610 mg/kg		42
Mouse/NR	NR	Intravenous	111 mg/kg		42
Potassium Acetate					
Rat/NR	NR	Oral	3250 mg/kg		42
Propyl Alcohol					
Rat/NR	NR	Oral	1870 mg/kg		94
Rat/NR	NR	Inhalation	2000 mg/kg for 4 hours		94
Isopropyl Alcohol					
Rat/NR	NR	Oral	4420 – 5840 mg/kg	Hind leg paralysis, lack of coordination, respiratory depression, stupor	25
Rabbit/NR	NR	Dermal	13,000 mg/kg		25

*Values in () were calculated by CIR

Table 7. Summary of the genotoxicity data available for the ingredients in this assessment.

Test substance	Type of test, test species	Dose*	Result	Reference
In vitro tests				
Methyl Acetate	Reverse mutation, <i>S. typhimurium</i> , TA97, TA98, TA100, TA1535, TA1537	10 mg/plate	Negative (w/ and w/o metabolic activation)	52
Propyl Acetate	Reverse mutation, <i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537, TA1538	10 mg/plate	Negative (w/ and w/o metabolic activation)	27
	Mitotic aneuploidy, <i>S. cerevisiae</i> , D61.M	1.23% (v/v)	Negative (w/o metabolic activation)	53
Isopropyl Acetate	Reverse mutation, <i>S. typhimurium</i> , TA97, TA98, TA100, TA1535, TA1537	10 mg/plate	Negative (w/ and w/o metabolic activation)	52
<i>t</i>-Butyl Acetate	Reverse mutation, <i>S. typhimurium</i> , TA98, TA100, TA102, TA1535, TA1537 and <i>E. coli</i> WP2uvrA/pKM101	5 mg/plate	Negative (w/ and w/o metabolic activation)	54
Acetic Acid	Reverse mutation, <i>E. coli</i> ; B/Sd-4/1,3,4,5; B/Sd-4/3,4	0.03% (v/v)	Slight	60
	Sister Chromatid Exchange (SCE), Chinese hamster K1 cells	10 mM	Negative w/o metabolic activation	61
Propyl Alcohol	Forward mutation, <i>S. pombe</i> , <i>ade6-60/rad10-198,h⁻</i>	10% (v/v) cytotoxic	Negative (w/ and w/o metabolic activation)	55
	Sister Chromatid Exchange (SCE), Chinese hamster V79 cells	100 mM (6 mg/mL) [†]	Negative (w/ and w/o metabolic activation)	56
	Sister Chromatid Exchange (SCE), Chinese Hamster Ovary (CHO) cells	0.1% (v/v)	Negative (w/o metabolic activation)	57
	Micronucleus Assay, Chinese hamster V79 cells	40 mg/mL	Negative (w/o metabolic activation)	58
Isopropyl Alcohol	Reverse mutation, <i>S. typhimurium</i> , TA97, TA98, TA100, TA1535, TA1537	10 mg/plate	Negative (w/ and w/o metabolic activation)	52
	Sister Chromatid Exchange (SCE), Chinese hamster V79 cells	100 mM (6 mg/mL) [†]	Negative (w/ and w/o metabolic activation)	56
In vivo tests				
Isopropyl Alcohol	Micronuclei, bone marrow erythrocytes of male and female ICR mice (n=40/group)	1173 mg/kg (IP) 2500 mg/kg caused mortality	Negative	59

*Doses are the highest ineffective dose.

† calculated by CIR

w/ - with

w/o - without

Final Report of the Cosmetic Ingredient Review Expert Panel

Safety Assessment of Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil

September 23, 2008

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Cosmetic Ingredient Review

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Cosmetic Ingredient Review

Final Report on the Safety Assessment of Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil

ABSTRACT: Several cosmetic ingredients derive from the desert shrub *Simmondsia chinensis*, including Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed, and Simmondsia Chinensis (Jojoba) Butter. Further processing produces other ingredients including Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, and Jojoba Alcohol. Synthetic Jojoba Oil also is used in cosmetics. In this group Simmondsia Chinensis (Jojoba) Seed Oil, the most widely used ingredient, and safe at concentrations up to 100% in body and hand creams, is expressed from seeds and is composed almost completely (97%) of wax esters of monounsaturated, straight-chain fatty acids and alcohols with high-molecular weights. Amounts and composition of the expressed oil varies with maturity of the seeds and somewhat with plant location and climate. Plant derived material may also contain pesticide residues and/or heavy metals. Most available safety test data examined the expressed oil. For example Simmondsia Chinensis (Jojoba) Seed Oil was reported to readily penetrate nude mouse skin and to increase penetration of other agents such as aminophylline in clinical tests. Simmondsia Chinensis (Jojoba) Seed Oil was not an acute oral toxicant to mice or rats (LD₅₀ generally greater than 5.0 g/kg). Short-term subcutaneous administration of Simmondsia Chinensis (Jojoba) Seed Wax to rats at 1 ml/kg was not toxic. Neither the wax nor the oil were toxic when applied dermally to the shaved backs of guinea pigs in short-term tests. A dermal irritation test found aqueous Hydrolyzed Jojoba Esters (20%) to be non-irritating to guinea pigs. Jojoba Alcohol was found to be non-irritating to the skin of albino marmots at 10.0%. Simmondsia Chinensis (Jojoba) Butter was classified as a non-irritant when applied to the intact and abraded skin of New Zealand white rabbits at 0.5 ml for 24 h under an occluded patch. Jojoba Alcohol at concentrations up to 50% was minimally irritating in rabbits. Simmondsia Chinensis (Jojoba) Seed Oil was non- to slightly irritating when instilled into the eyes of white rabbits, but Simmondsia Chinensis (Jojoba) Seed Wax, Jojoba Esters, and Jojoba Alcohol were not. Simmondsia Chinensis (Jojoba) Seed Wax was moderately comedogenic in tests using rabbits, but Jojoba Esters was noncomedogenic, and Jojoba Esters were non- to slightly- comedogenic. Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Jojoba Esters were non-mutagenic in Ames testing. No carcinogenicity and no reproductive or developmental toxicity data were available. In clinical tests, Simmondsia Chinensis (Jojoba) Seed Oil was neither a significant dermal irritant, nor a sensitizer. In repeat insult patch tests Jojoba Alcohol, Jojoba Esters and Hydrolyzed Jojoba Esters were not irritating during induction or sensitizing at challenge. Simmondsia Chinensis (Jojoba) Seed Oil and Jojoba Alcohol were not phototoxic. The available safety test data were combined with the expected uses of these ingredients, which includes use in aerosolized products. Because the particle size of aerosol hair sprays (~38 µm) and pump hair sprays (>80 µm) is large compared to respirable particulate sizes (≤10 µm), the ingredient particle size in cosmetic aerosols is not respirable. Relevant information also included uses with baby and eye products at low concentrations, and at 100% in hand and body creams. There were no structural alerts for the fatty acids, fatty alcohols, or other structures that would be found in these ingredients relative to reproductive/developmental toxicity, and these ingredients are not expected to easily penetrate skin. None of the tested ingredients were genotoxic and there were no structural alerts for carcinogenicity. The cosmetic industry should continue to limit pesticide and heavy metal impurities in the plant-derived ingredients before blending into cosmetic formulations. The CIR Expert Panel recognizes the gaps in use and use concentration data of these ingredients. Generally, the information available on the product types that include these ingredients and at what concentrations indicate a pattern to the Expert Panel when it assessed ingredient safety. Were unused ingredients used in the future, use is expected in comparable product categories and concentrations.

INTRODUCTION

Simmondsia Chinensis (Jojoba) Seed Oil and Simmondsia Chinensis (Jojoba) Seed Wax were previously reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel and were found to be "...safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1992). In the original safety assessment, the name of Simmondsia Chinensis (Jojoba) Seed Oil was Jojoba Oil and the name of Simmondsia Chinensis (Jojoba) Seed Wax was Jojoba Wax. The original safety assessment also considered data relevant to the safety of Jojoba-derived ingredients in addition to the oil and wax. Newly available published and unpublished data on all Jojoba-derived ingredients have been included in this report. Accordingly, this amended

safety assessment includes Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

CHEMISTRY

Definition and Structure

Simmondsia Chinensis (Jojoba) Seed Oil (CAS No. 61789-91-1) is defined as the fixed oil expressed or extracted from seeds of the desert shrub, Jojoba, *Simmondsia chinensis*. It is also known as Buxus Chinenesis Oil, Jojoba Oil, and Jojoba Seed Oil. Its chemical classification is ester. It only has plant sources

(Gottschalck and Bailey 2008).

According to Wendel (1980), the following chemical formula is typical of an ester found in Jojoba Oil.



Simmondsia Chinensis (Jojoba) Seed Wax (CAS No. 61789-91-1, same as the oil) is defined as the wax obtained from the seed of the jojoba plant, *S. chinensis*. Its chemical classification is wax, and it comes from plant sources (Gottschalck and Bailey 2008).

Hydrogenated Jojoba Oil (no CAS No.) is defined as the end product of the controlled hydrogenation of Simmondsia Chinensis (Jojoba) Oil. Its chemical classification is wax. It has both plant and synthetic sources (Gottschalck and Bailey 2008). According to the *International Cosmetic Ingredient Dictionary and Handbook*, a synthetic source is assigned to an ingredient that is prepared (“synthesized”) by the reaction of a substance with one or more other substances to form a new chemical entity. In cases when it is very clear that a raw material used to synthesize an ingredient is plant or animal derived, that source may be listed (Gottschalck and Bailey 2008).

Hydrolyzed Jojoba Esters (no CAS No.) is defined as the hydrolysate of Jojoba Esters (q.v.) derived by acid, enzyme, or other method of hydrolysis. Its chemical classification is esters. It has only a plant source (Gottschalck and Bailey 2008).

Isomerized Jojoba Oil (no CAS No.) is defined as a mixture of esters produced by the enzymatic intraesterification of Simmondsia Chinensis (Jojoba) Oil (q.v.). Its chemical classification is ester. It has both plant and synthetic sources (Gottschalck and Bailey 2008).

Jojoba Esters (no CAS No.) is defined as a complex mixture of esters produced by the transesterification/ interesterification of Simmondsia Chinensis (Jojoba) Oil (q.v.), Hydrogenated Jojoba Oil (q.v.), or a mixture of the 2. Its chemical classifications are transesters and waxes. It has both plant and synthetic sources (Gottschalck and Bailey 2008).

Simmondsia Chinensis (Jojoba) Butter (no CAS No.) is defined as the material obtained by the isomerization of Simmondsia Chinensis (Jojoba) Oil (q.v.). Its chemical classification is wax (natural and sythethic). It has only plant sources (Gottschalck and Bailey 2008).

Jojoba Alcohol (no CAS No.) is defined as the alcohol fraction obtained by the saponification of Simmondsia Chinensis (Jojoba) Oil (q.v.). Its chemical classification is fatty alcohols. It has only plant sources (Gottschalck and Bailey 2008).

Synthetic Jojoba Oil (no CAS No.) is defined as a synthetic oil intended to be generally indistinguishable from natural jojoba oil with regard to chemical composition and physical characteristics. Its chemical classification is wax and it only has synthetic sources (Gottschalck and Bailey 2008).

Physical and Chemical Properties

Simmondsia Chinensis (Jojoba) Seed Oil

The reaction of Simmondsia Chinensis (Jojoba) Seed Oil with sulfur yields a stable product; the liquidity of the oil is not affected by this reaction. Simmondsia Chinensis (Jojoba) Seed Oil also readily undergoes hydrogenation in the presence of a variety of nickel catalysts. The crystalline, hydrogenated product formed has a melting point of approximately 70°C. The epoxidation of Simmondsia Chinensis (Jojoba) Seed Oil and the amidation of transesterified Simmondsia Chinensis (Jojoba) Seed Oil have also been reported. Simmondsia Chinensis (Jojoba) Seed Oil is not easily oxidized and remains chemically unchanged for years. It also remains essentially unchanged when heated repeatedly to temperatures above 285°C, or after being heated to 370°C for 4 days. The yellow color of Simmondsia Chinensis (Jojoba) Seed Oil disappears permanently when the oil is heated to 300°C over a short period of time (McKeown 1983).

Rheological analysis of Simmondsia Chinensis (Jojoba) Seed Oil gave a viscosity of 37.7 mPa/s (Esquisabel et al 1997).

Chung et al. (2001) reported that Simmondsia Chinensis (Jojoba) Seed Oil formed stable emulsions in water with small particles (225 nm; polydispersity 0.21; viscosity 43.0 cSt/s).

Esquisabel et al. (2002) reported that the emulsion of Simmondsia Chinensis (Jojoba) Seed Oil and water encapsulating Bacillus Calmette-Guérin were stable after freeze-drying and storage at room temperature for a year.

Properties of what Habashy et al. (2005) referred to as “jojoba liquid wax”, thought to be Simmondisa Chinenesis (Jojoba) Seed Oil, are listed in Table 1.

Table 1. Physical properties of jojoba liquid wax (Habashy et al. 2005).

Property	Value
Freezing point	9°C
Boiling point	398°C
Smoke point ^a	195°C
Flash point	295°C
Refractive index at 25°C	1.46
Specific gravity at 15°C	0.87
Viscosity (25°C)	50 cP
Iodine value	81
Saponification value	93
Acid value	2
Acetyl value	2
Unsaponifiable matter	51%
Total acids	52%

^a Determined according to official method, Cc9a-48, of the American Oil Chemists' Society

Simmondsia Chinensis (Jojoba) Seed Wax

Kampf et al. (1986) reported that crude *Simmondsia Chinensis* (Jojoba) Seed Wax has an initial peroxide value of 17 meq/kg, and reaches almost zero after stripping or bleaching. The induction time was 45 to 50 h for crude wax, 12 h for bleached, and 2 h for stripped. Freshly bleached *Simmondsia Chinensis* (Jojoba) Seed Wax had a low peroxide value of 0 to 0.5 meq/kg for several months when stored in the dark at room temperature; the value elevated to 70 meq/kg within 6 to 7 weeks when stored in a transparent glass bottle. The authors suggest that crude *Simmondsia Chinensis* (Jojoba) Seed Wax contains a natural antioxidant that is lost in the bleaching and stripping processes.

Simmondsia Chinensis (Jojoba) Seed Wax is a hard crystalline material with properties that are comparable to carnauba and beeswax, and it is miscible with polyethylene glycol in all proportions. The properties of *Simmondsia Chinensis* (Jojoba) Seed Wax are as follows: appearance of white to off-white free flowing hard wax flakes, slight fatty odor, saponification number of 90 to 95, iodine value of 1, and melting point of 69°C (Reinhardt and Brown 1990).

Jojoba Esters

The physical consistency of Jojoba Esters ranges from a semisolid paste to a liquid with properties that are almost identical to those of *Simmondsia Chinensis* (Jojoba) Oil. The properties of 2 Jojoba Esters are as follows: soft white to off-white appearance, typical fatty odor, saponification number of 90, iodine values of 60 and 40, and melting points of 29 and 58°C (Reinhardt and Brown 1990).

Brown et al. (1997) tested the stability of Jojoba Esters 15 (melting point 15°C) and Jojoba Esters 60 (melting point 60°C) using an oxidative stability index (OSI; also referred to oil stability index) using a method developed by the American Oil Chemists' Society (AOCS 1997). Jojoba Esters 15 had a stability of ~35 OSI hours and Jojoba Esters 60 175 OSI hours. For comparison, the stability of sesame oil was ~15 OSI hours, palm oil ~30 OSI hours, macademia oil ~30 OSI hours, hybrid sunflower oil ~35 OSI hours, traditional sunflower oil ~5 OSI hours, and almond oil ~10 OSI hours. Table 2 shows the OSI for the Jojoba Esters when exposed to cosmetic actives.

The melting point of Jojoba Esters-70 is 70°C (Arquette et al. 1998). Jojoba Esters have melting points ranging from 15°C to 70°C. The texture and crystallinity of Jojoba Esters may be modified by rapid cooling, thus altering their properties. Jojoba Esters are resistant to oxidation (International Jojoba Export Council 2004).

Floritech (2005a,b,c) reported on 5 Jojoba Ester products (see COMPOSITION SECTION). The properties are reported in Table 3. The shelf life of all 5 Jojoba Esters in an unopened container at or below 35°C is 1 year.

Table 2. OSI of Jojoba Esters 15 and 60 when exposed to cosmetic actives (Brown et al. 1997).

Cosmetic active (%)	15 h	60 h
None	~35	~175
Tocopherols*	~80	~230
Iron oxides (10%) and tocopherols	~80	~225
Zinc oxides (10%) and tocopherols	~15	~90
Titanium dioxide (10%) and tocopherols	~135	~300
Malic acid (5%) and tocopherols	~110	~20
Salicylic acid (2%) and tocopherols	~25	~50
Salicylic acid (2%), titanium dioxide (10%), and tocopherols	~60	~180
Malic acid (5%), titanium dioxide (10%), and tocopherols	~120	~20
Arbutin (7%) and tocopherols	~50	~90
Kojic acid (1%) and tocopherols	~100	~250
Magnesium ascorbyl phosphate (3%) and tocopherols	~85	~170

* concentration of tocopherols not provided.

Hydrolyzed Jojoba Esters

Hydrolyzed Jojoba Esters mixed with water (20:80 wt.%) are described as a soft white to off-white viscous liquid. The maximum saponification value is 1 mg KOH/g, no trans isomers were detected, the peroxide value was a maximum of 5 meq/kg, and the wax ester content was a maximum of 0.5 area %. The expected shelf life in an unopened container at or below 35°C is 1 year (Floritech 2005d).

Jojoba Alcohol

The properties of Jojoba Alcohol are as follows: specific gravity (25°C) of 0.8499, refractive index (20°C) of 1.4621, acid value of 0.01, saponification number of 0.75, hydroxy value of 178.4, iodine value of 83.1, and freezing point of 12°C (Reinhardt and Brown 1990).

Mixtures

Floritech (2006) analyzed a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters, and tocopherol (approximate weight % 35:35:30:0.1). It was described as a clear pale yellow liquid at or above room temperature (24°C). Below room temperature, partial crystallization may appear as cloud-like formations which may settle to the bottom. This can be used as is or warmed to remove cloudiness. The product may slightly darken over time. The product was said to have a shelf life of 1 year. The other values reported are listed in Table 4.

Table 3. Chemical properties of 5 Jojoba Ester products (Floritech 2005a,b,c).

Property	Jojoba Ester 15	Jojoba Ester 20	Jojoba Ester 30	Jojoba Ester 60	Jojoba Ester 70
Appearance	Clear, colorless liquid	Creamy white paste	Soft white paste	Firm white paste	Crystalline jojoba wax particles, hard, white, odorless
Saponification Value	88-96 mg KOH/g	88-96 mg KOH/g	88-96 mg KOH/g	88-96 mg KOH/g	88-96 mg KOH/g
Trans isomers	none	none	none	none	none
Acid value	1 mg KOH/g	1 mg KOH/g	1 mg KOH/g	1 mg KOH/g	1 mg KOH/g
Dropping point	10-15°C	42-48°C	47-51°C	56-60°C	-
Iodine value	78-85 g/100 g	64-70g/100 g	57-61 g/100 g	40-44 g/100 g	2 g/100 g
Monounsaturated Esters	-	25-35 area %	40-47 area %	46-53 area %	-
Peroxide value	4 meq/kg	4 meq/kg	4 meq/kg	4 meq/kg	2 meq/kg
Absence of microbial contamination	100 CFU/g	100 CFU/g	100 CFU/g	100 CFU/g	100 CFU/g
Refractive index @ 40°C	1.458-1.460 n_D	-	-	-	-
Specific gravity	0.862-0.867	-	-	-	-
Triglyceride content	1 wt. %	-	-	-	-
Melting Point	-	-	-	-	66-70°C

Table 4. Properties of an Isopropyl Jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol mixture (Floritech 2006).

Property	Value
Dropping point	6 - 12°C
Hydroxyl value	40 - 70 mg/KOH/g
Iodine value	75 - 85 g/100 g
Refractive Index (40°C)	1.452 - 1.454 n_D
Saponification value	80 - 90 mg KOH/g
Specific gravity	0.855 - 0.860
Trans isomers	none detected
Viscosity (25°C)	15 - 25 cP
Acid value	5 mg KOH/g
Peroxide value	3 meq/kg
Absence of microbial contamination	100 CFU/g

Composition

Simmondsia Chinensis (Jojoba) Seed Oil is composed almost completely (97%) of wax esters of monounsaturated, straight-chain acids and alcohols with high-molecular weights (C16-C26). These wax esters exist principally (83%) as combinations of C20 and C22 unsaturated fatty acids and alcohols (McKeown 1983). The long aliphatic chains of both the acids and alcohols make *Simmondsia Chinensis* (Jojoba) Seed Oil a highly lipophilic chemical (Shani 1983).

The unsaturated fatty acids are mixtures of cis-11-eicosenoic acid (C20) and cis-13-docosenoic acid (C22); small quantities of oleic acid (C18) and cis-15-tetracosenoic acid (C24) are also present. The unsaturated alcohols are mixtures of cis-11-eicosenol, cis-13-docosenol, and cis-15-tetracosenol. Total free acids (C16 to C24) and total alcohols (C16 to C26) each account for 1% of the composition of *Simmondsia Chinensis* (Jojoba) Seed Oil. Small quantities of sterols (< 0.5%) are also present (McKeown 1983).

Miwa (1971) reported that the composition of *Simmondsia Chinensis* (Jojoba) Seed Oil was consistent between 2 adjacent regions of Arizona even in samples collected 5 years apart. *Simmondsia Chinensis* (Jojoba) Seed Oil collected in the California desert had a similar composition to the oil collected in Arizona. However, *Simmondsia Chinensis* (Jojoba) Seed Oil collected near the ocean in San Diego had a shift in composition toward larger molecule sizes. *Simmondsia Chinensis* (Jojoba) Seed Oil from an unknown source had shorter chain lengths than the Arizona samples. The major component, eicosenoic acid, was consistent at 35% for all samples.

Simmondsia Chinensis (Jojoba) Seed Oil contains ~0.05% tocopherols (Yaron 1987).

Simmondsia Chinensis (Jojoba) Seed Wax

Yermanos (1975) reported on the *Simmondsia Chinensis* (Jojoba) Seed Wax from seeds collected weekly for the 8 weeks leading up to maturity. The amount of the wax increased from 13.5% to 49.4% of the seed weight over time. The composition of the wax as characterized by the carbon chain length and the level of saturation also changed over time as shown in Table 5.

Table 5. Fatty acids and alcohols in *Simmondsia Chinensis* (Jojoba) Seed Wax in immature and mature seeds^A (Yermanos 1975).

Number of carbon atoms and double bonds	Acids % in seeds collected on:			Alcohols % in seeds collected on:		
	6/20	7/25	8/25	6/20	7/25	8/25
16:0	2.6	0.9	0.8	-	-	-
18:1	16.1	7.7	7.0	-	-	-
20:1	26.3	35.3	36.4	28.4	27.7	28.8
22:0	-	-	-	5.2	5.4	5.4
22:1	5.0	6.0	5.8	16.5	16.9	15.8

^A Data represent means from 3 bulk wax samples, each from 15 single plant seed samples/date of sampling.

The main constituents of *Simmondsia Chinensis* (Jojoba) Seed Wax were the wax esters: eicosenyl octadecenoate (C20:1-C18:1; 5.5%), docosenyl eicosenoate (C20:1-C20:1; 21.4%), docosenyl eicosenoate (C22:1-C20:1; 37.8%), eicosenyl docosenoate (C20:1-C22:1), and tetracosenyl eicosenoate (C24:1-C20:1) (Tada et al. 2005).

Jojoba Esters are proper waxes, with no triglyceride components. Jojoba Esters are a complex mixture of long chain (C35 to C46) fatty acids and fatty alcohols joined by an ester bond and do not contain any trans-unsaturation (International Jojoba Export Council 2004).

Floritech (2005a,b) reported the ester chain length and saturation of 4 Jojoba Ester products as shown in Table 6. Each was reported as being 99.95% Jojoba Esters and 0.05% tocopherol.

Table 6. Ester chain length composition and saturation of Jojoba Ester 20, 40, 60, and 80 (Floritech 2005a,b).

Number of carbons and double bonds	% of different chain lengths in Jojoba Ester:			
	20	30	60	70
38:0	1	1	1 - 4	5 - 8
38:1	1 - 2	2 - 4	3 - 4	-
38:2	3 - 5	2 - 4	1 - 3	-
40:0	1 - 2	2 - 4	7 - 18	26 - 34
40:1	8 - 13	14 - 18	18 - 20	-
40:2	20 - 28	17 - 21	5 - 15	-
42:0	1 - 4	2 - 4	6 - 15	44 - 56
42:1	22 - 30	17 - 21	4 - 12	-
42:2	1	2	2 - 5	8 - 12
44:0	2 - 6	4 - 7	4 - 7	-
44:1	2 - 6	4 - 7	4 - 7	-
44:2	5 - 9	4 - 7	1 - 4	-

Floritech (2005b) reported the ester chain length composition of Jojoba Ester 15 as shown in Table 7, without specifying saturation.

Table 7. The ester chain length composition of Jojoba Ester 15 (Floritech 2005b).

Ester chain length	% in Jojoba Ester 15
C 36	2
C 38	5-8
C 40	34-40
C 42	35-44
C 44	11-15
C 46	2

Methods of Manufacture

Jojobutter-51 is an isomorphous mixture of *Simmondsia Chinensis* (Jojoba) Seed Oil, partially Isomerized Jojoba Oil, and Hydrogenated Jojoba Wax (Brown 1984).

Simmondsia Chinensis (Jojoba) Seed Wax is the product of complete reduction of the unsaturated alcohols and acids comprising the wax ester combinations of *Simmondsia Chinensis* (Jojoba) Seed Oil (Reinhardt and Brown 1990).

Jojoba Alcohols are prepared via the sodium reduction of *Simmondsia Chinensis* (Jojoba) Seed Oil and Hydrogenated *Simmondsia Chinensis* (Jojoba) Seed Wax. The alcohols are then further refined to render them suitable for use in cosmetics (Reinhardt and Brown 1990).

Simmondsia Chinensis (Jojoba) Seed Oil is combined with Hydrogenated Jojoba Oil and sodium methylate (catalyst) to get mixed Jojoba Esters (Floritech 2005a). Refined *Simmondsia Chinensis* (Jojoba) Seed Oil is combined with sodium methoxide to get randomized Jojoba Esters. Tocopherol is then added to make the commercial Jojoba Ester 15 (Floritech 2005b).

Simmondsia Chinensis (Jojoba) Seed Oil is combined with nickel (catalyst) to get Hydrogenated Jojoba Oil. This is converted to powder to get Jojoba Esters (Floritech 2005c). Simmondsia Chinensis (Jojoba) Seed Oil is combined with isopropyl alcohol and sodium methoxide (catalyst) to get isopropyl esters, Jojoba Alcohols, and Jojoba Esters (interesterified [randomized] Simmondsia Chinensis (Jojoba) Seed Oil) in approximately equal amounts (Floritech 2006).

Synthetic Jojoba Oil

Kalscheuer et al. (2006) developed a recombinant strain of *Escherichia coli* that produced an oil that was similar to Simmondsia Chinensis (Jojoba) Seed Oil. Cultivation in the presence of oleate produced $C_{23:1}$, $C_{34:1}$, and $C_{36:2}$ wax esters which were chemically similar to jojoba wax esters. The amounts produced were small.

Analytical Methods

Simmondsia Chinensis (Jojoba) Seed Oil has been analyzed via the following methods: thin layer chromatography (TLC), gas chromatography (GC), nuclear magnetic resonance spectroscopy, infrared spectroscopy, differential scanning calorimetry, and equivalent carbon number analyses (Miwa 1973; Hamm 1984).

Garver et al. (1992) used reversed-phase C_{18} high-performance liquid chromatography (HPLC) coupled with efficient and sensitive detection by an on-line flow-through radiochemical detector to analyze the components of crude jojoba seed homogenate.

Van Boven et al. (1997) used GC, mass spectrometry (MS), gas chromatography/mass spectrometry (GC/MS), and TLC to isolate and identify the phytosterols and fatty alcohols in Simmondsia Chinensis (Jojoba) Seed Oil. Tada et al. (2005) used liquid chromatography/mass spectrometry (LC/MS) and GC/MS analysis to find the main constituents of Simmondsia Chinensis (Jojoba) Seed Wax.

Impurities

The Cosmetic, Toiletry, and Fragrance Association (CTFA) specification for Simmondsia Chinensis (Jojoba) Seed Oil defines positive identification of the oil as a close match to the infrared (IR) spectrum, with no indication of foreign materials (CTFA 1989).

The specification for crude Simmondsia Chinensis (Jojoba) Seed Oil includes less than 0.8 ppm elemental lead (Pb) and less than 0.1 ppm arsenic (as As_2O_3) (Taguchi and Kunimoto 1977).

When Simmondsia Chinensis (Jojoba) Seed Oil was refined via a standard alkali refining process (Swern 1982), a trace amount of nitrogen-containing compounds (6.0 ± 2 ppm) was found (Hamm 1984). Data on the presence and nature of terpenoid compounds were not available.

Jojoba Alcohols contain less than 20 ppm lead and less than 2 ppm arsenic (Reinhardt and Brown 1990).

SGS Canada Inc. (2005a, 2006) analyzed samples of two materials: (1) a mixture of isopropyl jojobate, Jojoba Alcohol and Jojoba Esters, and (2) Hydrolyzed Jojoba Esters and water to determine the presence of impurities (data given in Table 8).

Table 8. Impurities found in a mixture of isopropyl jojobate, Jojoba Alcohol and Jojoba Esters and Hydrolyzed Jojoba Esters and water (SGS Canada Inc. 2005a, 2006).

Impurity	Jojoba mixture	Hydrolyzed Jojoba Esters and water	Detection Limit
As	0.1 µg/g	none	0.1 µg/g
Ca	18 µg/g	none	0.2 µg/g
Cd	none	none	2 methods: 0.1 and 0.2 µg/g
Co	none	none	0.3 µg/g
Cr	none	none	1 µg/g
Cu	6 µg/g	none	0.2 µg/g
Fe	none	1.6 µg/g	2 µg/g
Hg	none	none	0.1 µg/g
K	1 µg/g	10376 µg/g	-
Mg	none	2.5 µg/g	3 µg/g
Mn	none	none	0.7 µg/g
Na	none	72.1 µg/g	10 µg/g
Ni	none	none	2 µg/g
P	none	4.3 µg/g	5 µg/g
Pb	0.8 µg/g	none	0.2 µg/g
Sr	none	none	0.2 µg/g
Zn	4 µg/g	none	0.2 µg/g

SGS Canada Inc. (2005b,c,d,e,f 2006) reported the analysis of Jojoba Esters 15, 20, 30, 60, and 70 as shown in Table 9. Detection limits are not given in Table 9, but were comparable to those shown in Table 8.

USE

Cosmetic

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Registration Program (VCRP), Simmondsia Chinensis (Jojoba) Seed Oil was used in a total of 188 cosmetic products, at the time of the original safety assessment, at use concentrations up to 25% (Elder 1989). Currently VCRP data indicated that Simmondsia Chinensis (Jojoba) Seed Oil is used in 1123 products (FDA 2007). A survey of current use concentrations conducted by the CTFA reported use concentrations up to 100% (CTFA 2007). These data are given in Table 10, as a function of product category, along with the total number of products reported in each category. From Table 10, for example, it can be seen that the Seed Oil is used in 109 of a total of 715 conditioners, at a wide concentration range from 0.001 to 67%. In some cases, there were no reported uses to the VCRP, but a current use concentration is provided — for example, the Seed Oil in hair coloring rinses. It should be presumed that there is at least 1 use. In other cases, there is a reported use (Seed Oil in shampoos), but no use concentration is provided.

Simmondsia Chinensis (Jojoba) Seed Wax had no uses listed in 1989 and is currently reported to be used in 8 cosmetic products (FDA 2007) at up to 2% (CTFA 2007).

Hydrogenated Jojoba Oil is reported to be used in 71 cosmetic products, Jojoba Esters in 121 cosmetic products, Hydrolyzed Jojoba Esters in 86 cosmetic products, Simmondsia Chinensis (Jojoba) Butter in 18 cosmetic products, Jojoba Alcohol in 21 cosmetic products, and Synthetic Jojoba Oil in 6 cosmetic products (FDA 2007) at up to 31%, 44%, 2%, 6%, 1%, and 0.1%, respectively (Table 10) (CTFA 2007).

Isomerized Jojoba Oil is not reported as being used, nor were any use concentrations provided.

Apropos of the use of certain of these ingredients in product categories known to be aerosols or sprays, Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, d_a , defined as the diameter of a sphere of unit density possessing the same terminal settling velocity as the particle in question. These authors reported a mean aerodynamic diameter of $4.25 \pm 1.5 \mu\text{m}$ for respirable particles that could result in lung exposure (Jensen and O'Brien, 1993).

Bower (1999), reported diameters of anhydrous hair spray particles of 60 - 80 μm and pump hair sprays with particle diameters of $\geq 80 \mu\text{m}$. Johnsen (2004) reported that the mean particle diameter is around 38 μm in a typical aerosol spray. In practice, he stated that aerosols should have at least 99% of particle diameters in the 10 - 110 μm range.

Table 9. Impurities found in Jojoba Ester 15, 20, 30, 60, and 70 (SGS Canada Inc. 2005b,c,d,e,f, 2006).^a

Impurity	Jojoba Esters 15	Jojoba Esters 20	Jojoba Esters 30	Jojoba Esters 60	Jojoba Esters 70
As	none	none	none	none	none
Ca	9 $\mu\text{g/g}$	none	none	none	none
Cd	none	none	none	none	none
Co	none	none	none	none	none
Cr	none	1 $\mu\text{g/g}$	1 $\mu\text{g/g}$	1 $\mu\text{g/g}$	none
Cu	2 $\mu\text{g/g}$	none	none	none	none
Fe	none	none	none	5 $\mu\text{g/g}$	none
Hg	none	none	none	none	none
K	2 $\mu\text{g/g}$	13 $\mu\text{g/g}$	2 $\mu\text{g/g}$	none	3 $\mu\text{g/g}$
Mg	none	none	none	none	4 $\mu\text{g/g}$
Mn	0.8 $\mu\text{g/g}$	none	9 $\mu\text{g/g}$	none	0.8 $\mu\text{g/g}$
Na	none	none	none	none	none
Ni	none	none	none	none	2 $\mu\text{g/g}$
P	none	none	none	none	none
Pb	0.4 ppm	none	0.2 ppm	none	0.5 ppm
Sr	none	none	none	none	none
Zn	none	none	1 $\mu\text{g/g}$	none	none

^a Detection limits comparable to those given in Table 8.

Table 10. Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Simmondsia Chinensis (Jojoba) Seed Oil</i>		
Baby products		
Lotions, oils, powders, and creams (67)	7	1
Other (64)	2	-
Bath products		
Oils, tablets, and salts (207)	17	0.002-100
Soaps and detergents (594)	15	0.1-5
Bubble baths (256)	3	0.002-2
Capsules (5)	-	2
Other (276)	8	0.08-2
Eye makeup		
Eyebrow pencils (124)	3	0.08-0.1
Eyeliners (639)	20	0.1-4
Eye shadow (1061)	7	0.7-7
Eye lotions (32)	11	0.1-0.5
Eye makeup remover (114)	2	0.1-5
Mascara (308)	2	0.1-1
Other (229)	9	0.1
Fragrance products		
Colognes and toilet waters (948)	-	5
Perfumes (326)	1	5
Powders (324)	1	5
Sachets (28)	-	5
Other (187)	9	5
Noncoloring hair care products		
Conditioners (715)	109	0.001-67
Sprays/aerosol fixatives (294)	12	0.001-1
Straighteners (61)	9	0.01-20
Permanent waves (169)	1	0.01-0.9
Rinses (46)	2	0.01
Shampoos (1022)	51	0.001-2
Tonics, dressings, etc. (623)	30	0.01-4
Wave sets (59)	-	1-2
Other (464)	30	0.1-2 ^a
Hair coloring products		
Dyes and colors (1600)	84	0.2
Rinses (15)	-	0.2
Shampoos (1022)	1	-
Color sprays (4)	-	0.3
Bleaches (103)	2	0.05

Table 10 (continued). Historical and current cosmetic product uses and concentrations for *Simmondsia Chinensis* (Jojoba) Seed Oil, *Simmondsia Chinensis* (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, *Simmondsia Chinensis* (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Simmondsia Chinensis</i> (Jojoba) Seed Oil (continued)		
Makeup		
Blushers (459)	12	0.4-53
Face powders (447)	10	0.1-53
Foundations (530)	29	0.5-53
Leg and body paints (10)	1	0.1
Lipsticks (1681)	110	1-46
Makeup bases (273)	2	5-53
Rouges (115)	-	12
Makeup fixatives (37)	1	53
Other (304)	24	5-53 ^b
Nail care products		
Basecoats and undercoats (43)	2	0.0001-0.2
Cuticle softeners (20)	4	0.1-10
Creams and lotions (13)	-	0.1-25
Extenders (1)	-	0.2
Nail polishes and enamels (398)	20	0.000005-0.001
Nail polish and enamel removers (39)	-	0.0001-0.2
Other (58)	5	0.0001-13 ^c
Personal hygiene products		
Underarm deodorants (281)	-	0.002-5
Douches (8)	-	5
Feminine deodorants (7)	-	5
Other (390)	4	0.05-9 ^d
Shaving products		
Aftershave lotions (260)	3	0.002-3
Preshave lotions (20)	2	1
Shaving cream (135)	3	0.002-2
Shaving soap (2)	-	0.01
Other (64)	4	0.002
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	29	0.001-53
Depilatories (49)	3	0.001-53
Face and neck creams, lotions, powder and sprays (546)	67	0.5-53 ^e
Body and hand creams, lotions, powder and sprays (992)	106	0.00003-100 ^f
Foot powders and sprays (43)	-	53
Moisturizers (1200)	114	0.5-100 ^g
Night creams, lotions, powder and sprays (229)	33	0.8-53 ^h
Paste masks/mud packs (312)	7	0.5-53
Skin fresheners (212)	3	53
Other (915)	51	1-53 ⁱ

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Simmondsia Chinensis (Jojoba) Seed Oil (continued)</i>		
Suntan products		
Suntan gels, creams, liquids and sprays (138)	3	0.1
Indoor tanning preparations (74)	20	0.0003-2
Other (41)	3	0.1
Total uses/ranges for Simmondsia Chinensis (Jojoba) Seed Oil	1123	0.000005-100
<i>Simmondsia Chinensis (Jojoba) Seed Wax^j</i>		
Bath products		
Soaps and detergents (594)	1	0.1
Eye makeup		
Mascara (308)	1	-
Noncoloring hair care products		
Conditioners (715)	-	0.05
Shampoos (1022)	2	0.05
Other (464)	1	-
Shaving products		
Shaving cream (135)	-	2
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	-	1
Face and neck creams, lotions, powder and sprays (546)	1	-
Body and hand creams, lotions, powder and sprays (992)	1	-
Paste masks/mud packs (312)	1	-
Total uses/ranges for Simmondsia Chinensis (Jojoba) Seed Wax	8	0.05-2
<i>Hydrogenated Jojoba Oil^k</i>		
Bath products		
Soaps and detergents (594)	5	0.01-0.5
Other (276)	1	0.1-2
Eye makeup		
Eyeliner (639)	1	-
Eye shadow (1061)	1	2
Eye lotions (32)	1	1
Mascara (308)	30	7
Noncoloring hair care products		
Conditioners (715)	1	-
Sprays/aerosol fixatives (294)	-	0.001
Tonics, dressings, etc. (623)	1	-

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Hydrogenated Jojoba Oil (continued)</i>		
Hair coloring products		
Dyes and colors (1600)		
Hair tints (56)	-	0.1
Rinses (15)	-	0.1
Color sprays (4)	-	0.1
Lighteners with color (14)	-	0.1
Bleaches (103)	-	0.1
Other (73)	-	0.1
Makeup		
Blushers (459)	3	0.1-2
Face powders (447)	-	0.1
Foundations (530)	3	0.1-10
Lipsticks (1681)	1	31
Makeup bases (273)	-	0.1
Makeup fixatives (37)	-	0.1
Other (304)	-	0.1-2
Nail care products		
Creams and lotions (13)	-	0.8
Oral hygiene products		
Other (10)	3	-
Personal hygiene products		
Underarm deodorants (281)	-	0.01
Douches (8)	-	
Feminine hygiene deodorants (7)	-	0.01
Other (390)	-	0.01
Shaving products		
Shaving soap (2)	1	-
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	9	1-5
Depilatories (49)	-	0.1
Face and neck creams, lotions, powder and sprays (546)	2	0.1 ^l
Body and hand creams, lotions, powder and sprays (992)	1	0.01-8 ^m
Foot powders and sprays (43)	-	0.1
Moisturizers (1200)	-	0.1 ⁿ
Night creams, lotions, powder and sprays (229)	-	0.1 ^o
Paste masks/mud packs (312)	-	0.01-0.4
Skin fresheners (212)	-	0.1

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Hydrogenated Jojoba Oil (continued)</i>		
Suntan products		
Other (41)	1	-
Other (915)	6	0.1
Total uses/ranges for Hydrogenated Jojoba Oil	71	0.001-31
<i>Jojoba Esters</i>		
Bath products		
Soaps and detergents (594)	7	0.2-2
Other (276)	1	-
Eye makeup		
Eyebrow pencils (124)	1	5
Eyeliners (639)	3	5-14
Eye shadow (1061)	3	0.5-5
Eye lotions (32)	4	0.5-5
Eye makeup remover (114)	-	5
Mascara (308)	6	3-5
Other (229)	2	5
Fragrance products		
Colognes and toilet waters (948)	-	0.05
Perfumes (326)	-	0.002
Other (187)	1	0.8
Makeup		
Blushers (459)	1	7
Face powders (447)	1	3-7
Foundations (530)	14	1-7
Leg and body paints (10)	-	5
Lipsticks (1681)	8	5-44
Makeup bases (273)	2	7
Rouges (115)	-	5-7
Makeup fixatives (37)	1	7
Other (304)	2	5-11 ^b
Nail care products		
Basecoats and undercoats (43)	-	18
Cuticle softeners (20)	-	18
Creams and lotions (13)	-	18
Extenders (1)	-	18
Nail polishes and enamels (398)	-	0.5-18
Nail polish and enamel removers (39)	-	18
Other (58)	-	18
Personal hygiene products		
Other (390)	1	2-4 ^q

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Jojoba Esters (continued)</i>		
Shaving products		
Aftershave lotions (260)	1	0.002
Other (64)	-	0.000005
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	26	0.3-10
Depilatories (49)	-	7
Face and neck creams, lotions, powder and sprays (546)	9	0.2-7 ^r
Body and hand creams, lotions, powder and sprays (992)	7	0.3-7 ^r
Foot powders and sprays (43)	-	7
Moisturizers (1200)	14	7 ^r
Night creams, lotions, powder and sprays (229)	4	7 ^r
Paste masks/mud packs (312)	1	1-7
Skin fresheners (212)	-	7
Other (915)	1	7
Total uses/ranges for Jojoba Esters	121	0.000005-44
<i>Hydrolyzed Jojoba Esters</i>		
Fragrance products		
Colognes and toilet waters (948)	53	2
Perfumes (326)	23	0.07
Other (187)	-	0.0002
Noncoloring hair care products		
Tonics, dressings, etc. (623)	1	-
Shaving products		
Aftershave lotions (260)	7	0.07
Other (64)	-	0.0002
Skin care products		
Face and neck creams, lotions, powder and sprays (546)	1	-
Moisturizers (1200)	1	-
Total uses/ranges for Hydrolyzed Jojoba Esters	86	0.0002-2
<i>Simmondsia Chinensis (Jojoba) Butter</i>		
Bath products		
Soaps and detergents (594)	2	0.8
Eye makeup		
Mascara (308)	1	6
Makeup		
Lipsticks (1681)	1	3

Table 10 (continued). Historical and current cosmetic product uses and concentrations for Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Simmondsia Chinensis (Jojoba) Butter (continued)</i>		
Noncoloring hair care products		
Conditioners (715)	1	-
Personal hygiene products		
Other (390)	1	-
Skin care products		
Face and neck creams, lotions, powder and sprays (546)	-	-
Body and hand creams, lotions, powder and sprays (992)	6	0.1
Moisturizers (1200)	4	-
Night creams, lotions, powder and sprays (229)	1	-
Other (915)	1	-
Total uses/ranges for Simmondsia Chinensis (Jojoba) Butter	18	0.1-6
<i>Jojoba Alcohol⁶</i>		
Eye makeup		
Eye shadow (1061)	1	1
Eye Lotion (32)	2	-
Noncoloring hair care products		
Conditioners (715)	-	0.5
Sprays/aerosol fixatives (294)	-	0.5
Straighteners (61)	-	0.1
Permanent waves (169)	-	0.1
Rinses (46)	-	0.1
Shampoos (1022)	-	0.1
Tonics, dressings, etc. (623)	-	0.5
Wave sets (59)	-	0.5
Other (464)	-	0.5
Makeup		
Foundations (530)	2	1
Shaving products		
Shaving cream (135)	-	0.1
Shaving soap (2)	-	0.1
Skin care products		
Face and neck creams, lotions, powder and sprays (546)	1	-
Body and hand creams, lotions, powder and sprays (992)	11	-
Moisturizers (1200)	4	-
Total uses/ranges for Jojoba Alcohol	21	0.1-1

Table 10 (continued). Historical and current cosmetic product uses and concentrations for *Simmondsia Chinensis* (Jojoba) Seed Oil, *Simmondsia Chinensis* (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Jojoba Esters, Hydrolyzed Jojoba Esters, *Simmondsia Chinensis* (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil.

Product Category (Total number of products in each category) (FDA 2008)	2007 uses (FDA 2007)	2007 % concentration (CTFA 2007)
<i>Synthetic Jojoba Oil</i>		
Eye makeup		
Eyeliners (639)	1	-
Noncoloring hair care products		
Conditioners (715)	5	-
Skin care products		
Depilatories (49)		0.1
Total uses/ranges for <i>Synthetic Jojoba Oil</i>	6	0.1

^a 0.1% in a liquid hair lotion, 2% in a hair mask; ^b 5% in a concealer; ^c 0.0001% in a solution used to dilute nail enamel, 10% in a hand and foot exfoliator; ^d 0.05%, 1%, and 9% in body scrubs; ^e 53% in face and neck sprays; ^f 0.00003 - 53 in body and hand sprays; ^g 53% in moisturizing sprays; ^h 5% in night sprays; ⁱ 1% in an oil stick; ^j listed as Jojoba Wax by the FDA; ^k listed as both Hydrogenated Jojoba Oil and Wax; ^l 0.1% in face and neck sprays; ^m 0.1% in body and hand sprays; ⁿ 0.1% in moisturizing sprays; ^o 0.1% in night sprays; ^p 2% in a shower gel; ^q 7% in face and neck creams, body and hand sprays, moisturizing sprays, and night sprays; ^r listed as both Jojoba Alcohol and Jojoba (*Simmondsia Chinensis*)

Non-cosmetic

Yaron (1987) reported that jojoba seeds are used by Native American Indians as food and medicine. It is reported that jojoba seeds are good for the stomach, facilitate parturition when mixed with chocolate, and treat sores that erupt on the face. The seeds are also reported to treat sores, scratches, and cuts rapidly; treat suppression of the urine; promote hair growth; and considered a remedy for cancer.

Dweck (1997) reported that the jojoba plant has been used by Native Americans for wound healing and as a skin salve. The expressed juices of the seeds are used to treat eye soreness.

Simmondsia Chinensis (Jojoba) Seed Oil

Non-cosmetic uses of *Simmondsia Chinensis* (Jojoba) Seed Oil include: high-temperature lubricant for high-speed machinery, sulfurization for extreme-pressure lubricants, treatment of leather, benzene or gasoline-soluble factice for rubber, varnishes, linoleum, or chewing gum, and hydrogenation into hard wax for use as polishing wax, in carbon paper, or as candles that give a brilliant flame with no smoke (Miwa 1973). Jojoba Oil is also used in the pharmaceutical industry as an antifoaming agent in the fermentation of tetracycline and penicillin (Buckley 1981) and as a substitute for sperm whale oil (Scott and Scott 1982).

Simmondsia Chinensis (Jojoba) Seed Oil may be used in the microencapsulation of live cells and enzymes as a drug delivery system (Esquisabel et al. 1997).

Simmondsia Chinensis (Jojoba) Seed Oil is used in pesticides to control white flies. Jojoba products are used for controlling powdery mildew on grapes and on ornamental plants at a

concentration $\leq 1\%$ (Environmental Protection Agency [EPA] 2006).

Simmondsia Chinensis (Jojoba) Seed Wax is used to extract metal ions from aqueous solutions so that the ions may be reused (Binman et al. 1998).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism and Excretion

Simmondsia Chinensis (Jojoba) Seed Oil was detected in the feces of dd Y-S mice (5 weeks old) 1 week after the mice were force-fed doses of 0.5, 0.75, 1.13, and 1.69 mg/10 g. Four groups of 20 mice were evaluated (Taguchi and Kunimoto 1977).

Yaron (1987) reported that nude mouse skin was used to study *Simmondsia Chinensis* (Jojoba) Seed Oil penetration. After 22 h, there was 6.7-fold more penetration than at 1 h. The cell solution contained ~4 meq *Simmondsia Chinensis* (Jojoba) Seed Oil/area tested. Based on histological examination of the skin, the main route of penetration was the hair follicle.

Verschuren and Nugteren (1989) tested the effects of *Simmondsia Chinensis* (Jojoba) Seed Oil on intestinal transit time in 7-week-old, male SPR Wistar rats (Cpb/WU). After 1 week of acclimation on a commercial diet, the diet of the control group (n = 19) was changed to the commercial diet mixed with lard/sunflower seed oil (4:1) with a fat content of 18% (equivalent to 40% energy). The diet of the experimental group was changed to the commercial diet with the lard/sunflower seed oil (9%) and *Simmondsia Chinensis* (Jojoba) Seed Oil (9%). The rats were fed ad libitum for 10 d, then were trained to eat all of their food in 2 half-hour shifts (7:00 AM to 7:30 AM and 7:00 PM to 7:30 PM). The rats were allowed to eat ad libitum during meal times for 10

d; in the last 3 d, the exact food consumption was recorded. The meals were then adjusted over the next 8 d so that the rats ate exactly the same amount at each meal time.

After a total of 4 weeks, the morning meal was marked by incorporation of [³H]retinol (1 µCi/animal) and the marker carmine (37.5 mg/kg). After 5 h the feces were sampled every 30 min up to 20 h, then hourly up to 33 h, then at 36, 41, 48, 60, 72, 84, and 96 h.

The feces were examined for carmine and the level of radioactivity was determined by liquid scintillation counting. After the subsequent meal, the rats were killed in groups of 4 at 0, 1.5, 3, 6, and 12 hr and the stomach contents sampled, freeze-dried, and weighed.

The treatment group had a lower growth rate (299 ± 4.1 g vs 239 ± 5.3 g). Food consumption over the period of fixed meal times was lower for the *Simmondsia Chinensis* (Jojoba) Seed Oil-fed rats than for the controls (6.3 ± 0.46 g vs. 5.2 ± 0.78 g). The absolute amounts of radioactivity measured over 96 h were not different between the groups, even with the difference in food consumption. The *Simmondsia Chinensis* (Jojoba) Seed Oil fed rats excreted more retinol than the control group ($p < .01$), possibly due to reduced retinol absorption. There was no difference in transit time of the radioactivity.

Comparison of the weights of feed consumed and the amount of feed in the rats' stomachs showed that the emptying of the animals' stomachs was not affected by *Simmondsia Chinensis* (Jojoba) Seed Oil ingestion. No ill effects from the consumption of *Simmondsia Chinensis* (Jojoba) Seed Oil were reported by the authors.

In a second experiment, the authors fed 10 male rats the treatment diet from the first experiment. After 3 weeks, the rats were anesthetized (2 rats/d) and the ductus thoracicus was cannulated for 1 h. The animals were then killed and the small intestine

ligatured and removed. The intestinal mucosa and contents were sampled separately. Lymph was collected. The intestinal mucosa and contents and lymph were analyzed for lipid content as were fecal samples over the previous week by TLC.

The free fatty acids concentration in the intestinal contents was < 5%, with larger amounts in the feces (30%). The authors stated that these findings suggested that hydrolysis of *Simmondsia Chinensis* (Jojoba) Seed Oil must have continued in the gut beyond the small intestine, possibly by bacteria. Table 11 gives the analysis of the fatty acids and fatty alcohols chain length and saturation found as a function of location (Verschuren and Nugteren 1989).

Simmondsia Chinensis (Jojoba) Seed Wax

Yaron et al. (1980) determined the absorption and distribution of *Simmondsia Chinensis* (Jojoba) Seed Wax (described as the semisolid fraction of *Simmondsia Chinensis* (Jojoba) Seed Oil) using 24 male albino mice (5 weeks old; 25-30 g). The animals were divided equally into 4 groups and [¹⁴C]*Simmondsia Chinensis* (Jojoba) Seed Wax (90 ± 10 mg; specific activity 1.14 µCi/g) was injected subcutaneously into the right leg of each animal. Randomly labeled *Simmondsia Chinensis* (Jojoba) Seed Wax was obtained by exposure of fruiting branches of the shrub (*S. chinensis*) to ¹⁴CO₂ fluxes. The 4 groups of animals were killed 1, 8, 15, and 23 days after injection, and radioactivity in the testis, skin, carcass, and lipid and aqueous fractions of the brain and liver was counted. The results indicated that only a small fraction of the injected [¹⁴C]*Simmondsia Chinensis* (Jojoba) Seed Wax was absorbed. At day 1 post-injection, most of the [¹⁴C]*Simmondsia Chinensis* (Jojoba) Seed Wax was detected in the carcass and in lipid fractions of the brain and liver. In the brain lipid fraction, the amount decreased from 108 ± 46 µg (day 1) to 9 ± 4 µg (day 23), and, in the liver lipid fraction, from 57 ± 16 µg (day 1) to 15 ± 7 µg (day 23). The amount of [¹⁴C]*Simmondsia Chinensis* (Jojoba) Seed Wax in the carcass (100 ± 4 g) was detected on day 1, but not on day 23.

Table 11. Analysis of the fatty acid content (%), of the semi-synthetic diets containing 9% *Simmondsia Chinensis* (Jojoba) Seed Oil fed to rats and of the lipids extracted from the various components of the digestive system (Verschuren and Nugteren 1989).

Fatty acid/fatty alcohol chain length/saturation	As given in the diet			As measured in the rat		
	Lard/sunflower seed oil	Jojoba Oil	Lymph	Intestinal mucosa	Intestinal content	Feces
14:0	-	-	0.9	0.7	0.5	0.4
16:0	23.0	-	15.4	14.0	6.0	5.2
16:1 (1)	-	-	2.0	1.5	0.4	0.3
18:0	11.5	-	8.3	12.4	7.0	6.7
18:1 (2)	29.0	10/1 ^a	26.3	20.2	15.8	10.2
18:2 (2)	19.0	-	11.2	9.8	5.4	1.5
20:1 (2)	-	71/44 ^a	20.6	20.0	39.4	41.9
20:4 (2)	-	-	1.4	3.6	1.9	9.9
22:1 (2)	-	14/45 ^a	4.4	4.7	11.9	16.2

^a Mean of 2 determinations

In a second experiment, 10 albino mice (5 males, 5 females) were injected subcutaneously with [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax (same dose and specific activity) and killed at intervals after injection. Most of the ^{14}C (>99%) was detected in the carcass. At 8 and 23 days post-injection, the radioactivity TLC profile of carcass lipids indicated that 75% to 83% of the ^{14}C remained in the lipid form in which it had been injected. The remaining ^{14}C was incorporated mainly into neutral lipids, such as triglycerides and fatty acids.

The absorption and distribution of radioactivity from [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax were further evaluated using 21 male albino mice (5 weeks old; 25-30 g). In this study, the specific activity of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax was greater than that used in the preceding 2 experiments. The animals were divided equally into 3 groups, and [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax was injected subcutaneously into the neck at doses of 9, 23, and 120 mg. Animals were killed 8 days after injection. Following the injection of each dose, radioactivity was detected in the liver, brain, testes, lungs, heart, spleen, kidneys, and carcass lipids, but not in the skin or epididymal fat. The greatest counts of radioactivity were frequently detected in the liver, brain, lungs, and carcass lipids. The smallest amount of radioactivity (all organs included) was detected in the animals injected with 9 mg of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax. There were no significant differences between counts of radioactivity in animals injected with 23 mg and those given 120 mg of [^{14}C]Simmondsia Chinensis (Jojoba) Seed Wax (Yaron et al 1980).

Heise et al. (1982) used weanling rats to study the digestibility of Simmondsia Chinensis (Jojoba) Seed Wax. The rats were fed: 1) a standard diet 12% of which was Simmondsia Chinensis (Jojoba)

Seed Wax; 2) standard diet with an equivalent amount in calories to the Simmondsia Chinensis (Jojoba) Seed Wax of corn oil; 3) standard diet with an equivalent amount in calories of medium-chain triglycerides; 4) standard diet with equivalent amount in calories of 1:1 mixture of Simmondsia Chinensis (Jojoba) Seed Wax and corn oil; or 5) standard diet with an equivalent amount in calories of 1:1 mixture of Simmondsia Chinensis (Jojoba) Seed Wax and triglycerides. Digestibility was determined during weeks 2 and 4 with the 30-d growth assay.

Weight gain on the Simmondsia Chinensis (Jojoba) Seed Wax diet was half that of the control groups. The mixed diets had minimal weight reduction compared to controls. Digestibility of Simmondsia Chinensis (Jojoba) Seed Wax was 41%. The fecal matter contained 51% fat in the 12% Simmondsia Chinensis (Jojoba) Seed Wax group; this was the only group in which the carcass fat was not increased above baseline level. The efficiency of energy conversion into tissue was half that of the mixed groups and one-third that of the control diets. Biological nitrogen was decreased; the authors suggest that there was an increased use of dietary protein as energy (Heise et al. 1982).

Yaron et al. (1982b) orally administered ^{14}C -Simmondsia Chinensis (Jojoba) Seed Wax (25% in peanut oil; 10.9 $\mu\text{Ci/g}$; 0.1 ml) to male albino mice (5 weeks old; $n = 20$). After 24 h, 10 of the mice were killed and the absorption and distribution of the radioactivity analyzed. The liver and epididymal fat were analyzed in detail using TLC. The remaining 10 mice were killed and analyzed on day 8 after treatment. The experiment was then repeated. Intestinal absorption and distribution of Simmondsia Chinensis (Jojoba) Seed Wax is shown in Table 12. Radiolabel was distributed among phospholipids, etc. in the liver and epididymal fat as given in Table 13.

Table 12. Distribution of ^{14}C in the body of mice 1 and 8 days after oral administration of ^{14}C -labeled Simmondsia Chinensis (Jojoba) Seed Wax (Yaron et al. 1982b).

Tissue	^{14}C sp act in the tissue (dpm/g wet tissue $\pm$ SE)			
	1 st Run		2 nd Run	
	Day 1	Day 8	Day 1	Day 8
Liver lipids	805 $\pm$ 88	136 $\pm$ 13	1570 $\pm$ 390	776 $\pm$ 280
Heart	2140 $\pm$ 880	980 $\pm$ 78	2080 $\pm$ 328	904 $\pm$ 248
Lungs	Not determined	Not determined	2300 $\pm$ 308	1170 $\pm$ 296
Spleen	2020 $\pm$ 560	685 $\pm$ 82	2300 $\pm$ 404	1180 $\pm$ 330
es	1266 $\pm$ 360	974 $\pm$ 196	1180 $\pm$ 224	772 $\pm$ 150
Kidneys	2964 $\pm$ 674	984 $\pm$ 32	3720 $\pm$ 544	1404 $\pm$ 310
Muscle	1414 $\pm$ 290	1346 $\pm$ 578	1210 $\pm$ 194	882 $\pm$ 136
Epididymal fat	3770 $\pm$ 430	1740 $\pm$ 770	7760 $\pm$ 2160	4460 $\pm$ 1335

Table 13. Radioactivity TLC profile of liver and epididymal fat lipids one day after ingestion of ^{14}C -labeled *Simmondsia Chinensis* (Jojoba) Seed Wax (Yaron et al. 1982b).

R_f	Incorporation of ^{14}C into lipid fraction (%)		Lipid standards
	Liver	Epididymal fat	
0.03	27.0 $\pm$ 3.1	0	Phospholipids and glycolipids
0.08	5.5 $\pm$ 0.5	5.7 $\pm$ 3.2	Cholesterol
0.19	5.5 $\pm$ 3.2	0	Fatty acids
0.31 - 0.35	51.3 $\pm$ 6.8	92.0 $\pm$.02	Triglycerides
0.80	11.6 $\pm$ 3.7	4.3 $\pm$ 4.1	Wax esters and cholesterol esters

Penetration Enhancement

Simmondsia Chinensis (Jojoba) Seed Oil

Schwarz et al. (1996) tested the effectiveness of *Simmondsia Chinensis* (Jojoba) Seed Oil, in the form of submicron particles of oil-in-water emulsion, for the delivery of diclofenac diethylammonium. The emulsion consisted of *Simmondsia Chinensis* (Jojoba) Seed Oil (20%) and diclofenac (diethyl ammonium salt; 1.16%) prepared by a proprietary high pressure homogenization process. Wistar rats ($n = 6$) were anaesthetized and iota-carrageenan (100 μl ; 1%) was injected into the plantar region of a hind paw. The rats were then topically treated with the Jojoba emulsion, a commercial anti-inflammatory cream with the same concentration of diclofenac, or nothing. Edema volume was measured at 0, 0.5, 1, 2, 3, 4, and 6 h. There were no signs of skin irritation observed. Anti-inflammatory activity in the Jojoba emulsion was evident at 1 h. At 3, 4, and 6 h, the edema in the Jojoba emulsion group was less than that of the commercial cream ($p < .05$). The relative activity for the control, commercial cream, and the Jojoba emulsion were $100 \pm 16\%$, $79 \pm 14\%$, and $46 \pm 18\%$. The authors concluded that the jojoba emulsion can be used to deliver moisturizing agents and lipids to the skin in cosmetics.

El laithy and El-Shaboury (2002) found that an emulsion of brij 96 (surfactant), capmul (cosurfactant), and *Simmondsia Chinensis* (Jojoba) Seed Oil with 40% water delivered fluconazole through new born mouse skin in a Franz diffusion cell at a greater rate than gel bases (cetyl palmitate; mixture of glyceryl stearate, cetearyl alcohol cetyl palmitate, and cocoglycerides; glyceryl stearate; and glyceryl monostearate) at 10% and 30%.

Wang et al. (2007) tested the dermal penetration enhancement properties of essential oils and plant oils including *Simmondsia Chinensis* (Jojoba) Seed Oil (10%). The oils were incorporated into microemulsions containing Span and Tween as emulsifying agents and aminophylline (5%). The attenuated total reflection was measured on the forearms ($7 \times 2 \text{ cm}$) of subjects ($n = 6$) before application and 30 and 60 min after application of the emulsion ($\sim 0.3 \text{ g}$). *Simmondsia Chinensis* (Jojoba) Seed Oil increased the permeability of the stratum corneum to aminophylline in comparison with treatment with aminophylline

alone. The hierarchy of penetration enhancement of the plant and essential oils was: *Simmondsia Chinensis* (Jojoba) Seed Oil > peppermint > lilacin = rosemary = corn germ > ylang > olive. The authors concluded that the choice of proper combination of oil phase lipids may allow drug-controlled delivery from a topical oil/water microemulsion.

Shevachman et al. (2008) tested the enhancement of diclofenac sodium by microemulsions of *Simmondsia Chinensis* (Jojoba) Seed Oil/hexanol/Brij 96V/water and compared it with similar microemulsions containing paraffin oil and isopropyl myristate. For comparison, an emulsion with Voltaren Emulgel (a commercial cream containing 1.16% diclofenac diethylammonium, corresponding to 1% diclofenac sodium) was used. The emulsions containing diclofenac sodium (0.5 ml) were applied to the trimmed abdominal area of anesthetized Sprague-Dawley rats in open containers glued to the skin. Blood samples were taken at 1, 2, 4, 6, and 8 h and analyzed for diclofenac. There was similar penetration of diclofenac with the *Simmondsia Chinensis* (Jojoba) Seed Oil emulsion as the commercial cream ($C_{\text{max}} = 0.116 \pm 0.031$ and $0.106 \pm 0.006 \text{ mg/ml}$ and area under the curve = 0.601 ± 0.107 and $0.558 \pm 0.172 \mu\text{g/ml/h}$, respectively). The paraffin oil and isopropyl myristate emulsions had great penetrations ($C_{\text{max}} = 0.962 \pm 0.191$ and $0.845 \pm 0.005 \text{ mg/ml}$ and area under the curve = 4.545 ± 0.615 and $4.067 \pm 0.482 \mu\text{g/ml/h}$, respectively).

In an in vitro study, the abdominal skin of freshly killed rats was clipped, washed, and the subcutaneous fat removed. The skin was installed onto Franz diffusion cells with the stratum corneum facing upwards. Microemulsions or Voltaren Emulgel (0.5 g) were applied to the skin. Samples of the receptor cell were taken periodically. The microemulsions consisted of *Simmondsia Chinensis* (Jojoba) Seed Oil/hexanol at 1:1 wt ratio (60%) and Brij 96 or Tween 60 (40%) with diclofenac sodium (1%) added.

The *Simmondsia Chinensis* (Jojoba) Seed Oil emulsion had lower penetration of diclofenac than did paraffin oil or isopropyl myristate, which were similar. The drug permeability in the *Simmondsia Chinensis* (Jojoba) Seed Oil was higher than the commercial cream, unlike the in vivo test. The authors suggest

that this could be due to the optimal perfusion and hydration of the skin in the diffusion cells compared to the skin in the animal study. The authors concluded that *Simmondsia Chinensis* (Jojoba) Seed Oil did not increase penetration of diclofenac through the skin and seemed to prevent active molecules from being freely diffused into the skin. The authors suggest that the 3-dimensional structure of the oil may result in delaying the diffusion of the drug (Shevachman et al. 2008).

Anti-inflammatory Effects

Jojoba Liquid Wax Habashy et al. (2005) investigated the anti-inflammatory effects of what the authors referred to as jojoba liquid wax in several experiments. In the first experiment, adult male Sprague-Dawley rats were used. The rats were fasted with free access to water for 16 h before treatment. Five groups (n = 6) of rats were treated. Groups I and II were administered saline by intubation; Groups III and IV were administered jojoba liquid wax (5 ml/kg (~4.35g) or 10 ml/kg (~8.7 g), respectively); and Group V was administered indomethacin (a standard anti-inflammatory drug; 10 ml/kg). Thirty min later, Group I was administered saline (0.05 ml) and Groups II through V were administered carrageenin (0.05 ml; 1% in saline) subcutaneously on the plantar surface of the right hind paw. The volume of the paw was immediately measured by water displacement and again 3 h later.

The right hind paws were removed after killing the rats. The eicosanoid-containing fluid was removed with the use of 10 μ M indomethacin in 0.1 ml saline.

The carrageenin injection resulted in severe inflammation and increase in mean volume of the paw (162.3%) compared to untreated paws. Pretreatment with jojoba liquid wax at both doses (5 or 10 ml/kg) inhibited the carrageenin-induced increase in edema volume by 26.4% and 34%, respectively. Indomethacin treatment reduced inflammation by 43.4%.

Carrageenin injection resulted in a 5-fold increase in prostaglandin E_2 (PGE_2) concentration in Group II compared to the untreated Group I. Jojoba liquid wax reduced the PGE_2 concentration by 58.15% and 77.4%, respectively. The 10 ml/kg dose of jojoba liquid wax and the indomethacin lowered the PGE_2 to almost normal levels.

The authors conducted a chick's embryo chorioallantoic membrane (CAM) test. Fertile chicken eggs were incubated for 8 d then divided into 4 groups (n = 6). Filter paper discs (10 mm in diameter) were placed on the surface of the CAM after opening the shells with a dental drill. The shell pieces were replaced and sealed with paraffin wax. The filter paper in Group I was not treated (control); Groups II and III were treated with jojoba liquid wax (3.5 (~3.05 mg; 30%) and 7 μ l (~6.1 mg; 50%), respectively) in saline. Group IV was treated with indomethacin (2.5 μ g). The eggs were incubated for 4 d and opened by cutting the shells circumferentially along the longer perimeter. CAM membranes were eased out of the shell and the disc (with any adhering or infiltrating granulation tissue) were cut with fine scissors. The discs and tissue were dried overnight and weighed individually.

The administration of jojoba liquid wax at 30% and 50% decreased the granulation tissue weight by 15.8% and 38%, respectively, compared to the control.

The authors induced ear edema in rats to assess the effects of jojoba liquid wax. Five groups of rats (n = 6) were treated topically: Group I was treated with solvent; Group II was treated with irritant (4 parts croton oil, 10 parts ethanol, 20 parts pyridine, 66 parts ethyl ether) and solvent; Groups III and IV were treated with irritant, jojoba liquid wax (30% or 50%, respectively), and solvent; and Group V was treated with irritant, solvent, and indomethacin (12.5% w/v). Each solution was administered in a volume of 20 μ l on both sides of the right ear. The left ear was left untreated and served as the control. One h after treatment, the right ears were treated again (Group I, solvent; Groups II through V croton oil solution). After 4 h, the rats were killed. An 8-mm cork borer was used to punch a disc out of each ear; the discs were weighed immediately.

The entire ear was homogenized in buffer and centrifuged and used to calculate myeloperoxidase (MPO) activity. Protein content was determined. Representative ear tissue was fixed, embedded, and sectioned for microscopic examination regarding leukocytic infiltration, edema, and extravasations.

Application of croton oil caused the ear disc to increase in size by 216% over the control. Pretreatment with jojoba liquid wax (30% and 50%) reduced the increase by 28% and 43.6%, respectively. MPO activity in ears treated with croton oil increased 83-fold. Pretreatment with jojoba liquid wax decreased MPO activity by 29% (p < .05) and 53.3% (p < .05), respectively, compared to ears not treated with jojoba liquid wax. Indomethacin treatment reduced MPO activity (p < .05). Ears treated with croton oil and no jojoba liquid wax had massive neutrophil infiltration with extraversion of red blood cells as well as edema in the dermal layer. Ears treated with jojoba liquid wax had less neutrophil infiltration and less hyperemia in a dose dependent manner.

The authors divided 30 rats into 5 groups (n = 6) and injected each of them with 20 ml sterile air in the suprascapular area of the back. Three days later, the pouches were re-inflated with 10 ml sterile air. After another 3 days, lipopolysaccharide from *E. coli* serotype 0111:B4 (LPS; 100 μ g/ml) in physiological saline (1 ml/kg) was injected into the air-formed pouches of Groups II through V.

Group I was administered only saline. The rats were treated 30 min later: Groups I and II were administered only saline; Groups III and IV were administered jojoba liquid wax (5 and 10 mg/kg, respectively); and Group V was administered indomethacin (10 mg/kg). Eight h later, the pouches were lavaged using 1 ml sterile physiological saline. The lavage fluid was centrifuged and analyzed for nitric oxide (NO) and tumor necrosis factor- α (TNF- α).

The air pouch caused a 60-fold increase of NO production compared to untreated animals. Jojoba liquid wax injection at 5 and 10 ml/kg reduced NO levels by 31.4% (p < .05) and 32.8% (p < .05), respectively, compared to Group II. Indomethacin

lowered NO levels by 36.6% ($p < .05$). There was an 8-fold increase in TNF- α levels compared to untreated animals. Jojoba liquid wax treatment at 5 and 10 ml/kg lowered TNF- α levels by 62.2% ($p < .05$) and 75.8% ($p < .05$), respectively. Jojoba liquid wax (at 30% and 50%) reduced MPO activity by 29% and 53.3%, respectively.

The authors concluded that jojoba liquid wax exerted anti-inflammatory activity in several animal models; jojoba liquid wax combats inflammation via multilevel regulation of inflammatory mediators (Habashy et al. 2005).

Blood Cholesterol Effects

The effects of ingested *Simmondsia Chinensis* (Jojoba) Seed Oil on blood cholesterol concentrations were evaluated using 4 groups of female New Zealand white rabbits (4 months old; $n = 4$). The following diets (100 g of chow per diet) were provided daily for 30 days: (group 1) chow supplemented with 2% *Simmondsia Chinensis* (Jojoba) Seed Oil, (group 2) chow containing 1% cholesterol and 2% *Simmondsia Chinensis* (Jojoba) Seed Oil, (group 3) chow containing 1% cholesterol supplemented with 6% *Simmondsia Chinensis* (Jojoba) Seed Oil, (group 4) chow supplemented with 1% cholesterol (cholesterol control), and (group 5) untreated chow (negative control). Uneaten chow was discarded each day. The study was repeated using different groups of rabbits. Blood cholesterol concentrations were slightly increased in rabbits fed a cholesterol-free diet containing 2% *Simmondsia Chinensis* (Jojoba) Seed Oil. Rabbits fed an atherogenic diet consisting of 1% cholesterol and 2% *Simmondsia Chinensis* (Jojoba) Seed Oil had a 40% decrease in blood cholesterol over that of the cholesterol control. There was no further decrease in blood cholesterol concentrations in rabbits fed a diet containing 1% cholesterol and 6% *Simmondsia Chinensis* (Jojoba) Seed Oil for an additional 30-day period (Clarke and Yermanos 1981).

Miscellaneous Studies

Simmondsia Chinensis (Jojoba) Seed Oil

Week and Sevigne (1949a) reported that *Simmondsia Chinensis* (Jojoba) Seed Oil contains factors inhibiting the hydrolysis of vitamin A esters in chicks.

Week and Sevigne (1949b) reported that *Simmondsia Chinensis* (Jojoba) Seed Oil contains factors inhibiting the hydrolysis of vitamin A esters in rats to a greater extent than corn oil.

Acute Animal Oral Toxicity

Simmondsia Chinensis (Jojoba) Seed Oil

The oral toxicity of crude *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 80 5-week-old, dd Y-S mice. The average weights of 40 male and 40 female mice were 22.5 and 21.3 g, respectively. The animals were divided equally into 4 groups (10 males, 10 females/group), and *Simmondsia Chinensis*

(Jojoba) Seed Oil was administered via gastric intubation at a single dose of 0.5, 0.75, 1.13, or 1.69 ml/10 g of body weight. Feed was withheld 6 h prior to intubation. At 7 d post-administration, the animals were killed and necropsied. Peritonitis was observed in 1 animal dosed with 1.69 ml/10 g, and discoloration of the renal capsule was observed among all groups. None of the gross alterations observed, including the single death, were attributed to the administration of *Simmondsia Chinensis* (Jojoba) Seed Oil. The actual causes of these deaths were not reported (Taguchi and Kunitomo 1977).

Following the administration of a single dose of *Simmondsia Chinensis* (Jojoba) Seed Oil (21.5 ml/kg) to male albino rats (number and weights not stated), fewer than 50% of the animals died (Wisniak 1977).

The acute oral toxicity of a lip balm product containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 10 Sprague-Dawley rats (5 males, 5 females; weights not stated). A single oral dose (5.0 g/kg) was administered to each animal via gavage. The animals were fasted during the night prior to dosing. None of the animals died during the 15-day observation period, and the product was classified as nontoxic (CTFA 1985a).

Simmondsia Chinensis (Jojoba) Seed Wax

The acute oral toxicity of a 50.0% solution of *Simmondsia Chinensis* (Jojoba) Seed Wax in corn oil (dose = 5.0 g/kg) was evaluated according to the procedure described above using 10 albino Sprague-Dawley rats (5 males, 5 females; 200-300 g). The only procedural variation was a 4-day observation period after dosing. *Simmondsia Chinensis* (Jojoba) Seed Wax was not classified as a toxic substance. Neither the mortality rate nor the results of macroscopic examinations were reported (Reinhardt and Brown 1990).

Jojoba Esters

Leberco Testing, Inc. (1988a) orally administered a single dose of Jojoba Esters 15 (5 g/kg) to white rats ($n = 10$; 5 male, 5 female) after 18 h of fasting as described in the Federal Hazardous Substances Act (Consumer Product Safety Commission 2007). The rats were observed for signs of toxicity for 14 d then necropsied. All the rats survived. There were no signs of toxicity.

Leberco Testing, Inc. (1988b) orally administered a single dose of Jojoba Esters 30 (5 g/kg) to white rats ($n = 10$; 5 male, 5 female) after 18 h of fasting. The rats were observed for signs of toxicity for 14 d then necropsied. All rats survived and there were no signs of toxicity.

Leberco Testing, Inc. (1988c) orally administered a single dose of Jojoba Esters 60 (5 g/kg) to white rats ($n = 10$; 5 male, 5 female) after 18 h of fasting. The rats were observed for signs of toxicity for 14 d then necropsied. All the rats survived. There were no signs of toxicity.

Leberco Testing, Inc. (1988d) orally administered a single dose of Jojoba Esters 70 (5 g/kg; 50% in corn oil) to albino Sprague Dawley rats (n = 10; 5 male, 5 female) after 18 h of fasting. The rats were observed for signs of toxicity for 14 d then necropsied. All the rats survived. There were no signs of toxicity.

In another study, the acute oral toxicity of 2 Jojoba Esters (iodine values 40 and 60) was evaluated using 2 groups of 10 white rats (5 males, 5 females per group). Animal weights ranged from 208 to 238 g in one group and from 212 to 238 g in the other group. Feed was withheld for 18 h, and the test substance (dose = 5.0 g/kg) was administered via a rigid stomach tube. The animals were then observed for signs of toxicity during a period of 14 days; all of the animals survived. At the conclusion of the observation period, the animals were killed and internal organs examined macroscopically. No gross abnormalities were observed in either test group (Reinhardt and Brown 1990).

Jojoba Alcohol

The acute oral toxicity of Jojoba Alcohol was evaluated using 3 groups of 20 mice of the dd Y-S strain (weights not stated). The test substance was administered via stomach tube to the 3 groups at doses of 32, 40, and 50 ml/kg, respectively. None of the animals in any of the 3 groups died (Taguchi no date).

Short-term Oral Toxicity

Simmondsia Chinensis (Jojoba) Seed Oil

The oral toxicity of refined *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 4 groups of 10 male Sprague-Dawley rats (avg. weight 80.6 g). Two of the groups were fed basal diets (5 g/feeding) containing 0.5 or 1.0 g of *Simmondsia Chinensis* (Jojoba) Seed Oil once daily for 7 days. The remaining 2 groups were fed basal diets containing 2.0 or 3.0 g of *Simmondsia Chinensis* (Jojoba) Seed Oil once daily for 4 d. The animals were given water ad libitum. Signs of toxicity were observed in 5 of the rats that were fed 1.0 g of *Simmondsia Chinensis* (Jojoba) Seed Oil (in diet) and all of the rats fed 2.0 and 3.0 g of *Simmondsia Chinensis* (Jojoba) Seed Oil. The mortality rate was 10% in each of these 3 groups. None of the rats fed 0.5 g of Jojoba Oil died (Hamm 1984).

Verschuren (1989) fed *Simmondsia Chinensis* (Jojoba) Seed Oil to male and female SPF Wistar rats (6 weeks old at acclimation) for 4 weeks. The rats were fed a purified diet with *Simmondsia Chinensis* (Jojoba) Seed Oil at 0 (n = 12), 2.2% (n = 10), 4.5% (n = 10), and 9% (n = 12). After 6 d on the diet, 2 of each sex in the control and high dose groups were killed and the hearts examined for fat deposition. After 3 weeks on the diet, blood was collected and analyzed. After 4 weeks on the diet, the feces were sampled and analyzed for lipid content. At the end of the experiment, the rats were killed and necropsied, blood collected and analyzed, and tissues were histologically examined.

No deaths occurred during the experiment. All the rats appeared to be in good health and no clinical signs were observed. There

was a dose-dependent growth retardation in both sexes. Feed intake and water consumption did not differ between the groups. The amount of feces produced increased with *Simmondsia Chinensis* (Jojoba) Seed Oil intake. The lipid content of the feces had a dose-dependent increase (up to > 6-fold). There were no hematological differences except for the white blood cell count which increased in the high dose group in both males (13.6 ± 0.67 vs 16.9 ± 1.02) and females (13.7 ± 0.90 vs 21.0 ± 2.03). Serum analysis showed an increase enzyme activities (isocitrate dehydrogenase [ICDH], saccharopine dehydrogenase [SDH], alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], hydroxybutyrate dehydrogenase [α -HBDH], and creatine kinase [CK]). Urea concentrations increased in a dose dependent manner. A negative correlation was found for creatine and triacylglycerols and dose levels.

Animals fed *Simmondsia Chinensis* (Jojoba) Seed Oil had less body fat deposition. Absolute weights of the organs decreased for both sexes except for the spleen in the females. There was no evident adverse effect to the heart after 6 d of the *Simmondsia Chinensis* (Jojoba) Seed Oil diet. The stomachs of the rats fed *Simmondsia Chinensis* (Jojoba) Seed Oil were much fuller compared to the controls. The small intestines were distended and the contents were more fluid and non-homogenous compared to controls. The contents of the cecum were coarse and heterogenous compared to controls. The jejunum and ileum of the treatment groups were characterized by massive vacuolization of the enterocytes, distension of the lamina propria, and an increase in cellular components. There was increased cell turnover in the crypts of Lieberkuhn.

In a second experiment, 2 groups of rats (n = 5) were fed the diet with either 0 or 9% *Simmondsia Chinensis* (Jojoba) Seed Oil. After 3 weeks, the rats were killed and the small intestine removed and examined. The entire small intestine was affected except the anterior section of the duodenum and the posterior section of the ileum. There was an accumulation of fat in the vacuoles of the enterocytes in the upper region of the villi. The ALP activity was decreased. In the livers, there was a slight increase in intracellular acidophilic vacuoles, acidophilic bodies, and the number of mitoses (Verschuren 1989).

Dermal

Jojoba Alcohol

Taguchi (no date) evaluated the dermal toxicity potential of Jojoba Alcohol using 10 white male rabbits. Jojoba Alcohol was tested at concentrations of 12.5, 25.0, and 50.0% (in refined *Simmondsia Chinensis* (Jojoba) Seed Oil). Oleyl alcohol, also tested at concentrations of 12.5, 25.0, and 50.0% (in refined *Simmondsia Chinensis* (Jojoba) Seed Oil), served as the control.

In 15- and 30-day tests, there were no reactions to 12.5% Jojoba Alcohol that were grossly visible. However, the results of

microscopic examinations were that reactions ranged from very light to light incrustation of the germinative zone of the epidermis in 4 rabbits (15-day test), and reactions ranging from very light to medium incrustation of the germinative zone and very light to light dermal infiltration in 4 rabbits (30-day test). Also, in the 15-day test, 25.0% Jojoba Alcohol induced redness (2 rabbits), and redness and induration (1 rabbit); 50.0% Jojoba Alcohol induced redness (1 rabbit), redness and induration (2 rabbits), and redness, induration, and swelling (1 rabbit). In the 30-day test, 25.0% Jojoba Alcohol induced redness (2 rabbits); 50.0% Jojoba Alcohol induced redness (2 rabbits) and redness, induration, and swelling (2 rabbits). Histopathological evaluations in both the 15- and 30-day tests were negative for any reactions that were more severe than light incrustation of the germinative zone of the epidermis or very light dermal infiltration (Taguchi no date).

Subcutaneous

Simmondsia Chinensis (Jojoba) Seed Wax

The subcutaneous toxicity of *Simmondsia Chinensis* (Jojoba) Seed Wax was evaluated using 3 groups of 6-week-old male rats (10 rats/group). The 2 experimental groups received subcutaneous injections of *Simmondsia Chinensis* (Jojoba) Seed Wax (1 ml/kg of body weight) 6 days per week for 7 weeks. Refined olive oil was administered to the control group according to the same procedure. At the end of the seventh week, 10 experimental animals and 5 controls were killed. The remaining animals were killed 6 weeks later. Urine tests, blood tests, and gross and microscopic examinations were performed. There were no traces of bilirubin, ketones, glucose, or urobilinogen in the urine of any of the tested animals. Occult blood was detected in the urine of 7 experimental animals and 5 controls. Additionally all experimental animals and 5 controls had proteinuria. The urinary protein could have resulted from the contamination of urine with traces of feed. Most of the results from blood chemistry and blood cell analyses were similar in experimental and control groups. Except for a slight increase in liver weight relative to the increase in body weight (experimental animals), there were no significant differences in body weight or organ weight between experimental and control groups. Microscopic changes were not observed in the skin or in any of the other organs examined (Yaron et al 1982b).

Subchronic Dermal Toxicity

Simmondsia Chinensis (Jojoba) Seed Wax

The subchronic dermal toxicity of refined *Simmondsia Chinensis* (Jojoba) Seed Wax was evaluated using 32 DH guinea pigs (320 ± 25 g). The animals were divided into 4 groups (4 males, 4 females/group). In the first 2 groups, *Simmondsia Chinensis* (Jojoba) Seed Wax was applied to shaved dorsal skin in doses of 0.25 and 0.5 g/kg, respectively. Applications were made 6 days per week for a total of 20 weeks. The application sites were not covered. The 2 control groups received applications of olive oil (0.5 g/kg) and saline, respectively, according to the same

procedure. At the end of the treatment period, the animals were killed and gross and microscopic examinations were performed. There were no differences in body weights or organ weights (liver, heart, kidneys, and testes) between the 4 groups of guinea pigs. Furthermore, lesions were not observed in tissues from the following organs (all groups): adrenal gland, thyroid gland, kidney, urinary bladder, spleen, liver, pancreas, heart, brain (2 sections), stomach, small and large intestine, and skin from treated and untreated areas (Yaron et al. 1982a).

Chronic Toxicity

No chronic toxicity data were available.

Dermal Irritation and Sensitization

Jojoba Alcohol

The primary skin irritation potential of Jojoba Alcohol (10.0% w/w in refined *Simmondsia Chinensis* (Jojoba) Seed Oil) was evaluated using 10 male and 10 female albino marmots with the Draize test (Taguchi no date). The test substance (0.5 ml) was applied, under a one-inch patch secured with adhesive tape, to each animal. The animals were immobilized in an animal holder, and the entire trunk of each animal was wrapped with rubberized cloth that remained throughout the 24 h exposure period. Reactions were scored at 24 and 48 h post-application according to the scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation); 0 (no edema) to 4 (severe edema). Reactions to the test substance were not observed in any of the animals tested.

The skin sensitization potential of Jojoba Alcohol (10.0% w/w in refined *Simmondsia Chinensis* (Jojoba) Seed Oil) was evaluated according to the maximization test using 10 male and 10 female albino marmots. Two groups of male and female marmots (10 animals per sex) served as the untreated controls. Initially, each of the following substances (0.05 ml) was injected at different paired sites, to the right and left of the midline, on the back of each animal: complete adjuvant/water (1/1 mixture), Jojoba Alcohol solution, and complete adjuvant/Jojoba Alcohol solution (1/1 mixture). The Jojoba Alcohol solution consisted of Jojoba Alcohol dissolved in refined *Simmondsia Chinensis* (Jojoba) Seed Oil (1/10 mixture). After 1 week, patches containing the 10.0% Jojoba Alcohol solution (0.5 ml) were applied to the same injection sites. Two weeks later (challenge phase), a patch containing the solution was applied to a new site that was posterior to the injection sites. No sensitization reactions were observed 24 or 48 h after application of the challenge patch.

In an additional study connected with the SHORT-TERM TOXICITY study above, the dermal irritation potential of Jojoba Alcohol (12.5, 25.0, and 50.0%; in refined *Simmondsia Chinensis* (Jojoba) Seed Oil) using white male rabbits (n = 10) was tested. Each animal was simultaneously patch tested (6 patches per animal) with the 3 concentrations of both the test substance and control; patches were applied to the back. The 2 repeated patch

tests performed involved 15 days of patch testing (5 rabbits) and 30 days of continuous patch testing (5 rabbits), respectively. Naked eye observations of reactions were made, according to the method of Draize, on the last day of each test.

The average skin irritation scores during the 15-day test were as follows: 12.5% Jojoba Alcohol (no reactions), 25.0% Jojoba Alcohol (0.2-0.8), and 50.0% Jojoba Alcohol (0.4-1.80). During the 30-day skin irritation test, the average skin irritation scores were as follows: 12.5% Jojoba Alcohol (0.5), 25.0% Jojoba Alcohol (0.2 to 1.0), and 50.0% Jojoba Alcohol (0.6 to 1.25). The results of skin irritation tests on 12.5, 25.0, and 50.0% Jojoba Alcohol were not considered different from those for the controls, 12.5, 25.0, and 50.0% oleyl alcohol (Taguchi no date).

Simmondsia Chinensis (Jojoba) Seed Oil

The skin irritation potential of refined *Simmondsia Chinensis* (Jojoba) Seed Oil (100%) was evaluated using 10 male albino guinea pigs (weights = 350 g; strain not stated). Olive oil and light liquid paraffin served as controls. Half of the animals were simultaneously patch tested with *Simmondsia Chinensis* (Jojoba) Seed Oil (0.5 ml) and each control (0.5 ml) daily for 15 days. Applications were made to shaved skin. The remaining animals were patch tested (same procedure) daily for 30 days. Reactions were scored according to the Draize scale: 0 (no erythema or edema) to 4 (severe erythema to slight eschar formation, and edema). No significant reactions to *Simmondsia Chinensis* (Jojoba) Seed Oil or olive oil were observed. However, flare reactions to liquid paraffin were observed on the third day of the study. The results of microscopic examinations indicated no edema or cellular infiltration. However, swelling of the epidermis and hypertrophy at the roots of hairs were evident in all groups. Swelling of the epidermis may have been due, in part, to the shaving of application sites (Taguchi and Kunimoto 1977).

The skin irritation potential of a lip balm product containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 6 New Zealand white rabbits. A single 24 h application of the test substance (0.5 ml) was made to abraded and intact skin of the back. The test sites were covered with occlusive patches during the 24-h period. At 24 and 72 h post-application, reactions (erythema and edema) were scored according to the Draize scale: 0 to 4. The product was considered minimally irritating (mean primary irritation score = 0.33) (CTFA 1985b).

Simmondsia Chinensis (Jojoba) Seed Wax

The preceding experimental procedure was used to evaluate the skin irritation potential of *Simmondsia Chinensis* (Jojoba) Seed Wax (100%) in 6 albino rabbits (ages not stated). Positive skin irritation reactions were defined as primary irritation scores of 5 or greater. The mean primary irritation score for *Simmondsia Chinensis* (Jojoba) Seed Wax was 0.17 (Reinhardt and Brown 1990).

Jojoba Esters

Leberco Testing, Inc. (1988e) applied Jojoba Esters 15 to the

intact and abraded skin of albino rabbits (n = 6). The rabbits were clipped of 10% their body hair; half of the exposed skin area was left intact and the other half was abraded so to penetrate the stratum corneum but not disturb the dermis. The Jojoba Esters 15 (0.5 ml) were applied to both sides of the exposed skin which were covered with a patch and polyethylene for 24 h. The sites were examined upon unwrapping and 48 h later. There was erythema for all the rabbits at the first reading and only 2 at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 1.08.

Leberco Testing, Inc. (1988f) repeated the experiment with Jojoba Esters 30. There was erythema formation for all the rabbits at the first reading and only 2 at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 0.42.

Leberco Testing, Inc. (1988g) repeated the experiment with Jojoba Esters 60. There was erythema formation for all the rabbits at the first reading and only 2 at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 1.08.

Leberco Testing, Inc. (1988h) repeated the experiment with Jojoba Esters 70. There was erythema formation on 2 the rabbits at the first reading (1 on just intact skin and the other on both intact and abraded skin) and none at the second reading but no edema formation. A score of ≥ 5 would indicate a positive irritant. The authors reported a mean score of 0.17.

The skin irritation potential of 2 Jojoba Esters (iodine values = 40 and 60) was evaluated using 2 groups of 6 albino rabbits (ages not stated). Prior to application of the test substance, 10.0% of the body area of each animal was clipped free of hair. The test substance (0.5 ml) was applied to abraded and intact skin sites on the back. The Esters were applied as received. The application sites (abraded and intact) were covered with a 1 x 2 inch patch that was sealed with transparent tape. The entire treatment area was also wrapped with a sheet of polyethylene that was secured with tape. At 24 h post-application, the patches were removed and excess test material was wiped from each test site. Reactions were then scored at 24 and 72 h post-application according to the scales: 0 (no erythema) to 4 (severe erythema to eschar formation) and 0 (no edema) to 4 (severe edema). Primary irritation scores of 5 or greater were defined as positive skin irritation reactions. The mean primary irritation scores for the 2 esters were 0.42 and 1.08, respectively (Leberco Testing, Inc. 1988h).

Hydrolyzed Jojoba Esters

Celsis Laboratory Group (1999a) performed an in vitro Dermal Irritation test, which looks at changes in a biomembrane barrier to predict in vivo effects, on a sample of a mixture of Hydrolyzed Jojoba Esters and water (20:80 wt.%). The sample was found to be non-irritating at volumes of 25 to 125 μ l. The researchers note that the pH of this sample was above the optimum range for the Irritation Assay System, thus there is a slight potential for irritation underestimation.

Simmondsia Chinensis (Jojoba) Butter

Brown (1984) evaluated the skin irritation potential of Jojobutter-51 using 6 male New Zealand white rabbits (2.3-3.0 kg). The test substance (0.5 ml, acid value = 2.8) was applied via gauze patches to abraded and intact sites (clipped free of hair) lateral to the midline of the back. The trunk of each animal was then wrapped with occlusive patches of polyethylene; patches and polyethylene coverings were secured with hypoallergenic tape for 24 h. Immediately after patch removal, excess test material was wiped from the skin with gauze. Reactions were scored at 24 and 72 h post-application according to the Draize scale: 0 (no erythema or edema) to 4 (severe erythema to slight eschar formation, and edema). At 24 h post-application, the following reactions were observed: no erythema (2 rabbits), very slight erythema (2 rabbits), and well-defined erythema (2 rabbits). Jojobutter-51 (acid value = 2.8) was classified as a mild irritant (Primary Irritation Index = 0.5). When samples of Jojobutter-51 with a reduced acid value (1.6) were applied to an additional 6 rabbits according to the same procedure, erythema was not observed. However, slight edema was observed at the abraded site of 1 rabbit at 24 h post-application. Jojobutter (acid value = 1.6) was classified as a nonirritant (Primary Irritation Index = 0.04).

Ocular IrritationSimmondsia Chinensis (Jojoba) Seed Oil

The ocular irritation potential of refined *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 6 male white rabbits. Immediately after the oil (0.1 ml) was instilled into the conjunctival sac of the right eye of each animal, slight atretoblepharia was observed. Slight conjunctival hyperemia was observed 1 h after instillation. Ocular irritation did not increase in severity, and all reactions had cleared by 24 h post-instillation (Taguchi and Kunimoto 1977).

The ocular irritation potential of a lip balm product containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 6 New Zealand white rabbits. The test substance (0.1 ml) was instilled once into the conjunctival sac of one eye. The untreated eye served as the control. Reactions were scored at 24, 48, and 72 h post-instillation according to the Draize scale. At 24 h post-instillation, the mean ocular irritation score was 0.3 ± 0.8 . No reactions were observed at 48 and 72 h. The product was classified as a nonirritant (CTFA 1985c).

Simmondsia Chinensis (Jojoba) Seed Wax

Reinhardt and Brown (1990) evaluated the ocular irritation potential of *Simmondsia Chinensis* (Jojoba) Seed Wax in 6 albino rabbits (ages not stated). The only procedural variation was the instillation of 0.05 ml of test substance. The following reactions were observed in 3 of the 6 rabbits tested: conjunctival chemosis, obvious swelling with partial eversion of lids (1 rabbit), and conjunctival redness, diffuse crimson red conjunctiva in which individual vessels were not discernible (2 rabbits). As the test ingredient did not produce a positive reaction in 4 or more test animals, it was not classified as an eye irritant.

Hydrolyzed Jojoba Esters

Celsis Laboratory Group (1999b) reported that a mixture of Hydrolyzed Jojoba Esters and water (20:80 wt.%) was non-irritating in a chorioallantoic membrane vascular assay for possible eye irritation. No further details were provided.

Jojoba Esters

Leberco Testing, Inc. (1988i) administered Jojoba Esters 15 (0.1 ml) to the right conjunctival sac of albino rabbits (n = 6). The left eye served as the control. The eyes were examined at 24, 48, and 72 h. Four of the treated eyes showed redness of the conjunctivae at 24 h that was resolved by 48 h. The authors concluded that Jojoba Esters 15 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

Leberco Testing, Inc. (1988j) repeated the experiment with Jojoba Esters 30 (0.1 ml). One of the treated eyes showed redness of the conjunctivae at 24 h that was resolved by 48 h. The authors concluded that Jojoba Esters 30 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

Leberco Testing, Inc. (1988k) repeated the experiment with Jojoba Esters 60 (0.1 ml). Four of the treated eyes showed redness of the conjunctivae at 24 h that was resolved by 48 h. The authors concluded that Jojoba Esters 60 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

Leberco Testing, Inc. (1988l) repeated the experiment with Jojoba Esters 70 (0.05 ml). Two of the treated eyes showed redness of the conjunctivae at 24 h that was resolved by 48 h. One of the treated eyes exhibited chemosis (swelling above normal) at 24 h that was resolved at 48 h. The authors concluded that Jojoba Esters 70 did not produce a positive reaction in 4 or more of the test rabbits so the test material was not classified as an eye irritant.

The ocular irritation potential of 2 Jojoba esters (iodine values 40 and 60, respectively) was evaluated using 2 groups of 6 albino rabbits (ages not stated) (Reinhardt and Brown 1990). The test substance (0.1 ml) was instilled, as received, into the right eye of each animal. Untreated eyes served as controls. Reactions were scored at 24, 48, and 72 h post-instillation according to the following scales: corneal opacity scores of 0 (no ulceration or opacity) to 4 (complete corneal opacity, iris not discernible); scores for the iris of 0 (normal) to 2 (no reaction to light, hemorrhage, gross destruction; any or all of these); conjunctival redness scores of 0 (vessels normal) to 3 (diffuse, beefy red); conjunctival chemosis scores of 0 (no swelling of the lids and/or nictitating membrane) to 4 (swelling with lids more than half closed); conjunctival discharge scores of 0 (no discharge) to 3 (discharge with moistening of the lids and hairs, and considerable area around the eye). Test results were classified as positive only if 4 or more animals had positive reactions in the cornea, iris, and conjunctiva and negative if only 1 animal had positive reactions in the cornea, iris or conjunctiva.

Of the 2 groups of rabbits tested, 1 of 6 had a reaction to one of

the esters (iodine value = 60) and 4 of 6 had reactions to the other ester (iodine value = 30). All of the reactions were classified as conjunctival redness (diffuse, crimson red; individual vessels not easily discernable). As the test ingredient did not produce a positive reaction in 4 or more test animals, it would not be classified as an eye irritant (Reinhardt and Brown 1990).

Leberco Testing, Inc. (1994a) performed the Eytex test on a sample of Jojoba Esters 15. The test substance was rated minimal for irritation level at 20 to 100 µl.

Leberco Testing, Inc. (1995a) performed the Eytex test on a sample of Jojoba Esters 20. The test substance was rated minimal for irritation level at 10 to 100 µl.

Leberco Testing, Inc. (1994b) performed the Eytex test on a sample of Jojoba Esters 30 (dose not provided). The test substance was rated minimal for irritation level.

Jojoba Mixtures

Leberco.Celsis Testing (1997) tested for the possibility of ocular irritation by a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (approximate weight % 35:35:30:0.1) using the chorioallantoic membrane vascular assay. The mixture (100%; 40 µl) did not cause slight/moderate hemorrhage, capillary injection, ghost vessels, or other abnormalities in 6 eggs after 30 min of contact time. The researchers concluded that this mixture was nonirritating.

Jojoba Alcohol

The ocular irritation potential of 12.5%, 25.0%, and 50% Jojoba Alcohol (in refined *Simmondsia Chinensis* (Jojoba) Seed Oil) was evaluated using 3 groups of 3 rabbits, respectively, according to the procedure by Draize. The test substance (0.05 ml) was instilled into the conjunctival sac of the right eye of each animal, and the untreated left eye served as the control. There were no reactions in the cornea or iris in any of the animals tested. Reactions in the conjunctiva were observed, but not beyond 24 h post-instillation. At concentrations of 12.5% and 50.0% Jojoba Alcohol, conjunctival reactions decreased in severity from Draize scores of 1.3 to 0.7 and from Draize scores of 4.0 to 0.7, respectively, up to 24 h post-instillation. At a concentration of 25.0%, reactions with a Draize score of 2 persisted up to 6 h post-instillation (Taguchi no date).

Comedogenicity

Simmondsia Chinensis (Jojoba) Seed Wax

Bio-Technics Laboratories, Inc. (1990a) evaluated the comedogenicity of *Simmondsia Chinensis* (Jojoba) Seed Wax. The comedogenicity score was 2.67, classifying the test substance as moderately comedogenic.

Jojoba Esters

Bio-Technics Laboratories, Inc. (1990b) evaluated the comedogenicity of a Jojoba Ester (iodine value = 60) using 4 young adult New Zealand white rabbits. Three animals were treated with the test substance and 1 animal was treated with the positive control, isopropyl myristate. The test substance (5 ml)

was added to 45 ml of mineral oil, and the solution was heated to a temperature of 70°C. Liberal applications of the test solution were made to the right external ear canal via a cotton-tipped applicator 5 days per week (once per day) for a total of 14 applications. After each application, the solution was rubbed into the skin with a glass rod. The untreated left ear served as the negative control. At the end of the application period, the animals were killed and treated and untreated external ears were removed, fixed in 10.0% buffered formalin, and evaluated histopathologically. Comedone formation was graded according to the scale: 0 (negative) to 5 (severe: widely dilated follicles filled with packed keratin, follicular epithelial hyperplasia causing partial or total involution of sebaceous glands and ducts; possible inflammatory changes). The test solution was noncomedogenic (score = 0), whereas, the positive control caused marked superficial acanthosis and hyperkeratosis.

Bio-Technics Laboratories, Inc. (1990c) evaluated another Jojoba Ester (iodine value = 40) according to the same procedure. The comedogenicity score was 0.65, classifying the test substance as between non-comedogenic and slightly comedogenic.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No reproductive or developmental toxicity data were available.

GENOTOXICITY

Simmondsia Chinensis (Jojoba) Butter

The Ames test was used to evaluate the mutagenicity of 2 samples of Jojobutter-51 in strains TA97, TA98, TA100, and TA102 of *Salmonella typhimurium* (Marshall et al. 1983). The test substance (in tetrahydrofuran) was evaluated at concentrations ranging from 1 to 1000 µg/plate with and without metabolic activation. The concentration of rat liver homogenate used for metabolic activation in the bioassay was 84 µg protein per plate. Tetrahydrofuran served as the solvent control, and positive controls were as follows: sodium azide, 2-nitrofluorene, 9-aminoacridine, methyl methane sulfonate, and 2-aminofluorene. Jojobutter-51 was not mutagenic at any of the concentrations tested. All of the positive controls were mutagenic; the solvent control was not mutagenic. Jojobutter-51 also was not mutagenic in a second bioassay (same procedure and test concentrations) in which the concentration of rat liver homogenate was increased to 140 µg per plate, or in the absence of metabolic activation. With the exceptions of methyl methane sulfonate and 9-aminoacridine, results with negative and positive controls were similar to those reported in the first bioassay.

Jojoba Alcohol

The mutagenicity of Jojoba Alcohol was evaluated by Taguchi (no date) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli* strain WP-2 (uvr A). All strains were tested with concentrations of Jojoba Alcohol ranging from 1.25 to 40.0 nl/plate both with and without metabolic activation. Untreated cultures of each strain tested served as negative controls. The following chemicals served as positive controls: N-ethyl-N-nitro-N-nitrosoguanidine (strains TA100, TA1535, and WP-2 (uvr A) without activation), benzo(a)pyrene

(strains TA98, TA100, TA1537, and TA1538 with activation), 2-aminoanthracene (strain WP-2 (uvr A) with activation), 2-nitrofluorene (strain TA 98 without activation), 9-aminoanthracene (strain TA1537 without activation), and 4-nitro-o-phenylenediamine (strain TA1538 without activation).

The highest numbers of revertants per plate, compared with controls, in each strain tested without activation were as follows: TA98 (1.5 x control, dose = 10 nl/plate), TA100 (1.2 x control, 10 nl/plate), TA1535 (2.7 x control, 20 nl/plate), TA1537 (1.4 x control, 40 nl/plate), TA1538 (1.8 x control, 20 nl/plate), and WP-2 (uvr A) (1.8 x control, 1.25 and 20 nl/plate). The highest numbers of revertants per plate, compared with controls, in each strain tested with activation were as follows: TA98 (1 x control, 2.5 nl/plate), TA100 (1 x control, 40 nl/plate), TA1535 (1 x control, 1.25 and 20 nl/plate), TA1537 (1.5 x control, 10 nl/plate), TA1538 (1.2 x control, 2.5 nl/plate), and WP-2 (uvr A) (1.2 x control, 5.0 and 40 nl/plate). In positive control cultures, the number of revertants per plate ranged from 3.2 to 41.7 times that of control cultures. The authors concluded that Jojoba Alcohol was not mutagenic (Taguchi no date).

Jojoba Mixture

Celsis Laboratory Group (1999c) conducted an Ames mutagenicity assay on a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters, and tocopherol (35:35:30:0.1 wt%) on *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) and *E. coli* (WP2). The positive controls with S9 used 2-aminoanthracene. Positive controls without S9 used 2-nitrofluorene for TA98 and TA1538, sodium azide for TA100 and TA1535, 9-aminoacridene for TA1537, and methyl methone sulfate for *E. coli*. For concentrations ranging from 1 to 100 mg/plate, there was no mutagenicity observed. There was no sign of toxicity.

CARCINOGENICITY

No carcinogenicity data were available.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Simmondsia Chinensis (Jojoba) Seed Oil

Taguchi and Kunimoto (1977) evaluated the skin irritation potential of refined and crude *Simmondsia Chinensis* (Jojoba) Seed Oil using 26 patients (18-59 years old) with histories of eczema or dermatitis. Olive oil, safflower oil, and white petrolatum served as controls. The test substances were applied to the upper back for 48 h via adhesive bandages. Reactions were scored 30 min and 24 h after patch removal. Slight eczema, the only reaction reported, was observed in 1 of the patients patch tested with crude *Simmondsia Chinensis* (Jojoba) Seed Oil. This reaction was not observed 24 h after patch removal. In another skin irritation study (same procedure), both test substances and controls were applied to 20 patients (19-42 years old) with histories of eczema or dermatitis. Positive reactions to crude *Simmondsia Chinensis* (Jojoba) Seed Oil and olive oil (1 patient) were observed 30 min after patch removal. Positive reactions to

refined *Simmondsia Chinensis* (Jojoba) Seed Oil, safflower oil, and white petrolatum (1 patient) were observed 30 min and 24 h after patch removal. Both patients were thought to have been inherently hyperallergic.

Scott and Scott (1982) tested a total of 6 patients who were suspected of being sensitive to *Simmondsia Chinensis* (Jojoba) Seed Oil in a contact dermatitis study. The patients were patch tested (muslin patches) with each of the following: (1) 20% *Simmondsia Chinensis* (Jojoba) Seed Oil mixed with 80% olive oil, (2) 20% *Simmondsia Chinensis* (Jojoba) Seed Oil mixed with 80% liquid petrolatum, (3) pure olive oil, (4) pure mineral oil, and (5) muslin only. Positive reactions (erythema or erythema and vesicles) to both *Simmondsia Chinensis* (Jojoba) Seed Oil mixtures were observed on the forearms of 5 patients within 24 or 48 h after patch application. None of the patients had reactions to olive oil, mineral oil, or muslin. When the patient with no reaction to *Simmondsia Chinensis* (Jojoba) Seed Oil mixtures subsequently used pure *Simmondsia Chinensis* (Jojoba) Seed Oil as a hairdressing, contact dermatitis of the scalp resulted. Reactions were not observed in a control group of 28 patients patch tested (muslin patches) with pure *Simmondsia Chinensis* (Jojoba) Seed Oil. These patients had no known sensitivities.

CTFA (1985d) submitted a clinical use test where a lip balm product containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was applied to the lips of 200 adult female subjects daily for 4 days. The subjects were evaluated at baseline and at 2 and 4 weeks post-application for signs of subjective/objective irritation. No adverse reactions were noted at any time during the study.

CTFA (1985e) submitted a report where the skin irritation and sensitization potential of a lip balm product containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated using 208 adult female subjects. The test substance (0.2 g) was applied for 24 h to the back of each subject, between the scapulae and waist (adjacent to the midline), via an occlusive patch. Applications were made 3 times per week for a total of 3 weeks. Patch removals on Tuesdays and Thursdays were followed by 24 h nontreatment periods, and those on Saturdays were followed by 48 h nontreatment periods. Reactions were scored prior to the next patch application according to the scale: 0 (no evidence of any effect) to 4 (deep red erythema with vesiculation or weeping). The application site was changed if a subject had a reaction of 2 (uniform, pink-red erythema) or greater during induction. If a 2+ reaction was observed at the new site, induction applications were discontinued. However, all subjects with induction reactions were patch-tested during the challenge phase. After a 10- to 19-day nontreatment period, a challenge patch was applied for 48 h to a new site. Reactions were scored at 48 and 72 h post-application. Mild, transient irritation, nonspecific in nature, was observed in 1 subject. The product was classified as a nonirritant and a nonsensitizer.

CTFA (1988) submitted a report where the skin irritation and sensitization potential of a topical oil product containing 0.5% *Simmondsia Chinensis* (Jojoba) Seed Oil was evaluated in the modified Draize-Shelanski repeat insult patch test using 152 normal subjects (38 males, 114 females; 18-65 years old). The

test substance (on occlusive patch) was applied to the upper back of each subject on Monday, Wednesday, and Friday for 3 consecutive weeks. Sites were scored 24 h after patch removal according to the scale: 0 (no reaction) to + + + + (bullae or extensive erosions involving at least 50% of the test area). After a 2-week nontreatment period, 2 challenge patches were applied consecutively to new sites (adjacent to old site) for 48 h. Sites were scored at 48 and 96 h. None of the subjects had allergic reactions. The product was neither a clinically significant irritant nor a sensitizer.

Hill Top Research, Inc. (1998b) performed a repeated insult patch test of *Simmondsia Chinensis* (Jojoba) Seed Oil. The test articles were 2 separate lots of Jojoba Oil (a yellow oil and a clear oil; 0.2 ml). They were repeatedly applied at 100% to the same site on the skin (site not specified) for 3 weeks to the subjects (100 men and women). After 2 weeks rest, the test articles were reapplied to different sites. The sites were read for sensitization at 48 and 96 h. One subject had a dermal response of grade 1 to both Oils at the 48-h observation which subsided by the 96-h observation. A second person had the same reaction to the clear *Simmondsia Chinensis* (Jojoba) Seed Oil which subsided by the 96-h observation. The researchers concluded that the *Simmondsia Chinensis* (Jojoba) Seed Oils showed no evidence of contact sensitization.

Consumer Product Testing Company (2003) conducted a repeated insult patch test of *Simmondsia Chinensis* (Jojoba) Seed Oil (100%) on 102 volunteers (males and females). The test material (0.2 ml) was applied to the upper back and covered by an absorbent pad held in place with a clear adhesive dressing (semi-occluded). Patches were applied 3 times/week for 3 weeks to the same location. Patches were removed by the volunteers 24 h after application and the test area was examined before each application for reaction. A challenge patch was applied 2 weeks after final induction patch to an area adjacent to the induction area. The patch was removed after 24 h and scored 24 and 72 h after application. All readings were negative throughout the test period. The authors concluded that *Simmondsia Chinensis* (Jojoba) Seed Oil does not have a potential for dermal irritation or allergic contact sensitization.

Hydrolyzed Jojoba Esters

International Research Services Inc. (2006) assessed the skin sensitization potential of a mixture of Hydrolyzed Jojoba Esters and water (20:80 wt.%). The test material (diluted to 10%) was applied to subjects (n = 104) Monday, Wednesday, and Friday for 8 applications. After a 10- to 14-day rest, the challenge patch was applied. The site was evaluated at 24 and 72 h. There were no adverse effects due to the test material. There was no evidence of sensitization. The researchers concluded that there was no evidence of potential clinical irritation under normal use conditions.

Jojoba Esters

Leberco Testing, Inc. (1995b) reported a repeated insult patch test of Jojoba Esters 70 (10% in mineral oil) to the upper back of subjects (n = 53) on Monday, Wednesday, and Friday for 3

weeks. The patches were left on for 24 h. After a 2-week rest, a new patch was applied to a new site on the upper back. After 24 h, the patch was removed and the site evaluated. The sites were evaluated again at 48 and 72 h. There were no reactions during the induction phase. One subject had a $\pm$ level reaction at the 24 and 48 h readings; it was resolved at the 72 h reading. The authors concluded that the sample of Jojoba Esters 70 demonstrated no potential for eliciting either dermal irritation or sensitization.

California Skin Research Institute (1997a) tested 4 Jojoba Esters (20, 30, 60, and 70) for irritation. The test materials (100%; 2 ml) were administered to the upper outer arm of the subjects (n = 15; ages 24 to 51 years) for 24 h under an occluded patch. The patch was removed and the test site observed at 15 min and 24 h after removal. There were no signs of irritant dermatitis.

Jojoba Alcohol

Taguchi (no date) evaluated the skin irritation potential of Jojoba Alcohol using 60 human subjects. Twenty subjects (healthy skin) were patch tested with 10.0 and 100.0% Jojoba Alcohol, and 40 subjects (contact dermatitis patients) were patch tested with 100.0% Jojoba Alcohol. Oleyl alcohol, at concentrations of 10.0% (normal subjects) and 100.0% (patients), served as the control. Patches containing the test substance were applied to the upper back for 48 h. Reactions were scored 30 min and 24 h after patch removal according to the scale: 0 to 4+. In the group of healthy subjects, one reaction ($\pm$ reaction to 10.0% Jojoba Alcohol) was observed at 30 min; no reactions were observed at 24 h. There were no reactions to 100.0% Jojoba Alcohol in healthy subjects. In the group of patients, 1 reaction ($\pm$ reaction to 100.0% Jojoba Alcohol) was observed at 30 min; no reactions were observed at 24 h. The reactions observed in the patient control group included one reaction ($\pm$ reaction to 100.0% oleyl alcohol) at 30 min and no reactions at 24 h. There were no reactions to 10.0% oleyl alcohol in the healthy group of control subjects. Jojoba Alcohol was not a skin irritant.

Jojoba Mixtures

California Skin Research Institute (1997a) performed a test on a Jojoba product (a mixture of Jojoba Esters, isopropyl jojobate, and Jojoba Alcohol) for irritation. There were no signs of irritant dermatitis.

Hill Top Research, Inc. (1998a) performed a repeated insult patch test of a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (approximate weight % 35:35:30:0.1). The test substance (100%; amount not provided) was applied to the same site on the skin of subjects (n = 100; 18 years old or older) for ~3 weeks. After ~2 weeks rest, the test substance was applied to a new site on the skin. There were no adverse reactions reported during the course of this study.

Hill Top Research, Inc. (1998b) performed a repeated insult patch test of Jojoba Esters/Hydrogenated Jojoba Oil. The test article was one lot of Jojoba Esters/Hydrogenated Jojoba Oil (white crystals; 0.2 g). It was repeatedly applied at 100% to the same site on the skin (site not specified) for 3 weeks to the subjects (100 men and women). After 2 weeks rest, the test article was

reapplied to different sites. The sites were read for sensitization at 48 and 96 h. One subject had a dermal response of grade 1 to the Jojoba Esters/Hydrogenated Jojoba Oil at the 48-h observation which subsided by the 96-h observation. A second person had the same reaction to the Jojoba Esters/Hydrogenated Jojoba Oil at the 48-h observation both of which subsided by the 96-h observation. The researchers concluded that the Jojoba Esters showed no evidence of contact sensitization.

Phototoxicity

Simmondsia Chinensis (Jojoba) Seed Oil

CTFA (1985e) submitted a report where the phototoxicity of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil was evaluated using 10 subjects. In half of the subjects, ~0.2 g of the test substance was applied for 24 h to the inner aspect of the right forearm, and, in the remaining half, to the inner aspect of the left forearm. Similarly, the nonirradiated control site was on the inner aspect of the right or left forearm. After patch removal, reactions were scored according to the scale: 0 (no evidence of any effect) to 4 (deep red erythema with vesiculation or weeping). The test sites were then irradiated for 15 min with UVA light (dose = 4,400 $\mu\text{W}/\text{cm}^2$) at a distance of approximately 10 cm. In each subject, the nonirradiated control site was shielded with aluminum foil during irradiation of the test site. Reactions were scored at the end of exposure and 24 and 48 h later. None of the subjects had reactions, and the product was classified as nonphototoxic.

CTFA (1985f) submitted a report where a total of 102 female subjects (18-49 years old) participated in an outdoor use test. Each subject used a sunscreen oil containing 0.5% Simmondsia Chinensis (Jojoba) Seed Oil for 2 h (in sunlight) on 2 consecutive days. The subjects were evaluated at 24 and 48 h post-exposure. Three subjects experienced slight, transient discomfort that was considered to be clinically insignificant.

Jojoba Alcohol

Taguchi (no date) evaluated the phototoxicity of Jojoba Alcohol using 60 subjects. Twenty subject (healthy skin) were patch tested with 10.0% and 100.0% Jojoba Alcohol, and 40 subjects (contact dermatitis patients) were patch tested with 100.0% Jojoba Alcohol. Oleyl alcohol, at concentrations of 10.0% (normal subjects) and 100.0% (patients), served as the control. Patches containing the test substance were applied to the upper back for 48 h. Each test site was then irradiated with the minimal erythema dose of black light. Neither the duration of exposure nor the intensity of the light source was stated. Reactions were scored at 24 h intervals according to the scale 0 and 4+. The only reaction was a $\pm$ reaction observed in one of the patients. Reactions were not observed in any of the normal subjects. No reactions were observed at control sites that had been treated with oleyl alcohol. The authors concluded that Jojoba Alcohol was not phototoxic.

Jojoba Mixtures

California Skin Research Institute (1997b) performed a phototoxicity study on a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (approximate weight %

35:35:30:0.1). The test substance (100%; 0.2 ml) and the control (distilled water) were applied to the paraspinal region of the subjects ($n = 17$; age 23 to 60) for ~24 h. The test sites with the test substance were exposed to UV radiation (16 J/cm² UVA) at each subject's minimal erythema dose and the controls sites were protected from the radiation. Visual evaluations were performed on all test sites 1, 24, 48, and 72 h after patch removal. There were no adverse effects during this study. There was 1 erythematous reaction at the 48-h evaluation which resolved by the 72-h evaluation. The researchers concluded that the mixture did not exhibit significant phototoxicity potential when compared to the negative control.

SUMMARY

Photoallergenicity

Simmondsia Chinensis (Jojoba) Seed Oil

CTFA (1985e) submitted a study that evaluated the photoallergenicity of a lip balm product containing 20.0% Simmondsia Chinensis (Jojoba) Seed Oil using 30 subjects. For half of the subjects, approximately 0.2 g of the product was applied for 24 h to the inner aspect of the left arm, and for the remaining half, to the inner aspect of the right arm. Likewise, sites on the inner aspect of the right or left arm served as control (nonirradiated) sites. Each application was made via an occlusive patch on Mondays, Wednesdays, and Thursdays for a total of 9 induction applications. If irritation was not observed, all applications were made to the same site.

After patch removal, each site was subjected to non-erythemogenic ultraviolet radiation for 15 min at a distance of 10 cm from the source. The dosage of UVA light was approximately 4,400 $\mu\text{W}/\text{cm}^2$. Each non-irradiated control site was covered during irradiation of the opposite arm. Irradiated sites were scored immediately after patch removal and 24 h after UV light exposure (72 h after irradiation on Friday) according to the scale: 0 (no evidence of any effect) to 4 (deep red erythema with vesiculation or weeping). After a 13- to 18-d nontreatment period, a challenge patch was applied for 48 h to a new site, and reactions were scored after patch removal. The test site was then irradiated and scored 24 h later. No reactions were observed, and the product was classified as non-photoallergenic.

Case Reports

Wantke et al. (1996) reported on a case of a 44-yr-old woman who applied moisturizing cream to her face daily for at least 5 yr. For the 3 months before presentation she had itching a few hours after application. The past 2 weeks there was dermatitis on her face. She was patch tested with the standard European ointment series, the cream she was using, and a related cream by the same manufacturer. She tested negative for everything except the moisturizing cream she had been using. She was then patch tested with all of the individual ingredients of the cream; 20 controls (10 men, 10 women) were also tested for irritation. The woman tested positive for "Jojoba Oil" (1.5%, ++), myristyl lactate (0.5%) and maleated soybean oil (1.5%, +), maleated soy bean oil (1.5%) not deodorized (?+), and glyceryl stearate (4.9%) and polyoxyethylene 23-lauryl ether (+). There was only 1

questionable reaction to glyceryl stearate (4.9%) and polyoxyethylene 23-lauryl ether by 1 male in the control group. Contact with the company revealed that the formulation had been changed about 2 years prior to the patient's presentation and there were 2 other suspected cases of contact dermatitis due to the cream.

SUMMARY

This safety assessment of the cosmetic ingredients *Simmondsia Chinensis* (Jojoba) Seed Oil (originally Jojoba Oil) and *Simmondsia Chinensis* (Jojoba) Seed Wax (originally Jojoba Wax) also includes Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, *Simmondsia Chinensis* (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil. Jojoba products (except Synthetic Jojoba Oil) are based on the esters from the fixed oil expressed or extracted from seeds of the desert shrub, Jojoba, *Simmondsia chinensis*. *Simmondsia Chinensis* (Jojoba) Seed Oil is composed almost completely (97%) of wax esters of monounsaturated, straight-chain acids and alcohols with high-molecular weights (C16-C26). These wax esters exist principally (83%) as combinations of C20 and C22 unsaturated acids and alcohols. *Simmondsia Chinensis* (Jojoba) Seed Oil is stable and resists oxidation. The amount and composition of the oil expressed from *S. chinensis* seeds varies with maturity of the seeds and somewhat with location and climate conditions surrounding the plant.

Impurities include lead up to 0.8 ppm and arsenic up to 0.1 ppm.

Simmondsia Chinensis (Jojoba) Seed Oil in cosmetic products has increased from 188 in 1989 (in concentrations up to 25%) to 1123 uses in 2007 at up to 100%. *Simmondsia Chinensis* (Jojoba) Seed Wax had no uses listed in 1989 and is currently reported to be used in 8 cosmetic products at up to 2%. Hydrogenated Jojoba Oil is reported to be used in 71 cosmetic products, Jojoba Esters in 121 cosmetic products, *Simmondsia Chinensis* (Jojoba) Butter in 18 cosmetic products, Jojoba Alcohol in 21 cosmetic products, and Synthetic Jojoba Oil in 6 cosmetic products at up to 31%, 44%, 6%, 1%, and 0.1%, respectively. Hydrolyzed Jojoba Esters are in 86 cosmetic products up to 2%. Isomerized Jojoba Oil is not reported as being used.

Simmondsia Chinensis (Jojoba) Seed Oil was detected in the feces of mice fed the ingredient at 0.5 to 1.69 mg/10 g.

Simmondsia Chinensis (Jojoba) Seed Oil penetrated nude mouse skin. The main route of penetration was the hair follicle. *Simmondsia Chinensis* (Jojoba) Seed Oil in an emulsion with Brij 96 and Capmul in 40% water delivered Fluconazole through new born mouse skin at a greater rate than gel bases. Only a small amount of radio-labeled *Simmondsia Chinensis* (Jojoba) Seed Wax injected subcutaneously into albino mice was absorbed into carcass and the lipid fractions of the brain and liver. Following the injection of the radio-labeled *Simmondsia Chinensis* (Jojoba) Seed Wax in mice, the greatest counts of radioactivity were in the liver, brain, lungs, and carcass lipids.

Simmondsia Chinensis (Jojoba) Seed Oil altered the penetration of aminophylline and Diclofenac when applied in a microemulsion.

Weanling rats fed *Simmondsia Chinensis* (Jojoba) Seed Wax had reduced weight gain. Digestibility of the Wax was 41%. Fecal matter contained 51% fat when the rats were fed 12% *Simmondsia Chinensis* (Jojoba) Seed Wax. Efficiency of energy conversion was half that of the control diets.

Orally administered jojoba liquid wax to rats inhibited carrageenin-induced edema at 5 and 10 ml/kg. In a chick's embryo chorioallantoic membrane test, jojoba liquid wax reduced the granulation tissue weight by 15.8% and 38% at 30% and 50%, respectively, compared to controls. Ear edema induced by a croton oil/ethanol/pyridine/ethyl ether solvent was reduced by 28% and 43.6% at 30% and 50%, respectively, with less neutrophil infiltration and hyperemia compared to controls. Jojoba liquid wax injected at 5 and 10 ml/kg reduced NO levels by 31.4% and 32.8%, respectively, after the injection of sterile air then lipopolysaccharides from *E. coli* compared to controls. Croton oil-induced myeloperoxidase activity of rats' ears was decreased by jojoba liquid wax at 30% and 50% by 29% and 53.3%, respectively.

Simmondsia Chinensis (Jojoba) Seed Oil increased blood cholesterol levels in rabbits fed a cholesterol-free diet. Rabbits fed a diet consisting of 1% cholesterol and 2% *Simmondsia Chinensis* (Jojoba) Seed Oil was 40% lower compared with controls.

Simmondsia Chinensis (Jojoba) Seed Oil inhibits hydrolysis of vitamin A esters in chicks and rats.

When tested for acute toxicity, *Simmondsia Chinensis* (Jojoba) Seed Oil was not toxic to mice at 1.69 ml/10 g. Fewer than 50% of rats died when administered 21.5 ml/kg *Simmondsia Chinensis* (Jojoba) Seed Oil. The acute oral toxicity of a lip balm with 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was greater than 5.0 g/kg. *Simmondsia Chinensis* (Jojoba) Seed Wax was not classified as a toxic substance in rats at 5.0 g/kg. Orally administered Jojoba Esters (15, 30, 60, 70) were not toxic to rats at 5 g/kg. Jojoba Esters (iodine values 40 and 60) were not toxic to white rats at 5.0 g/kg; the rats survived for 14 d after administration. Orally administered Jojoba Alcohol was not toxic to rats at 50 ml/kg.

Simmondsia Chinensis (Jojoba) Seed Oil administered in the diet of rats resulted in 10% mortality in all 3 exposures (1.0, 2.0, and 3.0 g/d). *Simmondsia Chinensis* (Jojoba) Seed Oil fed to rats reduced food consumption but did not affect food transit time. When rats in another study were fed up to 9% *Simmondsia Chinensis* (Jojoba) Seed Oil in their diet for up to 4 weeks, there were no deaths and no clinical signs. Lipid content in the feces and urea concentration increased dose-dependently. White blood cell counts increased in the high dose group.

Rats administered *Simmondsia Chinensis* (Jojoba) Seed Wax subcutaneously 6 d/week for 7 weeks at 1 ml/kg survived. Blood chemistry values were similar between controls and treatment groups. *Simmondsia Chinensis* (Jojoba) Seed Wax was not toxic when applied to the shaved backs of guinea pigs 6 d/week for 20 weeks up to 0.5 g/kg.

Simmondsia Chinensis (Jojoba) Seed Oil was not dermally

irritating when applied to guinea pigs at 0.5 ml for 15 d. When applied to intact and abraded skin of white rabbits in a lip balm at 20%, *Simmondsia Chinensis* (Jojoba) Seed Oil was minimally irritating with a mean score of 0.33 out of 4. Jojoba Esters (15, 30, 60, and 70) were not irritating to the intact and abraded skin of albino rabbits at 0.5 ml under an occluded patch for 24 h. When applied to the intact and abraded skin of albino rabbits, two Jojoba Esters (iodine values of 40 and 60) were non-irritating after 24 h under an occluded patch. *Simmondsia Chinensis* (Jojoba) Seed Wax was not irritating to albino rabbits. A Dermal Irritation test found Hydrolyzed Jojoba Esters and water (20:80 wt.%) to be non-irritating at 25 and 125 ml. Jojoba Alcohol was found to be non-irritating to the skin of albino marmots at 10.0% (in refined *Simmondsia Chinensis* (Jojoba) Seed Oil).

Simmondsia Chinensis (Jojoba) Butter was classified as a non-irritant when applied to the intact and abraded skin of New Zealand white rabbits at 0.5 ml for 24 h under an occluded patch. Jojoba Alcohol, up to 50% in refined *Simmondsia Chinensis* (Jojoba) Seed Oil, showed no signs of irritation at the macroscopic level when applied to the intact and abraded skin of white rabbits for 15 and 30 d. Microscopic evaluation revealed light to medium incrustation of the germinative zone of the epidermis and light dermal irritation. After 15 d, 25% Jojoba Alcohol induced redness, induration, and swelling. After 30 d, 25% Jojoba Alcohol induced redness; 50% induced redness, induration, and swelling. Histopathological examination was negative for other signs of irritation. The Draize test on albino marmots was negative at 10% Jojoba Alcohol, in refined *Simmondsia Chinensis* (Jojoba) Seed Oil.

Simmondsia Chinensis (Jojoba) Seed Oil was non- to slightly irritating when instilled into the eyes of white rabbits. *Simmondsia Chinensis* (Jojoba) Seed Wax was not classified as an ocular irritant when instilled into the eyes of white rabbits. Jojoba Esters (15, 30, 60, and 70) were not classified as ocular irritants when instilled into the eyes of albino rabbits. Jojoba Esters (iodine values of 40 and 60) were not classified as ocular irritants when instilled into the eyes of albino rabbits. In the Eytex test, Jojoba Esters (15, 20, and 30) were found to be non-irritating. Jojoba Esters in water (20:80 wt.%) was found to be non-irritating in a chorioallantoic membrane vascular assay. Jojoba Alcohol, at 12.5%, 25.5%, and 50% in refined *Simmondsia Chinensis* (Jojoba) Seed Oil, produced no reactions in the cornea or iris when instilled into the eyes of rabbits. Reactions in the conjunctivae did not last past 24 h. A mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (35:35:30:0.1 wt.%) was found to be non-irritating in a chorioallantoic membrane vascular assay.

Simmondsia Chinensis (Jojoba) Seed Wax was moderately comedogenic, score 2.67. Jojoba Esters was noncomedogenic, when tested on white rabbits. Jojoba Esters were found to be non- to slightly- comedogenic in mineral oil.

Simmondsia Chinensis (Jojoba) Butter was found to non-mutagenic in an Ames test using *S. typhimurium* (strains TA97, TA98, TA100, and TA 102) up to 1000 mg/plate with and without metabolic activation. Jojoba Alcohol was found to be non-

mutagenic using *S. typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E. coli* (strain WP-2) at 1.25 to 40.0 nl/plate, with and without metabolic activation. There was no mutagenicity observed in an Ames test of a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters, and tocopherol (35:35:39:0.1 wt.%) using *S. typhimurium* (strains TA98, TA100, TA1535, TA153, and TA1538) and *E. coli* (strain WP-2).

One of 26 patients, all with a history of either eczema or dermatitis, had a slight eczema reaction to refined and crude *Simmondsia Chinensis* (Jojoba) Seed Oil after 24 h of exposure. When repeated with 20 more patients, there was 1 patient with a reaction after patch removal. There were no reactions among the control group. In a contact dermatitis study of 6 patients suspected of sensitivity to *Simmondsia Chinensis* (Jojoba) Seed Oil, 5 had positive reactions to 20% *Simmondsia Chinensis* (Jojoba) Seed Oil in olive oil and 20% *Simmondsia Chinensis* (Jojoba) Seed Oil in liquid petrolatum. When applied to the person with no reaction, pure *Simmondsia Chinensis* (Jojoba) Seed Oil as a hair dressing resulted in contact dermatitis of the scalp. There were no reactions among the control group.

A lip balm with 20% *Simmondsia Chinensis* (Jojoba) Seed Oil was applied to the lips of 200 adults for 4 d, there was no irritation observed. The skin irritation and sensitization potential of this lip balm was tested on the backs of healthy subjects. One subject in 208 had mild, transient irritation in a non-specific nature. There were no other reactions.

In a modified Draize-Shelanski repeat insult patch test of *Simmondsia Chinensis* (Jojoba) Seed Oil, there were no allergic reactions in 152 normal subjects.

In a repeated insult patch test of Jojoba Esters 70 (10% in mineral oil) applied to the backs of subjects 3 d/week for 3 weeks, did not produce a reaction during the induction phase. When reapplied 2 weeks later, 1 subject had a low level reaction at the 24 h reading.

Jojoba Esters (20, 30, 60, and 70) and a Jojoba mixture (Jojoba Esters, isopropyl jojobate, and Jojoba Alcohol) applied to 15 subjects produced no signs of irritant dermatitis. In a repeated insult patch test of a mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (35:35:30:0.1 wt.%) on 100 subjects, there were no adverse reactions.

In a repeated insult patch test of *Simmondsia Chinensis* (Jojoba) Seed Oil (2 separate lots, yellow and clear) and Jojoba Esters/Hydrogenated Jojoba Oil on 100 subjects there was 1 grade 1 reaction to all 3 test substances at 48 h which resolved by the 96-h reading. One other person had a similar reaction to the clear *Simmondsia Chinensis* (Jojoba) Seed Oil and another to the Jojoba Esters/Hydrogenated Jojoba Oil. In a repeated insult patch test of *Simmondsia Chinensis* (Jojoba) Seed Oil at 100% on 100 subjects, there were no dermal reactions during course of the study.

In a skin sensitization test of Hydrolyzed Jojoba Esters in water (20:80 wt.%) diluted to 10% there were no reactions nor evidence of sensitization.

In a patch test of Jojoba Alcohol at 10.0% and 100.0% on 20 healthy patients and 40 contact dermatitis patients, there were no reactions in the healthy test group. In the dermatitis patients, there was 1 mild reaction to the 100.0% Jojoba Alcohol at the 30 min observation.

Lip balm containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil was applied to the forearms and irradiated with UVA for 15 min. There were no reactions and the lip balm was classified as non-phototoxic. *Simmondsia Chinensis* (Jojoba) Seed Oil in a sunscreen at 0.5% was administered to 102 subjects in sunlight for 2 consecutive days and found to be non-phototoxic. A mixture of isopropyl jojobate, Jojoba Alcohol, Jojoba Esters and tocopherol (35:35:30:0.1 wt.%) was found to be non-phototoxic at 100%. In a photoallergenicity test of a lip balm containing 20.0% *Simmondsia Chinensis* (Jojoba) Seed Oil on 30 subjects, the lip balm was applied and irradiated with UVA to the inner arm 3 d/week for 3 weeks. After a 13- to 18-day rest, the lip balm was reapplied for 48 h. There were no reactions observed and the product was classified as non-photoallergenic. Jojoba Alcohol, at 10.0% and 100.0%, applied to healthy patients and contact dermatitis patients and irradiated with UVA, resulted in 1 mild reaction in one of the dermatitis patients.

There was a case history of a woman who had itching dermatitis after using a moisturizing cream. Patch tests were negative for the ingredients in the cream except for “jojoba oil” and other ingredients.

DISCUSSION

The Cosmetic Ingredient Review Expert Panel noted that there were new uses listed in baby and eye products. Since the original safety assessment did not break down the categories of use to the extent that is now in practice, it was considered likely that *Simmondsia Chinensis* (Jojoba) Seed Oil and Wax were used in these products. *Simmondsia Chinensis* (Jojoba) Seed Oil is used up to 100% in bath products, which would be diluted when used, and in body and hand creams, etc., which would not be diluted. The Expert Panel considered, therefore, that exposure to 100% use concentration was possible.

In the absence of inhalation toxicity data, the Panel determined that *Simmondsia Chinensis* (Jojoba) Seed Oil, Hydrogenated Jojoba Oil, Jojoba Esters, and Jojoba Alcohol can be used safely in hair sprays, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (~38 µm) and pump hair sprays (>80 µm) is large compared to respirable particulate sizes (≤10 µm).

The Expert Panel recognized that these ingredients can enhance the penetration of other ingredients through the skin (e.g. fluconazole and aminophylline). The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

Based on the composition of these ingredients, there were no structural alerts for reproductive/developmental toxicity and these ingredients are not expected to easily penetrate skin. None of the

tested ingredients were genotoxic and there were no structural alerts for carcinogenicity. The Expert Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients, including Jojoba derivatives. They stressed that the cosmetic industry should continue to use the necessary procedures to limit these impurities in the ingredients before blending into cosmetic formulations. It was noted that the Synthetic Jojoba Oil was actually produced in the laboratory and not processed from the actual *Simmondsia Chinensis* (Jojoba) Seed Oil or Wax.

The CIR Expert Panel recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

CONCLUSION

Simmondsia Chinensis (Jojoba) Seed Oil, *Simmondsia Chinensis* (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, *Simmondsia Chinensis* (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil are safe as cosmetic ingredients in the practices of use and concentration as discussed in this safety assessment.¹

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¹ Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

² Available from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036.

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1

Final Report on the Safety Assessment of Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol

Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are long-chain saturated or unsaturated (Oleyl) fatty alcohols. They are used in numerous cosmetic product categories at concentrations of less than 0.1 percent to greater than 50 percent.

The metabolism of Stearyl Alcohol and Oleyl Alcohol in rats is described. The results of acute oral toxicity studies indicate a very low order of toxicity. In rabbit irritation tests, these alcohols produced minimal ocular irritation and minimal to mild cutaneous irritation. Stearyl Alcohol produced no evidence of contact sensitization or comedogenicity.

Clinical patch testing indicates a very low order of skin irritation potential and sensitization. Photoreactivity studies on products containing these ingredients were negative for phototoxicity or photosensitization.

Based on the available data, it is concluded that Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are safe as currently used in cosmetics.

INTRODUCTION

Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are long-chain fatty alcohols used in a variety of cosmetic products. The materials of commerce are mixtures of fatty alcohols, and the terms Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol refer to these mixtures for the purposes of this report. If data pertain to the pure compound rather than the cosmetic ingredient, the distinction is noted.

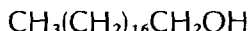
CHEMICAL AND PHYSICAL PROPERTIES

Composition

Stearyl Alcohol

Stearyl Alcohol is a mixture of solid fatty alcohols that consists predominantly of n-octadecanol (90 percent minimum assay) with varying amounts of n-hexa-

decanol, n-tetradecanol, n-eriosanol, and n-dodecanol along with unspecified uneven and branched-chain alcohols. The predominant component conforms to the formula: ⁽¹⁻³⁾

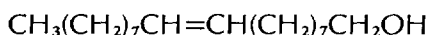


CAS Number: 112-92-5

Synonyms include Octadecanol, n-Octadecanol, Octa Decyl Alcohol, n-Octadecyl Alcohol, Stearol, USP XIII Stearyl Alcohol, and n-1-Octadecanol.

Oleyl Alcohol

Oleyl Alcohol is a mixture of fatty alcohols that consists predominantly of the straight-chain unsaturated 9-n-octadecenol (55 percent minimum assay) with varying amounts of 8-n-hexadecenol, 6-n-dodecenol, n-hexadecanol, n-octadecanol, n-tetradecanol, and 7-n-tetradecenol. The predominant component conforms to the formula: ^(2,4,5)

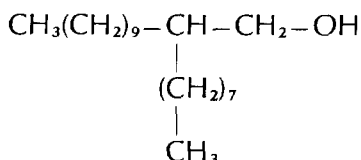


CAS Number: 143-28-2

Synonyms include cis-9-Octadecen-1-OL and Oleol.

Octyl Dodecanol

Octyl Dodecanol is an aliphatic alcohol with the structural formula:



Additional information concerning the composition of the material of commerce is unavailable. ^(2,6)

CAS Number: 5333-42-6

Synonyms include 2-Octyl Dodecanol.

Production and Occurrence

Stearyl Alcohol may be produced via Ziegler aluminum alkyl hydrolysis or the catalytic, high-pressure hydrogenation of stearic acid, followed by filtration and distillation. It may also be derived from natural fats and oils. ^(1,5,7-10)

Oleyl Alcohol is produced by catalytic, high-pressure hydrogenation of oleic acid followed by filtration and distillation. ^(4,5,7) It may also be prepared from butyl oleate by Bouveault-Blanc reduction with sodium and butyl alcohol or from triolein by hydrogenation in the presence of zinc chromite. Purification in these processes is obtained through fractional crystallization at -40°C from acetone followed by distillation. ⁽¹⁰⁾

Octyl Dodecanol is produced by the condensation of 2 molecules of decyl alcohol.⁽¹¹⁾ Further detail concerning the method of manufacture is unavailable.

Fatty alcohols occur in small quantities as components of wax esters in plants and animals. For example, Oleyl Alcohol has been found in the epidermis of many plants, and Stearyl Alcohol has been isolated from plants and insects. In both cases, the alcohols probably serve as components of the organisms' protective layers against water loss. Stearyl Alcohol has also been isolated from human sebaceous lipids and has been found in mammalian glands and organs. Oleyl Alcohol is found in fish oils.^(10,12-23)

Properties

Stearyl Alcohol is a white, waxy, practically inert solid with a faint odor.^(1,5,10,11,15) Oleyl Alcohol is a clear, odorless, viscous liquid.^(4,5,11) Octyl Dodecanol is a clear, odorless, free-flowing liquid.^(6,11) Other physical and chemical properties are listed in Table 1.

TABLE 1. Properties of Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol

Properties	Stearyl Alcohol ^(1,3,5,7,11)	Oleyl Alcohol ^(4,5,10,11,28)	Octyl Dodecanol ⁽⁶⁻¹¹⁾
Molecular weight (pure compound)	270.5	268.5	298.56
State	Flakes, granules	Viscous liquid	Liquid
Color	White	Clear colorless to light yellow	Colorless to pale yellow
Odor	Faint fatty	Faint	Odorless
Specific gravity	0.8124 (59°/4°C) 0.811 (35°/25°C)	0.850-0.966 (20°/20°C)	0.830-0.850 (20°/20°C)
Melting point	51-60°C 55-60°C	-7.5°C	-
Boiling point	210.5°C (15 mm)	333°C	-
Refractive index	1.4388 60°C	1.458-1.460	1.453-1.547 n _D ²⁰
Acid value	1.0 max 2.0 max	1.0 max	1.0 max
Saponification value	2.0 max 3.0 max	2.0 max	10 max
Iodine value	2.0 max 5.0 max	45-98 85-95	10 max
Hydroxyl value	195-220 200-220	195-220 205-215	165-180 175-190
Soluble in	Alcohol Acetone Ether Benzene Chloroform	Alcohol Ether Acetone Light mineral oil	-
Insoluble in	Water	Water	-

Analytical Methods

Analytical methods used to detect and identify fatty alcohols include gas-liquid chromatography, thin-layer chromatography, differential scanning calorimetry, and gas chromatography.⁽²⁴⁻²⁷⁾

Impurities

Stearyl Alcohol consists of not less than 90 percent stearyl alcohol. The remainder consists chiefly of cetyl alcohol,⁽³⁾ oleyl alcohol, palmityl alcohol, and other alcohols.⁽⁹⁾ The known major constituents and minor impurities are:⁽¹¹⁾

n-Octadecanol	90 percent minimum
n-Hexadecanol	Variable
n-Tetradecanol	Variable
n-Eriosanol	Variable
n-Dodecanol	Variable
Stearyl stearate	2 percent maximum
Octadecane	1 percent maximum
Stearic acid	0.5 percent maximum
Total hydrocarbons	1.8 percent (approx.)

Oleyl Alcohol consists of 9-n-octadecenol, but may contain some such unsaturated and saturated high molecular weight fatty alcohols as linoleyl, myristyl, and cetyl alcohols.^(5,28) The known major components and minor impurities are:⁽⁴⁾

9-n-Octadecenol	55 percent minimum
8-n-Hexadecenol	Variable
6-n-Dodecenol	Variable
n-Hexadecanol	Variable
n-Octadecanol	Variable
n-Tetradecanol	Variable
7-n-Tetradecenol	Variable
Oleyl oleate	1.9 percent maximum
Oleic acid	0.5 percent maximum

Information on the impurities of Octyl Dodecanol is unavailable.

USES

Noncosmetic Uses

Stearyl Alcohol is used in surface-active agents, lubricants, emulsions, resins, and USP ointments and as a substitute for cetyl alcohol and antifoaming agents.^(5,10,29)

Stearyl Alcohol (synthetic) has been approved as a direct food additive (DFA) ingredient, to be used under the same manufacturing practices as the natural alcohol product. It also has indirect food additive (IFA) status for use in food con-

tainers and coatings (21 CFR 172.864; 175.300; 176.200; 176.210; 177.1200; 178.3910).⁽³⁰⁾

Stearyl Alcohol is also used as an ingredient in over-the-counter (OTC) drugs of the miscellaneous external drug product category. It is considered to be safe at a concentration of 8 percent or less.⁽³¹⁾

Oleyl Alcohol is used in chemical and polymer synthesis, as a petroleum additive, and as a surfactant, plasticizer, and antifoaming agent. It is also used as an ingredient in pharmaceuticals, as a metal-machining lubricant, as a component of carbon paper, stencil paper, and ink, as an emulsifying agent, and as an emollient.^(5,10,28)

Oleyl Alcohol has been approved as an IFA ingredient for use in paperboard components, as a defoaming agent, and as a lubricant (21 CFR 176.170; 176.210; 177.1210; 178.3910).⁽³⁰⁾

Uses for Octyl Dodecanol, other than cosmetic, were not found in the review of the available literature.

Cosmetic Uses

Purpose in Cosmetic Products

The fatty alcohols, in general, are used primarily as emulsifiers, emollients, antifoaming agents, and surfactants.^(5,7,32,33)

Stearyl Alcohol is used in cosmetics as an emollient, stabilizer, antifoaming agent, emulsifier, and carrier. It is used as a water in oil (w/o) emulsifier to produce firm cosmetic products at ordinary temperatures.^(1,5,7,33) A personal communication from the Society of Cosmetic Chemists to the Cosmetic, Toiletry and Fragrance Association⁽³⁴⁾ states:

Stearyl Alcohol is used in creams and lotions as an emollient, auxiliary emulsifier, bodying and pearlizing agent, thickener, and emulsion stabilizer. Stearyl Alcohol is hydrophobic in nature and will, therefore, produce a semioclusive film on the skin that aids in inducing hydration. When used in sufficient concentrations, in the absence of liquid fats, Stearyl Alcohol emulsions leave a matte finish on the skin. In addition, Stearyl Alcohol has a sufficiently high melting point to deposit nongreasy films on the skin. When used in powders, Stearyl Alcohol improves adhesion and imparts a soft feel to the skin. Stearyl Alcohol is stable in high pH formulations, such as hair straighteners, depilatories, and cuticle removers. It is also used in shampoos and bubble baths as an opacifier.

Oleyl Alcohol is used as an emollient, emulsion stabilizer, surfactant, lubricant, and antifoaming agent.^(4,7) A personal communication from the Society of Cosmetic Chemists to the Cosmetic, Toiletry and Fragrance Association⁽³⁴⁾ states:

Oleyl Alcohol is used in a variety of cosmetic preparations as an emollient, superfatting agent, emulsion stabilizer, and pigment suspending agent. Oleyl Alcohol is miscible with fats, oils, and wax mixtures and will blend well with the oil phase of a cosmetic emulsion. Oleyl Alcohol is easily emulsified and aids in the hydration of other ingredients in a cosmetic formulation. In lipsticks, Oleyl Alcohol has excellent solvent properties, improves glide and slip, and leaves a thin film on the lips. Oleyl Alcohol has an appreciable hydroalcohol solubility and is easily incorporated into a wide variety of such lotions.

In regard to Octyl Dodecanol, the same communication⁽³⁴⁾ states:

Octyl Dodecanol is a saturated liquid fatty alcohol with a total carbon length of 20. It is odorless, colorless, and has an indefinite shelf life. Octyl Dodecanol spreads easily when applied to the skin and leaves no visible trace of greasiness. It can be used as a carrier for oil soluble active ingredients, as an emollient, as a dispersant for pigments, and as a coupling agent for waxes and other fatty materials. Octyl Dodecanol is also used as a superfatting agent in shampoos, hair conditioners, and soaps.

Extent of Use in Cosmetic Products

The Food and Drug Administration (FDA), in voluntary cooperation with cosmetic ingredient manufacturers and formulators, compiles a list of cosmetic ingredients and the types of products and concentrations in which they are used. Filing of product formulation data with the FDA conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 part 720.4 of the Code of Federal Regulations.⁽³⁰⁾ Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the true concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, the opportunity exists for a 2- to 10-fold overestimation of the actual concentration of an ingredient in a particular product.

In 1981, Stearyl Alcohol was reported to be used in 425 cosmetic formulations at concentrations ranging from less than 0.1 percent to 50 percent. Oleyl Alcohol was present in 1018 different formulations at concentrations of less than 0.1 percent to greater than 50 percent. Octyl Dodecanol was listed in 371 products at concentrations of less than 0.1 percent to greater than 50 percent. Very few products contain these ingredients in the highest concentration ranges⁽³⁵⁾ (Table 2).

These compounds are found in a wide variety of cosmetic products and may, therefore, contact and enter the body through numerous routes. Some products may be applied several times daily and may remain in contact for extended periods (Table 2).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

Stearyl Alcohol is found naturally in various mammalian tissues. This fatty alcohol is readily converted to stearic acid, another common constituent of mammalian tissues. Results from several studies indicate that Stearyl Alcohol is poorly absorbed from the gastrointestinal tract. For a review of the literature written from the years 1933 to 1978 on the absorption, metabolism, and excretion of Stearyl Alcohol, see the Evaluation of the Health Aspects of Stearyl Alcohol as a Food Ingredient, prepared for the Food and Drug Administration by The Federation of American Societies for Experimental Biology.⁽³⁶⁾

Sieber et al.⁽³⁷⁾ studied the entry of octadecanol-1-¹⁴C (Stearyl Alcohol) into

the thoracic duct lymph of the rat. The thoracic duct, abdominal aorta, and the duodenum below the pyloric valve were cannulated in male Sprague-Dawley rats. The common bile duct of some animals was also cannulated. Lymph flows were monitored, and 24 hours after surgery the radiolabeled compound (25 mCi/mmol) was administered via either the duodenal or aortic cannula. Blood and lymph were monitored for radioactivity after dosing at 0.25, 0.5, 0.75, 1, 2, 4, 6, and 24-hour intervals. Intestinal radioactivity was determined by quantifying the ^{14}C or ^3H of the homogenate of the intestines, which showed the percent absorbed radioactivity in the lymph was 56.6 ± 14.0 . Of this, more than half was found in the triglycerides of the lymph, 6 to 13 percent in the phospholipids, 2 to 8 percent as the cholesterol esters, and 4 to 10 percent unchanged octadecanol. Ninety percent of octadecanol was carried in the chylomicron fraction. The absorption of the compound appeared to be a function of its lipid solubility.

The metabolism of Oleyl Alcohol was studied in 1 adult sheep. The rumen was cannulated and the animal received 66.0 g per day of Oleyl Alcohol in the diet for 12 days. Continuous measurement showed increased excretion of lipids (9 g/day fatty acids and 30 g/day unsaponifiables) and increased excretion of stearic and oleic acid. Oleyl Alcohol had no effect on either methane or heat production.⁽³⁸⁾

Cis-9-octadecanol (Oleyl Alcohol) was reported to be a prominent constituent of long-chain alcohols in rat tissue. Ethanol (0.1 ml) containing 1.85 mEq cis-9-octadecanol-1- ^{14}C was injected into the tail veins of rats, and the animals were sacrificed at 1, 24, 48, or 76 hours after injection. After 1 hour, the highest amount of radioactivity was found in the lungs, less in the liver, and the lowest amount in the brain. At 24, 48, and 96 hours, the rate of decline of radioactivity was greatest in the lungs and liver and least in the heart and brain. The radioactivity was incorporated mainly in glycerophosphocholines, glycerophosphoethanolamines, and neutral lipids. It was rapidly used for biosynthesis of lipids in the rat.⁽³⁹⁾

The permeability of the blood-brain barrier to long-chain alcohols in plasma was studied using Oleyl Alcohol. Four groups of 4 male Wistar rats were fed either a standard diet (control) or the standard diet plus 160 mg of Oleyl Alcohol (available ad lib) for 7 or 14 days. The entire supplement was consumed every day by the individually caged rats. At the end of the specified times, the animals were fasted for 24 hours and killed, and the organs were analyzed. No differences in growth rates were found between experimental and control groups. The addition of Oleyl Alcohol to the diet for 7 days increased the free and esterified long-chain alcohols in the liver. After 14 days, there was a 3-fold increase in free and esterified alcohols when compared to control animals. The hepatic alk-1-enyl acyl and alkyl acyl phosphoglycerides increased 2- to 8-fold over control values during the 14-day feedings. No quantifiable changes were noted in brain lipids after 7 or 14 days.⁽⁴⁰⁾

The fate of dietary Oleyl Alcohol was studied using 8 weanling male rats. For the first 5 days after weaning, the animals were fed a standard diet; then 4 rats received a mixture of 85:15 lab diet:oleyl palmitate, and the other 4 received 96:4 lab diet:Oleyl Alcohol. Two weeks after commencement of feeding of the experimental diet, the animals were killed, and the liver and intestines were removed. Growth on the Oleyl Alcohol diet was poor when compared to the oleyl palmitate diet. The fecal distribution of ingested Oleyl Alcohol was 46 percent wax es-

TABLE 2. Product Formulation Data⁽³⁵⁾

Product Category*	Total Formulations in Category	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%) *								
			Unreported Concentration	>50	>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1	
Stearyl Alcohol											
Baby lotions, oils, powders, and creams	56	2	-	-	-	-	-	-	-	2	-
Eyebrow pencil	145	1	-	-	-	-	-	1	-	-	-
Eye shadow	2582	24	-	-	-	-	-	-	-	23	1
Mascara	3097	2	-	-	-	-	-	-	-	2	-
Other eye makeup preparations	230	2	-	-	-	-	-	-	-	1	1
Sachets	119	26	-	-	-	4	4	4	14	14	-
Hair conditioners	478	46	-	-	-	-	1	14	22	9	-
Hair straighteners	64	2	-	-	-	-	1	-	1	-	-
Permanent waves	474	5	-	-	-	-	-	-	2	3	-
Hair rinses (noncoloring)	158	21	-	-	-	-	-	-	5	10	6
Hair shampoos (noncoloring)	909	1	-	-	-	-	-	-	-	1	-
Hair dyes and color (all types requiring caution statement and patch test)	811	1	-	-	-	-	-	-	-	1	-
Hair bleaches	111	5	-	-	-	-	-	2	3	-	-
Other hair coloring preparations	49	2	-	-	-	-	-	2	-	-	-
Blushers (all types)	819	15	-	-	-	-	-	-	14	1	-
Makeup foundations	740	8	-	-	-	-	-	-	-	8	-
Leg and body paints	4	3	-	-	-	-	-	-	3	-	-
Lipstick	3319	3	-	-	-	-	-	-	-	1	2
Makeup bases	831	63	-	-	-	-	-	2	38	23	-
Rouges	211	1	-	-	-	-	-	-	-	-	1
Makeup fixatives	22	1	-	-	-	-	-	-	-	-	1
Other makeup preparations (not eye)	530	2	-	-	-	-	-	-	-	1	1
Cuticle softeners	32	2	-	-	-	-	-	-	2	-	-
Nail creams and lotions	25	1	-	-	-	-	-	1	-	-	-
Deodorants (underarm)	239	3	-	-	3	-	-	-	-	-	-

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Other personal cleanliness products	227	10	—	—	—	9	—	1	—	—
Beard softeners	4	1	—	—	—	—	1	—	—	—
Shaving cream (aerosol, brushless, and lather)	114	6	—	—	—	—	—	1	5	—
Other shaving preparation products	29	2	—	—	—	—	—	—	1	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	39	—	—	—	—	4	15	17	3
Depilatories	32	6	—	—	—	—	—	6	—	—
Face, body, and hand skin care preparations (excluding shaving preparations)	823	36	—	—	—	—	1	14	19	2
Moisturizing skin care preparations	747	49	—	—	—	—	1	22	24	2
Night skin care preparations	219	12	—	—	—	—	—	6	4	2
Paste masks (mudpacks)	171	2	—	—	—	—	—	1	1	—
Skin lighteners	44	6	—	—	—	—	1	4	1	—
Skin fresheners	260	1	—	—	—	—	—	—	1	—
Wrinkle smoothers (removers)	38	1	—	—	—	—	—	1	—	—
Other skin care preparations	349	9	—	—	—	—	1	6	1	1
Suntan gels, creams, and liquids	164	2	—	—	—	—	1	—	1	—
Indoor tanning preparations	15	1	—	—	—	—	—	1	—	—
TOTAL 1981 DATA		425	—	—	3	13	16	109	224	60
TOTAL 1979 DATA		414	23	—	—	12	16	101	208	54
<i>Oleyl Alcohol</i>										
Bath oils, tablets, and salts	237	17	—	—	—	5	2	8	1	1
Bubble baths	475	1	—	—	—	—	—	1	—	—
Bath capsules	3	1	—	—	—	—	1	—	—	—
Other bath preparations	132	3	—	—	—	—	—	3	—	—
Eyebrow pencil	145	1	—	—	—	—	1	—	—	—
Eye liner	369	15	—	—	—	7	7	1	—	—
Eye shadow	2582	124	—	—	—	36	60	19	7	2
Mascara	397	26	—	—	—	—	—	26	—	—
Other eye makeup preparations	230	8	—	—	—	3	2	2	1	—

TABLE 2. (Continued)

Product Category*	Total Formulations in Category	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)*							
			Unreported Concentration	>50	>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1
Colognes and toilet waters	1120	2	—	—	—	—	—	—	2	—
Perfumes	657	5	—	—	—	3	—	1	—	1
Sachets	119	2	—	—	—	—	—	2	—	—
Other fragrance preparations	191	9	—	—	—	—	—	8	1	—
Hair conditioners	478	9	—	—	—	—	—	3	6	—
Hair straighteners	64	4	—	—	—	—	—	4	—	—
Tonics, dressings, and other hair grooming aids	290	4	—	—	—	—	—	1	3	—
Other hair preparations (noncoloring)	177	1	—	—	—	—	—	1	—	—
Hair dyes and colors (all types requiring caution statement and patch test)	811	63	—	—	—	13	—	50	—	—
Hair tints	15	13	—	—	—	13	—	—	—	—
Hair bleaches	111	2	—	—	—	—	—	2	—	—
Blushers (all types)	819	13	—	1	2	1	7	2	—	—
Face powders	555	1	—	—	—	—	—	1	—	—
Makeup foundations	740	5	—	—	—	—	—	3	2	—
Lipstick	3319	633	—	2	6	236	225	138	19	7
Makeup bases	831	2	—	—	—	1	—	1	—	—
Rouges	211	3	—	—	—	2	—	1	—	—
Other makeup preparations (not eye)	530	10	—	—	—	7	3	—	—	—
Nail polish and enamel remover	41	1	—	—	—	—	—	1	—	—
Deodorants (underarm)	239	2	—	—	—	—	—	2	—	—
Feminine hygiene deodorants	21	1	—	—	1	—	—	—	—	—
Other personal cleanliness products	227	2	—	—	—	—	—	1	1	—
Aftershave lotions	282	2	—	—	—	—	—	—	—	—
Preshave lotions (all types)	29	1	—	—	—	—	—	2	—	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	2	—	—	—	—	—	—	1	—

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Face, body, and hand skin care preparations (excluding shaving preparations)	823	6	-	-	-	-	1	4	-	1
Hormone skin care preparations	10	1	-	-	-	1	-	-	-	-
Moisturizing skin care preparations	747	8	-	-	-	1	-	4	2	1
Night skin care preparations	219	2	-	-	-	1	-	1	-	-
Paste masks (mudpacks)	171	2	-	-	-	-	-	1	-	1
Skin fresheners	260	2	-	-	-	-	-	-	1	1
Other skin care preparations	349	4	-	-	-	1	-	2	-	1
Suntan gels, creams, and liquids	164	5	-	-	-	-	1	3	1	-
TOTAL 1981 DATA		1018	-	3	9	331	310	301	48	16
TOTAL 1979 DATA		1069	138	1	11	267	313	294	32	13
<i>Octyl Dodecanol</i>										
Bath oils, tablets, and salts	237	4	-	-	-	-	4	-	-	-
Eyebrow pencil	145	1	-	-	-	-	1	-	-	-
Eyeliner	369	14	-	-	-	-	11	1	2	-
Eye shadow	2582	82	-	-	-	6	60	16	-	-
Eye lotion	13	1	-	-	1	-	-	-	-	-
Eye makeup remover	81	3	-	-	-	2	-	1	-	-
Mascara	397	1	-	-	-	-	-	1	-	-
Other eye makeup preparations	230	4	-	-	-	2	2	-	-	-
Perfumes	657	3	-	-	3	-	-	-	-	-
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	4	-	-	-	-	-	-	4	-
Sachets	119	6	-	-	6	-	-	-	-	-
Other fragrance preparations	191	1	-	-	-	-	1	-	-	-
Hair conditioners	478	3	-	-	-	-	-	2	1	-
Hair sprays (aerosol fixatives)	265	2	-	-	-	-	-	1	1	-
Hair rinse (noncoloring)	158	2	-	-	-	-	-	-	2	-
Hair dyes and colors (all types requiring caution statement and patch test)	811	41	-	-	-	1	40	-	-	-
Blushers (all types)	819	6	-	-	-	3	2	1	-	-
Face powders	555	6	-	-	-	-	3	1	2	-

TABLE 2. (Continued)

Product Category*	Total Formulations in Category	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)*							
			Unreported Concentration	>50	>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1
Lipstick	3319	112	-	1	5	46	54	5	1	-
Makeup bases	831	1	-	-	-	-	-	-	1	-
Rouges	211	1	-	-	-	1	-	-	-	-
Makeup fixatives	22	1	-	-	-	-	1	-	-	-
Other makeup preparations (not eye)	530	2	-	-	-	-	1	1	-	-
Bath soaps and detergents	148	1	-	-	-	-	-	-	-	-
Deodorants (underarm)	239	1	-	-	-	1	-	-	-	1
Other personal cleanliness products	227	1	-	-	-	-	-	1	-	-
Preshave lotions (all types)	29	1	-	-	-	-	-	-	1	-
Shaving cream (aerosol, brushless, and lather)	114	1	-	-	-	-	-	-	1	-
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	9	-	-	-	-	3	5	-	1
Face, body, and hand skin care preparations (excluding shaving preparations)	823	23	-	-	3	2	7	9	2	-
Moisturizing skin care preparations	747	14	-	-	-	1	1	6	4	2
Night skin care preparations	219	3	-	-	-	2	-	1	-	-
Skin lighteners	44	4	-	-	-	-	-	3	1	-
Wrinkle smoothers (removers)	38	1	-	-	-	-	-	1	-	-
Other skin care preparations	349	7	-	-	-	2	2	3	-	-
Suntan gels, creams, and liquids	164	3	-	-	-	1	2	-	-	-
Other suntan preparations	28	1	-	-	-	-	-	1	-	-
TOTAL 1981 DATA		371	-	1	18	70	195	60	23	4
TOTAL 1979 DATA		295	294	-	-	-	-	1	-	-

*Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4); see Scope and Extent of Use in Cosmetics.

ter, 27 percent fatty alcohol, 16 percent monoglyceride, 6 percent free fatty acid, and 5 percent diglyceride. Oleyl Alcohol deposition in liver was manifested as 7 percent wax ester, 11 percent triglyceride, 3 percent free fatty acid, 6 percent free fatty alcohol, and 72 percent phospholipid.⁽⁴¹⁾

Two additional studies investigated the metabolism of orally administered Oleyl Alcohol in rats. The intragastric administration to rats of 200 mg/day of Oleyl Alcohol for 14 days increased the relative concentration of alkyl and alkyl-1-enyl moieties in alkoxy lipids in the small intestine.⁽⁴²⁾ In another study, the incorporation of long-chain alcohols and acyl glycerols into hepatic tissues of rat was studied. A group of 4 rats were fed a basic diet (control), and a second group of 4 were fed the basic diet plus 100 mg/day of cis-9-octadecenyl alcohol (Oleyl Alcohol) for 28 days. Experimental compounds were fed by stomach tube, and the animals were killed 10 hours after the last feeding. The alcohol produced no abnormalities in the rats and did not effect the distribution of lipid classes or fatty acid composition of the phosphoglycerides in the liver. Pronounced changes did occur in both the alkyl and alkyl-1-enyl moieties of the phosphoglycerides of the liver. Metabolites of long-chain alcohols become incorporated into the phosphoglycerides of the liver.⁽⁴³⁾

Miscellaneous Effects

Microbial Effects

Yanagi and Onishi⁽⁴⁴⁾ found that Oleyl and Stearyl Alcohol can be utilized as the sole source of carbon by some species of *Penicillium*, *Candida*, and *Pseudomonas*.

Cellular and Subcellular Effects

Stearyl Alcohol, a known tobacco smoke constituent, was studied for its effect on the plasma membrane of cultured human lung fibroblasts. The fibroblasts, labeled with ³H-uridine, were incubated for 30 minutes at 37°C with 25 mM alcohol in Tris-buffered saline. The leakage of radiolabeled intracellular substances was used to indicate plasma membrane damage. Stearyl Alcohol was inactive in inducing significant cellular damage.⁽⁴⁵⁾

The differential effects of Oleyl Alcohol on the osmotic fragility of erythrocytes were studied using heparinized adult male human blood. The erythrocytes from venous blood were washed, prepared as a 50 percent cell suspension, and then mixed with varying concentrations of saline solution. The alcohol was dissolved in methanol and added to the cells for 10 minutes. The cells were then centrifuged, and hemolysis was determined by measuring the supernatant hemoglobin absorbance at 540 nm. At high saline concentrations, those at which hemolytic activity was greatest, the alcohol did not stabilize the erythrocytes against hypotonic hemolysis.⁽⁴⁶⁾

Raz and Goldman⁽⁴⁷⁾ studied the effect of Oleyl Alcohol on the osmotic fragility of lysosomes. Rat livers were removed and homogenized, and their lysosomal fraction was extracted. To this fraction, Oleyl Alcohol was added in varying concentrations. Damage to lysosomes was determined by using the extent of leakage of lysosomal acid phosphatase. At 2×10^{-5} M, Oleyl Alcohol had significant stabilizing effect, and 5×10^{-5} M caused extensive damage to the lyso-

somes. The interaction of Oleyl Alcohol with lysosomes was biphasic; it was stabilizing at low concentrations and labilizing at high concentrations.

Animal Toxicology

Oral Toxicity

Acute Studies

Egan and Portwood⁽⁷⁾ reported the LD₅₀ of Stearyl Alcohol was not reached even at doses of 8 g/kg given orally to male and female Holtzman albino rats. Stearyl Alcohol is classified as "nontoxic" by the Federal Hazardous Substances Labelling Act (FHSLA) and "practically non-toxic" by the criteria of Hodge and Sterner. Other sources reported that Stearyl Alcohol had a low order of toxicity.^(29,48)

Undiluted Octyl Dodecanol was administered orally as a single dose to 5 rats at 5 g/kg, with no evident toxicity.⁽⁴⁹⁾

Product formulations containing Oleyl Alcohol or Octyl Dodecanol have been tested for acute oral toxicity in rats. Products containing 8.0 percent or 20 percent Oleyl Alcohol administered by gastric intubation at doses up to 10 g/kg caused no deaths and no toxic effects.⁽⁵⁰⁻⁵²⁾ A lipstick containing 10.2 percent Octyl Dodecanol was diluted to 50 percent and administered to 10 rats at a dose of 25 g/kg. The total dose of Octyl Dodecanol was 1.28 g/kg. There were no deaths.⁽⁵³⁾

Percutaneous Toxicity

Acute Studies

An acute percutaneous toxicity study was conducted with 100 percent Octyl Dodecanol on 6 guinea pigs. A single dose of 3.0 g/kg was applied under occlusion to each animal on abraded and intact skin. No deaths occurred, all animals appeared normal throughout the study, and there were no gross lesions at necropsy on the seventh day.⁽⁵⁴⁾

Subchronic Studies

A subchronic percutaneous toxicity study was conducted for 3 months on a cream product formulation containing 8.0 percent Stearyl Alcohol. In 2 groups of 10 rabbits each, animals received topical applications of the product at doses of 8.8 mg/cm² per 8.4 percent body surface area (BSA) or 13.2 mg/cm² per 11.2 percent BSA 3 days a week during a 3-month period. A third group of 10 rabbits served as an untreated control. The product caused very slight to well-defined erythema and mild desquamation during the first month of treatment, and mild inflammation at the site of application was noted at necropsy. The results of hematological and blood chemistry determinations, urinalyses, organ weight measurements, and necropsy indicated no treatment-related effects. No evidence of systemic toxicity attributable to topical application of the product was found.⁽⁵⁵⁾

Ocular Irritation

Studies of irritation to the rabbit eye were conducted on samples of undiluted Stearyl Alcohol from 4 separate commercial sources. Each of the samples

was instilled full strength into 1 eye of each of 6 rabbits. Minimal irritation was noted on Day 1 for 3 of the samples (maximum score of 5, scale 0 to 110), and there was no irritation from the remaining sample. Scores decreased to 0 by Day 4 in all cases.⁽⁵⁶⁾

An irritation test of 100 percent Oleyl Alcohol using 6 rabbits gave an ocular irritation score of 1 (max, 110) on Day 1; all scores were 0 by the second day.⁽⁵⁷⁾ The ocular toxicity of 4 lots of Oleyl Alcohol was tested in a modified version of the Official French Method.⁽⁵⁸⁾ The undiluted ingredient in a 0.1 ml volume was applied to 1 eye of each of 6 rabbits, and readings were made at 1, 24, and 48 hours. The scores were 7.17 (max, 110) at 1 hour, 0.33 at 24 hours, and 0.0 at 48 hours.⁽⁵⁹⁾

In an ocular irritation test 100 percent Octyl Dodecanol with 6 rabbits had an average irritation score of 4 (max, 110) on Day 1, with a score of 0 by Day 4.⁽⁶⁰⁾ In an identical test, 100 percent Octyl Dodecanol had scores of 1 on Days 1 and 2 and 0 on Day 3.⁽⁶¹⁾

Several ocular irritation studies using rabbits were conducted on product formulations containing 8.0 to 20 percent Oleyl Alcohol or 3.0 to 10.2 percent Octyl Dodecanol. In every case, there was either no or only minimal, transient ocular irritation induced by these products.^(52,62-67)

A Draize ocular irritation test was conducted on a hairdressing formulation containing 1.5 percent Oleyl Alcohol after several complaints of ocular irritation were reported from its use. A 0.1 ml volume of the undiluted product was instilled into the eyes of 3 albino rabbits both with and without tapwater rinse. The product was practically nonirritating. The product was also tested undiluted and in a 25 percent diluted form and caused no ocular irritation in squirrel monkeys. Furthermore, exposure of the hairdressing formulation to oxygen, UV irradiation, and 0.01 N sulfuric acid caused no increase in product-induced irritation. Instillation of the hairdressing did not potentiate the ocular irritancy of a saturated solution of NaCl, 4 percent Formosaline, or 15 percent Teepol. Irritation did occur after the instillation into the eyes of rabbits of rinsings taken from the human head after use of the hairdressing.⁽⁶⁸⁾

Skin Irritation

Acute Studies

Cutaneous irritation tests using rabbits were conducted on 4 samples of Stearyl Alcohol obtained from separate commercial sources. When each sample was applied full strength under occlusion to the clipped skin of 9 rabbits for 24 hours, irritation scores of 0.4, 0.5, 1.42, and 1.5 were recorded (scale 0 to 4). These scores were indicative of minimal to mild primary skin irritation.⁽⁶⁹⁾

Many studies on the irritant properties to the skin of Oleyl Alcohol have been reported. According to Drill and Lazar⁽⁷⁰⁾ 25 percent Oleyl Alcohol in mineral oil caused no to low skin irritation. Four lots of Oleyl Alcohol were tested for acute skin irritation according to a modified version of the Official French Method.⁽⁵⁸⁾ Samples were fixed for 24 hours under occlusion to the backs of rabbits. Irritation was evaluated according to a modification of the French Method scale of 0 to 8: nonirritant, less than 0.5; slight irritant, 0.5 to 2; moderate irritant, 2-5; severe irritant 5-8. The four lots were each tested in undiluted form and in a 10 percent aqueous dispersion, and 2 samples were assayed twice. Each assay was per-

formed on at least 6 animals. By this assay, Oleyl Alcohol was slightly irritating when undiluted and nonirritating when in a 10 percent aqueous dilution (Table 3).⁽⁵⁹⁾

A skin irritation test with 9 rabbits gave an irritation index of 0.17 (scale 0 to 4) for 100 percent Oleyl Alcohol applied for 24 hours under occlusion. This score was indicative of minimal primary skin irritation.⁽⁷¹⁾ When undiluted Oleyl Alcohol was applied to the skin of rabbits for 4 consecutive days, the greatest average irritation score was 2.33 (scale 0 to 4). This result was interpreted as mild primary skin irritation.⁽⁷²⁾

Three separate cutaneous irritation tests using rabbits were conducted on 100 percent Octyl Dodecanol or a 30 percent aqueous dilution of Octyl Dodecanol in which the test material was applied under occlusion to the backs of 9 rabbits for 24 hours. The ingredient produced skin irritation indices (scale 0 to 4) of 1.13,⁽⁷³⁾ 0.5,⁽⁷⁴⁾ and zero⁽⁷⁵⁾ for the alcohol full strength and zero⁽⁷⁵⁾ for the 30 percent aqueous dilution.

Technical grade Oleyl Alcohol and 2-octyl dodecanol were tested for skin irritation using rabbits, guinea pigs, rats, miniature swine, and man.⁽⁷⁶⁾ In the rabbit studies, the hair on 6 areas of each of 6 albino rabbits was shaved, and test materials were applied 24 hours later. Undiluted samples were applied in 0.1 g amounts to the test areas for 24 hours. The sites were graded for irritation, and the compounds were reapplied 30 minutes later. Second gradings were made 48 hours later (72 hours after the initial application), after which Evans blue solution was injected intravenously into each animal. One hour after injection, the animals were killed and the skin sampled. In guinea pig and rat studies, 2 dorsal areas of each of 6 male Hartley guinea pigs and 6 Wistar rats were clipped free of hair, and testing began 24 hours later. One site received a dose of 0.1 g of the test compound, and the other site was left untreated. Other test parameters were identical to the rabbit test procedure. In the swine test, the entire dorsal area of groups of 6 miniature Pitman-Moore improved strain swine was clipped free of

TABLE 3. Oleyl Alcohol, Acute Skin Irritation⁽⁵⁹⁾

Lot	Compound Concentration	Irritation		Interpretation
		Assay No.	Score	
1	Undiluted	1	1.71	Slight irritant
		2	1.58	Slight irritant
	10%	1	0.17	Nonirritant
		2	0.33	Nonirritant
2	Undiluted	1	1.67	Slight irritant
		2	1.75	Slight irritant
	10%	1	0.04	Nonirritant
		2	0.25	Nonirritant
3	Undiluted	1	1.50	Slight irritant
	10%	1	0.29	Nonirritant
4	Undiluted	1	1.33	Slight irritant
	10%	1	0.42	Nonirritant

hair, and testing began 24 hours later. The test compounds (0.05 g) were applied under occlusion for 48 hours and scored on a scale of (–), no reddening, to (+++), severe reddening. The results of these assays were expressed as scores of 0 (negative) to 3 (severely irritating) and compared to the results of human skin patch testing of these compounds by the same investigators. Although irritation was moderate to severe in the rabbit, guinea pig, and rat, no irritation occurred in swine or human skin. The two compounds were comparable in their ability to produce irritation (Table 4). Skin samples from the rabbit, guinea pig, and rat following exposure to the 2 alcohols had changes of acanthosis, hyperkeratinization, swelling of cells, and proliferation of basal cells. Vasodilatation, edema, alteration of collagenous fibers, and mononuclear and polymorphonuclear leukocyte infiltration were observed in the dermis. In the case of Oleyl Alcohol, edema of the epidermis developed into spongiosis, causing an “eruption” of the epidermis and “crust and ulcer” formation. Both the erupted epidermis and the infundibulum of the hair follicles were infiltrated by inflammatory cells.

Several primary skin irritation studies have been conducted on product formulations containing various concentrations of Oleyl Alcohol or Octyl Dodecanol.^(52,62,58,77–80) Single applications under occlusion for 24 hours of products containing 8.0 to 20 percent Oleyl Alcohol or 4.0 percent Octyl Dodecanol produced no to mild irritation with primary irritation indices (scale 0 to 4) of 0.0 to 1.08.^(52,77–79) Product formulations containing 12.7 percent Oleyl Alcohol or 10.2 percent Octyl Dodecanol applied to the skin of rabbits for 3 to 4 consecutive days produced minimal to mild irritation.^(62,80) A product containing 1.5 percent Oleyl Alcohol was tested for primary skin irritation undiluted and diluted 1:4 with water. Test materials were applied to the intact and abraded skin of rabbits and to the ears of female CF/1 mice, for 4 daily 0.01 ml applications. The product, both diluted and undiluted, was irritating to the skin of rabbits and mice.⁽⁶⁸⁾ The degree of irritation in these studies did not correlate with the concentration of Oleyl Alcohol or Octyl Dodecanol present.

Subchronic Studies

A 60-day modified cumulative irritation test as outlined in *Journal Officiel de la Republique Francaise*⁽⁵⁸⁾ was conducted on 4 lots of Oleyl Alcohol in undiluted form and in 10 percent dilutions. Materials were applied every day. Scoring

TABLE 4. Comparative Irritation of Oleyl Alcohol and 2-Octyl Dodecanol in Several Species⁽⁷⁶⁾

Species	Concentration (%)	Dose (g)	Irritation Score*	
			Oleyl Alcohol	2-Octyl Dodecanol
Rabbit	100	0.1	3	3
Guinea pig	100	0.1	3	2
Rat	100	0.1	2	2
Swine	100	0.05	0	0
Human	100	0.05	0	0

*0, negative; 2, moderately irritating; 3, severely irritating.

was expressed as a weekly average of daily observations. After 8 weeks, microscopic examinations of 2 samples of skin were conducted. A study of recovery from cutaneous injury was performed by interrupting application for 7 days and examining the skin thereafter. The results indicated that undiluted Oleyl Alcohol was poorly tolerated, with thickening and drying of skin and eschar formation. Microscopic changes were thinning of stratum corneum, acanthosis, and orthokeratosis. The 10 percent dilutions were "relatively well tolerated," with only slight exfoliation. Hyperplasia, moderate hypercanthosis, vascular congestion of superficial dermis, and slight erythema and edema were present.⁽⁵⁹⁾

Guinea Pig Skin Sensitization

Two guinea pig sensitization studies were conducted on a deodorant containing 24.0 percent Stearyl Alcohol using the Draize repeated topical application method.^(81,82) In one study,⁽⁸¹⁾ 25 animals received 9 induction applications of the deodorant, diluted to 50 percent in petrolatum, under occlusion for 24 hours on abraded skin sites. This was followed by a 2-week nontreatment period and then challenge applications to both intact and abraded untreated sites. Groups of 5 animals served as petrolatum and untreated controls. At challenge, 1 of 25 treated animals and 1 of 5 petrolatum controls gave a $\pm$ (equivocal) score at 24 hours on the intact skin sites; all other test sites were nonreactive. In the second similar experiment,⁽⁸²⁾ no evidence of reaction at challenge was noted, although 2 of the 10 test animals died during the experiment. Under these test conditions, Stearyl Alcohol was not a contact sensitizer.

Comedogenicity

Stearyl Alcohol was not comedogenic when applied to the ear canal of 2 rabbits 5 days per week, for 2 weeks.⁽⁸³⁾

Special Studies

Mutagenicity

Stearyl Alcohol was tested for mutagenic activity in an Ames assay using 4-histidine-requiring mutants of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537). The compound was tested both with and without metabolic activating S-9 fractions from the livers of rats pretreated with Aroclor 1254 or methylcholanthrene. Stearyl Alcohol was not mutagenic.⁽⁸⁴⁾

Tumorigenicity

Sice⁽⁸⁵⁾ studied the tumor-promoting activity of alkanes and 1-alkanols. Thirty female Swiss strain mice received an initiating dose of 7,12-dimethylbenz[a]anthracene to the shaved skin of the back. Beginning 1 week after the initiating dose, 1 drop (20 μ l) of a solution of Stearyl Alcohol in cyclohexane (20 g/100 ml) was applied 3 times weekly for 60 weeks over the initiated area. Twenty-three of the 30 mice survived the study, and 1 tumor appeared on the initiated area of one mouse at 30 weeks.⁽⁸⁵⁾

Clinical Assessment of Safety

Eye Irritation

Ten human volunteers used 3 ml of a hairdressing product containing 1.5 percent Oleyl Alcohol daily for 5 days. The head was rinsed daily with 50 ml of water. One drop of the rinse water was instilled 4 times daily for 5 days into the same eye. No irritation occurred in any volunteers.⁽⁶⁸⁾

Skin Irritation and Sensitization

Patch Testing

In 24-hour single insult occlusive patch tests, mild irritation was produced by 100 percent Stearyl Alcohol in 1 of 80 subjects⁽⁸⁶⁾ and by 100 percent Octyl Dodecanol in 1 of 40 subjects (Table 5).⁽⁸⁷⁾

Occlusive 48-hour patches using undiluted technical grade Oleyl Alcohol and Octyl Dodecanol in 0.05 g amounts were applied to randomized sites on the skin of the back of 50 adult male volunteers.⁽⁷⁶⁾ The patches were removed, and 30 minutes later the sites were evaluated. Observations also were made at 72 and 96 hours and, if necessary, at 120 hours. There were no signs of skin irritation.

The North American Contact Dermatitis Group reported results of 48- and 96-hour screening patch tests of 30 percent Stearyl Alcohol in petrolatum from several 1-year intervals. Allergic reactions occurred in 2 of 172 individuals tested during the year ending in June 1976,⁽⁸⁸⁾ 1 of 446 during the year ending June 1977,⁽⁸⁹⁾ 6 of 824 during the year ending June 1979,⁽⁹⁰⁾ and 6 of 634 during the year ending June 1980⁽⁹¹⁾ (Table 5).

Hjorth and Trolle-Lassen⁽⁹²⁾ studied allergic skin reactions to ointment bases. Out of a test population of 1664 panelists, each tested with all 3 ingredients, Stearyl Alcohol (30 percent in liquid paraffin) caused 4 positive reactions, Oleyl Alcohol (30 percent in petrolatum) produced 10 positive reactions, and Octyl Dodecanol (30 percent in petrolatum) caused 6 positive reactions (Table 5). Of the 10 patients sensitive to Oleyl Alcohol, 3 were also sensitive to Stearyl Alcohol, and the investigators suggest that cross-sensitization may have occurred.

Lanette-0 (20 percent in petrolatum) is a mixture of Cetyl and Stearyl Alcohols. Lanette-0 was patch tested on 21 patients, and Stearyl Alcohol (50 percent in petrolatum) was tested on those patients who were sensitive to the Lanette-0. Of 7 individuals who were sensitive to the Lanette-0, 4 were sensitive to the Stearyl Alcohol.⁽⁹³⁾

Calnan and Connor⁽⁹⁴⁾ reported 4 positive reactions to carbon paper among 40,000 subjects tested. One of the four had dermatitis and a positive reaction to Oleyl Alcohol.

A number of product formulations containing various alcohols at concentrations of 2.5 to 24 percent have also been tested for human skin irritation (Table 6). Single insult occlusive patch tests on lipstick formulations containing 20 percent Oleyl Alcohol and a moisturizing cream containing 4.0 percent Octyl Dodecanol produced no or only minimal irritation.⁽⁹⁵⁻⁹⁷⁾ Daily patch testing of 5 product formulations containing 8.0 to 24 percent Stearyl Alcohol, 2.5 percent Oleyl Alcohol, or 3.0 percent Octyl Dodecanol for 21 days produced ratings of "essentially nonirritating" or "slightly irritating."⁽⁹⁸⁻¹⁰²⁾ Controlled use of a lipstick containing 8.0 percent Oleyl Alcohol for 4 weeks produced no irritation.⁽¹⁰³⁾ Re-

TABLE 5. Clinical Skin Patch Tests with Stearyl Alcohol, Oleyl Alcohol, or Octyl Dodecanol

<i>Test Method</i>	<i>Material Tested</i>	<i>Concentration of Alcohol (%)</i>	<i>No. of Subjects</i>	<i>Results</i>	<i>Reference</i>
24-hour single insult occlusive patch	Stearyl Alcohol	100	80	Mild irritation in 1 subject	86
	Octyl Dodecanol	100	40	Mild irritation in 1 subject	87
Single insult screening patch for contact sensitization	Stearyl Alcohol	30 in petrolatum	172	2 positive reactions; 1.2 %	88
	Stearyl Alcohol	30 in petrolatum	446	1 positive reaction; 0.22 %	89
	Stearyl Alcohol	30 in petrolatum	824	6 positive reactions; 0.73 %	90
	Stearyl Alcohol	30 in petrolatum	634	6 positive reactions; 0.95 %	91
Single insult screening patch for contact sensitization	Stearyl Alcohol	30 in liquid paraffin	1664	4 positive reactions; 0.24 %	92
	Oleyl Alcohol	30 in petrolatum	1664	10 positive reactions; 0.60 %	92
	Oleyl Dodecanol	30 in petrolatum	1664	6 positive reactions; 0.36 %	92

TABLE 6. Clinical Skin Patch Tests with Product Formulations Containing Stearyl Alcohol, Oleyl Alcohol, or Octyl Dodecanol

Test Method	Material Tested	Concentration of Alcohol (%)	No. of Subjects	Results	Reference
24-hour single insult occlusive patch	Lipstick	20 Oleyl Alcohol	19	No signs of irritation	95
	Lipstick	20 Oleyl Alcohol	16	No signs of irritation	96
	Moisturizing cream	4.0 Octyl Dodecanol	20	PII, 0.03 (max 4.0); minimal irritation in 1 subject	97
21-day cumulative irritancy (23-hour occlusive patch for 21 consecutive days)	Deodorant	24 Stearyl Alcohol	12	Slightly irritating; total composite score was 128/630 max	98
	Antiperspirant Cream	17 Stearyl Alcohol 8.0 Stearyl Alcohol	27 9	Essentially nonirritating Essentially nonirritating; total composite score was 36/630 max	99 100
	Moisturizer	2.5 Oleyl Alcohol	10	Slightly irritating; total composite score was 59/630 max	101
	Eye pencil	3.0 Octyl Dodecanol	16	Essentially nonirritating; total composite score was 7.5/630. Patches applied 5 days/week for 21 total patches	102
	Lipstick	8.0 Oleyl Alcohol	52	No irritation	103
Controlled use (4 weeks of daily use) Schwartz-Peck prophetic patch test (open and closed 48-hour patches, repeated after 2 weeks)	Lipstick	8.0 Oleyl Alcohol	308	Mild irritation with closed patch in 3 subjects at first exposure; no evidence of sensitization. Supplemental UV exposure after second insult produced no reactions	104
	Antiperspirant	17 Stearyl Alcohol	52	Minimal irritation; no sensitization	105
Modified repeated insult patch test (12- or 24-hour patches 4 days/week for 8 induction patches; challenge patch after 2-week rest)	Antiperspirant	17 Stearyl Alcohol	45	Minimal to mild irritation with evidence of fatigue; no evidence of sensitization	106
	Antiperspirant	14 Stearyl Alcohol	50	No irritation; no sensitization	107

TABLE 6. (Continued)

Test Method	Material Tested	Concentration of Alcohol (%)	No. of Subjects	Results	Reference
Draize-Shelanski repeated insult patch test (24- or 48-hour patches 3 days/week for 10 induction patches; challenge after 2-week rest)	Deodorant	24 Stearyl Alcohol	176	Minimal irritation; no sensitization	108
	Deodorant	24 Stearyl Alcohol	150	Minimal irritation; no sensitization	109
	Antiperspirant	17 Stearyl Alcohol	50	Minimal irritation; 1 subject demonstrated reaction indicative of allergic contact dermatitis at challenge; however, rechallenge at untreated site was negative	110
	Antiperspirant	14 Stearyl Alcohol	100	No irritation; no sensitization	111
	Hand cream	12 Stearyl Alcohol	205	Minimal irritation; no sensitization	112
	Deodorant	12 Stearyl Alcohol	48	Mild irritation; no sensitization	113
	Deodorant	12 Stearyl Alcohol	154	Minimal irritation; no sensitization	114
	Cream	8.0 Stearyl Alcohol	213	Minimal irritation; no sensitization	115
	Cream	12.7 Oleyl Alcohol	102	No irritation; no sensitization	116
	Lipstick	8.0 Oleyl Alcohol	154	Minimal irritation; no sensitization. Supplemental UV exposure after induction patches 1, 4, 7, and 10 and after challenge showed no photosensitization	104
	Cream	2.5 Oleyl Alcohol	210	Mild irritation in 1 subject during induction and 1 at challenge; none thought to be indicative of sensitization	117
	Cream	2.5 Oleyl Alcohol	205	Minimal to mild irritation during induction and at challenge; none were thought to be indicative of sensitization	118
	Lipstick	10.2 Octyl Dodecanol	197	No irritation; no sensitization	119
	Unspecified product formulation	3.0 Octyl Dodecanol	210	Isolated mild induction reactions in 2 subjects; no reactions at challenge	120

sults indicative of irritation from product formulations are difficult to interpret with respect to a single ingredient.

Several product formulations containing the alcohols have been tested for skin sensitization on a total of 2629 subjects using a variety of test methods. These studies included: 1 Schwarz-Peck prophetic patch test on a product formulation containing 8.0 percent Oleyl Alcohol, 3 modified repeated insult patch tests on antiperspirant formulations containing 14 or 17 percent Stearyl Alcohol, and 14 Draize-Shelanski repeated insult patch tests on products containing 8.0 to 24 percent Stearyl Alcohol, 2.5 to 12.7 percent Oleyl Alcohol, or 3.0 or 10.2 percent Octyl Dodecanol. Of the 2629 subjects in these studies, there were no reactions indicative of sensitization (Table 6).

Case Reports

Contact sensitization to Stearyl Alcohol has been reported in 3 individuals: 2 had an urticarial-type reaction, and 1 of these reactions was thought to be due to impurities in the Stearyl Alcohol sample.^(9,121,122)

Photoreactivity

A phototoxicity study was conducted on a cream product formulation containing 2.5 percent Oleyl Alcohol using 10 subjects. A single 24-hour skin patch of the product with 1X Minimal Erythema Dose (MED) exposure to a Krohmer Hot Quartz Lamp produced no reactions.⁽¹²³⁾ The same product was tested for photoallergenicity with 25 subjects. Five daily 24-hour induction patches with exposure for 30 seconds to a windowglass-filtered Krohmer Hot Quartz Lamp were followed by a 12-day nonexposure period and then a single 24-hour challenge with the same UV light exposure. No signs of photosensitivity were present.⁽¹²³⁾

A repeated insult photosensitization test using 23 subjects was conducted on a lipstick formulation containing 10.2 percent Octyl Dodecanol. Each subject had applied a 24-hour occlusive patch of the test material followed by UV irradiation of the test site with 3 times the individual's MED. The light source was a filtered 150W Xenon Arc Solar Simulator that produced a continuous emission spectrum in the UVA and UVB region (290 to 400 nm). Patches and irradiation were repeated twice weekly for a total of 6 exposures. Following a 10-day nonexposure period, patches and irradiation were repeated on a previously untreated site. There were no reactions and thus no evidence of phototoxicity or photoallergenicity.⁽¹²⁴⁾

Schwarz-Peck and Draize-Shelanski skin sensitization tests on a lipstick formulation containing 8.0 percent Oleyl Alcohol (summarized in Table 6) also included supplemental UV light exposure, with no resultant reactions.⁽¹⁰⁴⁾

SUMMARY

Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are long-chain saturated or unsaturated (Oleyl) fatty alcohols. The materials of commerce are mixtures of fatty acids, with the predominant species being the named compound.

These alcohols have a wide variety of uses in pharmaceutical, food, and other industries. Stearyl Alcohol is approved for use in certain over-the-counter drugs, and Stearyl and Oleyl Alcohols are approved for some food additive appli-

cations. They are used in numerous cosmetic product categories at concentrations of less than 0.1 percent to greater than 50 percent. They are chiefly used at concentrations less than 25 percent.

The metabolism of Stearyl Alcohol and Oleyl Alcohol in rats is well described. They are used in the biosynthesis of lipids and other naturally occurring cellular constituents or enter metabolic pathways for energy production.

Stearyl Alcohol was not mutagenic in the Ames Assay, and it did not promote tumor formation when tested with DMBA. Oleyl Alcohol and Octyl Dodecanol were not tested in these assays. Due to the chemical nature and benign biological activity of these compounds, they are not suspected of significant potential for carcinogenesis.

The results of acute oral toxicity studies in rats of undiluted Stearyl Alcohol and Octyl Dodecanol and of products containing Oleyl Alcohol and Octyl Dodecanol at concentrations up to 20 percent indicate a very low order of toxicity. Results of percutaneous toxicity studies with 100 percent Octyl Dodecanol and with products containing 8.0 percent Stearyl Alcohol or 8.0 percent Oleyl Alcohol also indicate a low order of toxicity. In rabbit irritation tests, these alcohols produced minimal ocular irritation and minimal to mild primary cutaneous irritation. In 1 assay system, the skin irritancy of technical grade Oleyl Alcohol and Octyl Dodecanol was moderate to severe in rabbits, guinea pigs, and rats, whereas no irritation was seen in swine and human skin. Observations made in a subchronic skin irritation study indicated that 100 percent Oleyl Alcohol was "poorly tolerated" when applied to the skin of rabbits daily for 60 days, whereas 10 percent dilutions were "relatively well tolerated." A product containing 24 percent Stearyl Alcohol produced no evidence of contact sensitization in the guinea pig. A rabbit ear comedogenicity test on Stearyl Alcohol was negative.

The results of single insult clinical patch testing indicate a very low order of skin irritation potential for undiluted Stearyl Alcohol and Octyl Dodecanol. Several studies of screening patch testing for contact sensitization in large populations had rates of 19 of 3740 (0.51 percent) for Stearyl Alcohol, 10 of 1664 (0.60 percent) for Oleyl Alcohol, and 6 of 1664 (0.36 percent) for Octyl Dodecanol. Reports of isolated cases of contact dermatitis from Stearyl Alcohol are available. Tests of product formulations in humans demonstrated low potentials for significant skin irritation or sensitization from the alcohols in formulation. Photoreactivity studies on products containing 2.5 percent Oleyl Alcohol or 10.2 percent Octyl Dodecanol were negative for phototoxicity or photosensitization. A hair-dressing product containing 1.5 percent Oleyl Alcohol was nonirritating to the human eye.

CONCLUSION

Based on the available data, Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are safe as currently used in cosmetics.

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