Safety Assessment of Alkane Diols

as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, 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 Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.org

INTRODUCTION

This assessment reviews the safety of 10 alkane diols as used in cosmetic formulations. Throughout this report, the information on these ingredients will be presented based on order of increasing chain length, followed by increasing extent of branching, as follows:

Propanediol
1,4-Butanediol
1,5-Pentanediol
Hexanediol
Octanediol
1,10-Decanediol
Methylpropanediol
2,3-Butanediol
Butyl Ethyl Propanediol
Isopentyldiol

The alkane diols reviewed in this safety assessment have various reported functions in cosmetics (Table 1), as indicated in the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)*, including uses as solvents, humectants, and skin conditioning agents.[1] Propanediol, for example, is used as a solvent and viscosity decreasing agent; Butyl Ethyl Propanediol is used as a skin-conditioning agent and humectant.

The alkane diol ingredients in this report are structurally related to each other as simple, small diols. Diols with 1,2-substitution regiochemistry (e.g., 1,2-Butanediol) have been reviewed previously by the Panel, and the conclusion for each is summarized in Table 2.[2-10] All of these ingredients are safe as used with the qualification that Propylene Glycol is safe as used when formulated to be non-irritating.

Study reports and data summaries from industry included in this safety assessment were found on the European Chemicals Agency (ECHA) website and on the Australian Government Department of Health's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) website; in reports published by the World Health Organization (WHO), the Organization for Economic Co-operation and Development Screening Information Data Sets (OECD SIDS), and National Toxicology Program (NTP); and in reports made available by the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and by the National Technical Information Service (NTIS). The above references are cited when data from these sources is summarized and the primary references were not readily obtainable.

CHEMISTRY

Definition and Structure

All of the ingredients in this report are structurally related to each other as simple, small diols (i.e. three to ten carbon alkyl diols). The ingredients in this report include regiochemistry other than 1,2-substitution. For example, 2,3-butanediol is a vicinal diol with the first hydroxyl substitution at the 2-position and 1,4-butanediol is a terminal diol with substitution at the 1- and 4-positions (Figure 1).

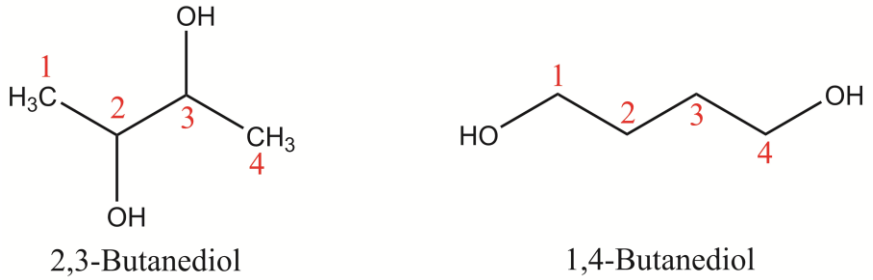


Figure 1. 2,3-Butanediol and 1,4-Butanediol

Variations in the regiochemistry of small alkane diols may lead to significant differences in toxicity. For example, 2,5-hexanediol, which is not a cosmetic ingredient, is known to be a neurotoxic metabolite of hexane.[11,12] However, the structurally similar cosmetic ingredient, 1,6-Hexanediol, is not a neurotoxin.

The ingredients included in this safety assessment are listed in order by increasing chain length, followed by increasing branching (Table 1).

Physical and Chemical Properties

Alkane diols can be liquids or crystals. Generally, they are fairly soluble in alcohol and have variable solubility in water (Table 3).

Method of Manufacture

Propanediol

Propanediol may be prepared from corn-derived glucose using a biocatalyst (non-pathogenic strain of *Escherichia coli* K-12).[13] It can be manufactured by heating γ,γ-dihydroxydipropyl ether with hydrobromic acid, followed by hydrolysis with sodium hydroxide. It is also obtained from plants that produce glycerol.[14] Propanediol can be prepared by reducing ethyl glycidate with lithium aluminum hydride.[15]

1,4-Butanediol

Industrial chemical companies manufacture 1,4-Butanediol using cupric acetylide catalysts in the condensation reaction of acetylene with formaldehyde.[14] Some manufacturers convert propylene oxide to allyl alcohol, which is then hydroformulated to 4-hydroxybutyraldehyde.[16] 1,4-Butanediol is produced by the hydrogenolysis of 4-hydroxybutyraldehyde. Maleic acid and succinic acid can be used to manufacture 1,4-Butanediol during the vapor phase hydrogenation of their corresponding esters and anhydrides. *E. coli* can be genetically engineered to metabolize sugar that produces 1,4-Butanediol.[17]

1,5-Pentanediol

1,5-Pentanediol can be prepared in the presence of copper chromite by hydrogenolysis of tetrahydrofurfuryl alcohol.[15]

1,10-Decanediol

1,10-Decanediol may be prepared by reducing diethyl or dimethyl sebacate with ethyl alcohol and sodium. It is also prepared by catalytic hydrogenation of sebacic esters.[15]

Methylpropanediol

In industry, carbon monoxide and hydrogen are used in the hydroformylation of allyl alcohol to produce the intermediate hydroxymethylpropionaldehyde, which then undergoes hydrogenation to yield Methylpropanediol.[18]

2,3-Butanediol

2,3-Butanediol has been commercially produced by fermentation of molasses or sugar using *Mesentericus* bacteria; fermentation of potatoes or wheat mash also yields 2,3-Butanediol.[14] Various microorganisms yield 2,3-Butanediol during glucose fermentation by enteric bacteria (e.g., *Aerobacter*, *Klebsiella*, *Serratia*). *Bacillus polymyxa*, *Lactobacilli* and *Staphylococci* strains, and filamentous fungi (e.g., *Rhizopus nigricans*, *Penicillium expansum*) produce 2,3-Butanediol. Mixtures of gases containing isobutylene and normal butenes, when combined with hydrogen peroxide and formic acid, yield a product containing 2,3-Butanediol, fractions of which are collected by distillation. The *meso*-form of 2,3-Butanediol can be prepared from *trans*-2,3-epoxybutane; the D- form can be prepared by fermenting carbohydrate solutions with *Bacillus subtilis* organisms.[15]

Specifications

Propanediol

The following Food Chemicals Codex acceptance criteria apply for Propanediol in relation to food preparation: cobalt (not more than-(NMT) 1.0 mg/kg or 1 ppm); lead (NMT 1.0 mg/kg or 1 ppm); nickel (NMT 1.0 mg/kg or 1 ppm).[13]

Natural Occurrence

2,3-Butanediol

2,3-Butanediol occurs naturally in certain foods, "…0.006 mg/kg in fish (lean), up to 90 mg/kg in cheddar cheese, up to 2.3 mg/kg in raspberry, up to 850 mg/kg in vinegar, 1.9 mg/kg in sherry and up to 2900 mg/kg in various types of wine."[19]

USE

Cosmetic

The Panel evaluates the safety of the cosmetic ingredients included in this assessment based on the expected use of and potential exposure to the ingredients in cosmetics. The data received from the FDA are collected from manufacturers through the FDA's Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category. VCRP data obtained from the FDA in 2016[20] indicated that alkane diols are being used in cosmetic formulations (Table 4). Among the ingredients most frequently used are Propanediol (815 reported uses), Methylpropanediol (400 reported uses), and Isopentyldiol (127 reported uses). The remaining 2 of the 5 in-use alkane diols are each reported to have 15 or less uses. Concentration of use survey data in 2015-2016[21] (Table 4) indicated the highest maximum reported concentrations of use were as follows: 39.9% Propanediol (in non-spray deodorants), 21.2% Methylpropanediol (in non-spray body and hand products), 15% Isopentyldiol (in hair conditioners, non-coloring shampoo, and other hair preparations, non-coloring).

The 3 alkane diols included in this safety assessment, but not reported to be in use based on both the VCRP data and the Council survey, are 1,5-Pentanediol, Octanediol and 2,3-Butanediol.

In some cases, uses of alkane diols were reported in the VCRP, but concentration of use data were not provided in the Council survey. For example, 1,4-Butanediol is reported to be used in 4 cosmetic formulations, but no use concentration data were reported.[20] Conversely, there were instances in which no uses were reported in the VCRP, but use concentrations were provided in the industry survey. For example, Hexanediol was not reported to be in use in the VCRP, but the Council survey indicated that it is used at concentrations in leave-on formulations up to 0.5% and in rinse-off formulations up to 0.45%.[21] It should be presumed in these cases that there is at least one use in every category for which a concentration of use is reported.

Alkane diols were reported to be used in cosmetic sprays, including perfumes, hair sprays, deodorants, and powders, and could possibly be inhaled. For example, Propanediol is reportedly used in aerosol and pump hair sprays at concentrations up to 0.12% and 1.5%, respectively.[21] Propanediol is used in face and neck sprays at concentrations up to 3% and Isopentyldiol is reportedly used in perfumes and aerosol deodorants at concentrations up to 5% and up to 1%, respectively.[21] In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[22-25] Most droplets/particles incidentally inhaled from cosmetic sprays would not be respirable because they would be deposited in the nasopharyngeal and bronchial regions, and therefore would not enter the lungs to any appreciable amount.[22,24] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[24] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[26-28]

Alkane diols were reported to be used in cosmetic formulations indicative of potential eye exposure (Propanediol up to 10% in eye makeup removers) and possible mucous membrane exposure and ingestion (Propanediol up to 10% in dentifrices). Propanediol was reported to be used in baby shampoos, baby lotions, oils, powders, and creams (no concentrations of use were reported).

None of the alkane diols named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[29]

Non-Cosmetic

The non-cosmetic uses of the alkane diols (see Table 5), as specified in the Code of Federal Regulations Title 21, are largely as indirect food additives. None of the 10 alkane diols presented in this safety assessment are listed as inactive ingredients in FDA approved drug products.[30]

Propanediol

A GRAS exemption claim for 1,3-propanediol (referred to as Propanediol in this safety assessment) was submitted by an industry company to the FDA in 2009 with the intent to use 1,3-propanediol as an alternative food ingredient to 1,2-Propanediol.[31] The claim stated that 1,3-propanediol is exempt from the requirement of premarket approval for its use in food, based on the company's assertion that 1,3-propanediol is GRAS as defined by Section 201(s) of the Federal Food, Drug, and Cosmetic Act. The FDA, in 2010, responded with a letter to the company stating that the FDA had no questions regarding the company's claim that 1,3-propanediol was GRAS given the intended use, however the agency had made no decision concerning the GRAS status of 1,3-propanediol.[32]

1,4-Butanediol

1,4-Butanediol is known to be an illicit drug of abuse because of its conversion to gamma-hydroxybutyric acid (GHB, aka-the "date rape drug") after oral administration.[33] GHB, occurring endogenously in mammals, is a neurotransmitter with a high affinity for pre- and postsynaptic neuron GHB-receptors.[34] In 1999, the FDA issued a warning about products (i.e., dietary supplements advertised to aid in sleep) containing 1,4-Butanediol and gamma-butyrolactone (GBL is a structurally similar analog of GHB) because of reports linking these compounds to adverse health effects (e.g., decreased respiration) and 3 deaths.[35] The FDA considers 1,4-Butanediol to be a Class I Health Hazard (potentially life-threatening risk). GHB has been used in dietary supplements because it can increase physiological concentrations of growth hormone, leading to an increase in lean muscle mass; weight control and sedation were other effects of GHB ingestion advertised by health food stores.[34] In 1997, the FDA re-issued a warning for GHB used recreationally and in body building because it caused serious adverse health effects.[35] As of 2000, the Drug Enforcement Agency (DEA) reported GHB to be a Schedule I Controlled Substance and 1,4-Butanediol and GBL to be controlled substance analogs if they are intended for human consumption pursuant to 21 U.S.C §§802(32)(A) and 813.[33] Sodium oxybate (a form of GHB) is a prescription FDA approved drug product (schedule III controlled substance)[33] labeled as Xyrem® (500 mg/ml oral solution) and used to treat attacks of muscle weakness and daytime sleepiness in narcolepsy patients.[36-38]

Pentylene Glycol

Pentylene Glycol (source did not specify whether 1,2-Pentanediol or 1,5-Pentanediol was used or the concentration used) was listed as an ingredient in a prescription hydrogel wound dressing (medical device classified under 21CFR878.4022), which was approved by

the FDA (Section 510(k)) to be marketed without a premarket approval application. The medical device was considered equivalent to "legally marketed predicate devices".[40]

1,5-Pentanediol

1,5-Pentanediol has been reported to have antimicrobial and antifungal properties in pharmaceutical applications.[41]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Propanediol

A dermal penetration study conducted using human cadaver skin evaluated the penetration of Propanediol.[42] The stratum corneum (abdominal region of human cadaver skin, n=6 representing 3 donors) was mounted onto an *in vitro* static diffusion cell (skin surface area 0.64 cm^2). The experiment was conducted using Good Laboratory Practice (GLP) in accordance with OECD Test Guideline (TG) 428 (Skin Absorption: *in vitro* Method). A solution containing 1.059 g/ml Propanediol (vehicle not specified) was applied to the skin in the donor chamber (opening to chamber was occluded). The receptor fluid (0.9% saline) was maintained @ 32°C in a recirculating water bath and was sampled at time zero and every 4-6 hours up to 48 hours post-application. The permeability coefficient was calculated to be 1.50×10^{-5} cm/h, based on the slope at steady state (15.9 µg/cm^2/h) and the concentration of Propanediol applied (test solution density 1,059,700 µg/cm^3). The percentage of the applied Propanediol recovered from the receptor chamber 48 hours post-application was 0.12%.

Penetration Enhancement

In Vitro

Provided below is a summary of penetration experiments that are presented in greater detail in Table 6.

Penetration enhancement tests *in vitro* showed 1,5-Pentanediol to be a penetration enhancer for certain pharmaceutical drugs.[43] Test cream formulations containing 0.1% tri-iodothyroacetic acid (TRIAC; a thyroid hormone analog) and either 1,5-Pentanediol (10%) or 1,2-Propanediol (10%) showed 1,5-Pentanediol to be a more effective penetration enhancer than 1,2-Propanediol for TRIAC in a multilayer membrane system (MMS) experiment.

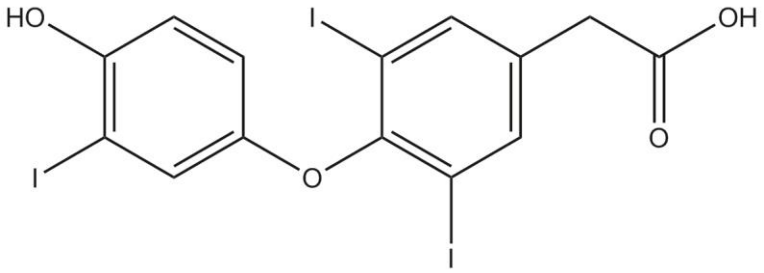


Figure 2. TRIAC

Results for 1,5-Pentanediol indicated that 33% of the TRIAC was released from the formulation (in MMS) by 30 minutes post-application and 62% was released by 300 minutes. In a separate experiment, test cream formulations containing 1% hydrocortisone and either 1,5-Pentanediol (25%) or 1,2-Propanediol (25%) were evaluated using human breast skin.

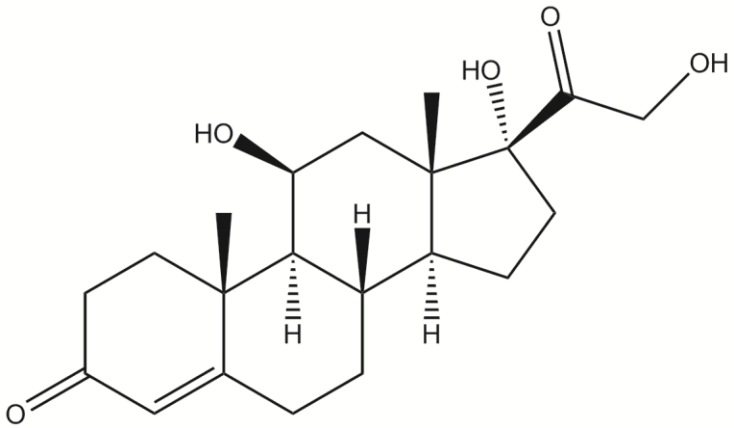


Figure 3. Hydrocortisone

Both 1,5-Pentanediol and 1,2-Propanediol were shown to be penetration enhancers. However 1,2-Propanediol enhanced the transport of the drug through the skin more effectively, whereas 1,5-Pentanediol was better at increasing the retention of the drug into the skin (receptor fluid was collected up to 60 hours post-application). Another experiment evaluating test cream formulations containing 0.1% mometasone furoate and either 1,5-Pentanediol (25%) or Hexylene Glycol (12%) revealed that both formulations were percutaneous absorption enhancers in human breast skin (receptor fluid was collected up to 60 hours post-application).

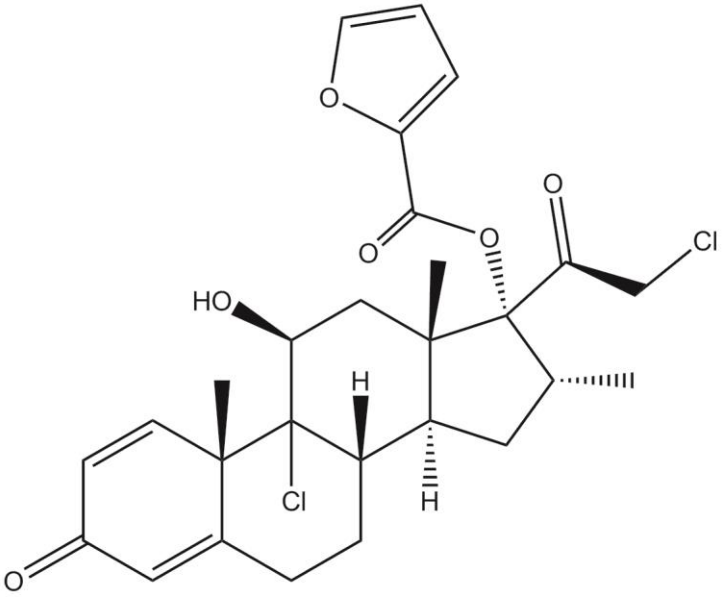


Figure 4. Mometasone

Absorption, Distribution, Metabolism, Excretion

Absorption, distribution, metabolism, and excretion studies are summarized below; details are presented in Table 7.

In Vitro

Metabolism experiments conducted using rat liver homogenates revealed that Propanediol was converted to malondialdehyde (5.6 nmol/h/100 mg tissue);[44] Methylpropanediol was a substrate for rat liver alcohol dehydrogenase;[18] 10 nmol of diacetyl, acetoin, and 2,3-Butanediol were interconvertible with a molar equilibrium ratio of 0:3:7, respectively, in rat liver homogenates.[45] Competitive inhibition between 1,4-Butanediol (0.5 mM) and ethanol (0.5 mM) occurred in a test performed using liver alcohol dehydrogenase.[46]

Animal

Experiments in rabbits that were administered single doses of alkane diols via a stomach tube revealed metabolites isolated from the urine 1 to 3 days post-dosing. Propanediol glucuronic acid conjugation accounted for up to 2% of the administered dose (4 mmol/kg); 1,4-Butanediol (9 g) was metabolized to succinic acid (7% of administered dose); phenacyl glutarate (0.5% of dose) was identified after 1,5-Pentanediol (8.5 g) administration; Hexanediol glucuronic acid conjugation accounted for up to 9% of the administered dose (2 mmol/kg) and adipic acid was detected; 2,3-Butanediol glucuronic acid conjugation accounted for up to 26% of the administered dose (4 mmol/kg).[47]

Rats were intragastrically exposed to a single dose of 1 g/kg 1,4-Butanediol and at 75 minutes post-dosing, 96 µg/g were detected in the brain, 52 µg/g were detected in the liver, and 58 µg/g were detected in the kidney; endogenous levels of 1,4-Butanediol in rats dosed with ethanol only were found to be 0.02 to 0.05 µg/g; 1,4-Butanediol levels in the liver (50 µg/g tissue) peaked 1.5 to 3 hours post-dosing; 30 minutes post-dosing sedation and ataxia were observed and by 60 minutes catalepsy was noted (these effects were synergistically intensified when ethanol was concurrently administered).[46] Rats dosed intragastrically with 1 g/kg 1,4-Butanediol showed hyperemia in the brain, liver, and kidney 24 hours post-administration. The mortality rate of rats 24 hours after administration of a single 1 g/kg 1,4-Butanediol dosage was 1 death per 18 rats. In rats orally administered up to 400 mg/kg 1,4-Butanediol (radiolabels on C1 and C4), >75% of the radioactivity was excreted as $^{14}CO_2$ (by 24 hours post-administration), up to 6% of the radioactivity was excreted in urine (by 72 hours post-administration), and up to 0.6% of the radioactivity was excreted in feces (by 72 hours post-administration).[48]

Endogenous concentrations of 1,4-Butanediol in rats were found to be 165 ng/g (in stomach) and 30 ng/g (in liver) in aqueous phase tissues and in lipid phase tissues were 150 to 180 ng/g.[49]

Methylpropanediol orally administered to rats (neither dosage nor radioactivity were specified) was rapidly metabolized and eliminated in the urine as 3-hydroxybutyric acid and in the exhaled breath as CO_2.[18] Experiments in rats orally administered 1 M diacetyl, acetoin, or 2,3-Butanediol showed that these compounds interconvert.[45]

Liver perfusion experiments in rats (*in vivo*) that were administered 1 mM 2,3-Butanediol resulted in the oxidation of 2,3-Butanediol to small amounts of diacetyl and acetoin; 33% of the perfused 2,3-Butanediol was metabolized or conjugated in the liver.[45]

Human

Human subjects orally exposed to 1,4-Butanediol (single dose of 25 mg/kg) in fruit juice exhibited measurable plasma concentrations of GHB between 5 and 30 minutes post-dosing, indicating rapid conversion of 1,4-Butanediol to GHB; 4 hours post-dosing plasma levels were below the limit of quantitation (1 mg/l).[50] Clearance of 1,4-Butanediol was rapid in some subjects and relatively slower in other subjects, who were confirmed to have a genetic mutation of variant alleles (G143A single nucleotide-polymorphism of ADH-1B). Lightheadedness, headaches, and increased blood pressure were observed by 15 minutes post-dosing, and reports of subjects feeling less alert or dizzy were observed for up to 4 hours post-dosing. A study in which human subjects were injected intravenously with 1,4-Butanediol (15 or 30 mg/kg) showed rapid and nearly 100% conversion of 1,4-Butanediol to GHB; 1,4-Butanediol and GHB had essentially the same decay curves when equal doses of each were administered.[48] In another study, human subjects were orally administered GHB (single dose of 25 mg/kg) in water; absorption and elimination (linear kinetics) of GHB were rapid.[51] Terminal plasma elimination half-life was 17.4 to 42.5 min. The majority of subjects showed the highest concentrations in urine 60 minutes post-dosing; the total urine recovered 24 hours post-dosing was up to 2% of the administered dose. Confusion, sleepiness, and dizziness were observed, with substantial variation among the subjects.

Metabolic Pathways

1,4-Butanediol

In mammals, 1,4-Butanediol is metabolized endogenously to gamma-hydroxybutyraldehyde by alcohol dehydrogenase and then by aldehyde dehydrogenase to GHB.[34] This metabolism has been reported to occur in rat brain and liver.[49] Ethanol, a competitive substrate for alcohol dehydrogenase, can inhibit 1,4-Butanediol metabolism.[34,46] GHB is metabolized to succinic semialdehyde by GHB dehydrogenase, and then to succinic acid by succinic semialdehyde dehydrogenase; succinic acid then enters the Krebs cycle.[34] Alternatively, succinic semialdehyde can be metabolized by gamma-aminobutyric acid (GABA) transaminase to produce the neurotransmitter GABA.

2,3-Butanediol

2,3-Butanediol plays an integral part in the metabolism of alcohol.[52] Ethanol is converted to acetaldehyde via alcohol dehydrogenase. Acetaldehyde in greater quantities, produced after consuming large amounts of ethanol, can be toxic. This is especially true for individuals who cannot metabolize alcohol efficiently because of a genetic defect for the aldehyde dehydrogenase gene. When human subjects (male) consumed 0.4 g ethanol/kg after fasting for 12 hours, one subject with a deficient aldehyde dehydrogenase gene had five times higher acetaldehyde levels 30 minutes post-administration than those without the same genetic defect. Signs and symptoms after consuming ethanol, of the subject with the deficient gene, were flushing and an "uncomfortable feeling", while the subjects without the genetic defect exhibited no flushing and could perform normal work activities.

The body can detoxify acetaldehyde through aldehyde dehydrogenase to form acetate.[52] Acetaldehyde also reacts with pyruvate, enzymatically and non-enzymatically, in the presence of thiamine to form acetoin. Acetoin can interconvert between diacetyl and 2,3-Butanediol. 2,3-Butandiol will react with freely available uridine diphosphate glucuronic acid, by the catalysis of uridine diphosphate-glucuronyltransferase, to form 2,3-Butanediol β-glucuronide. This glucuronide metabolite of 2,3-Butanediol is readily excreted in the urine. Endogenous concentrations of ethanol in male human subjects who had not ingested alcohol were determined to be 42 and 84 µM in plasma and urine, respectively. In male human subjects, endogenous levels of acetaldehyde were determined to be 6.9 and 22.6 µM and of 2,3-Butanediol were found to be 7.1 µM and 56.4 µM in plasma and urine, respectively. The intrinsic presence of 2,3-Butanediol, as well as of diacetyl and acetoin, was reported in rat tissues and urine with higher amounts in the liver and brain.

TOXICOLOGICAL STUDIES

Acute Toxicity

Provided below is a summary of the acute toxicity studies; details are presented in Table 8.

Dermal

Dermal exposure animal studies evaluating the toxicity of the alkane diols indicated an LD_{50} > 20 g/kg in rats for Propanediol,[53] > 20 ml/kg in rabbits for 1,5-Pentanediol,[54] > 10 g/kg in rabbits for Hexanediol,[54,55] and > 2 g/kg in rabbits for Butyl Ethyl Propanediol.[56] Reported for 1,4-Butanediol and Methypropanediol were LD_{50}s > 2 g/kg in dermally exposed rats[57] and rabbits.[58] Systemic toxicity findings noted after dermal exposure (5 g/kg 1,4-Butanediol) in rats included dermal lesions (48 h post-application) and abnormalities in the liver (14 days post-application), but no mortality;[59] at necropsy, 14 days post-application, abnormalities in kidney and gastrointestinal tract of rabbits were reported (2 g/kg Methylpropanediol, no treatment-related mortality).[58] Clinical signs observed in

rats within 2 hours after exposure to 2 g/kg 1,4-Butanediol were dyspnea and poor general state; slight erythema was noted 24 hours post-exposure.[57] Clinical signs reported in rabbits following exposure to 2 g/kg Methylpropanediol (time between exposure and appearance of signs not specified) were slight erythema, diarrhea, yellow nasal discharge, bloated abdomen, soiling of anogenital area, gastrointestinal tract abnormalities, and lung and liver abnormalities.[58]

Oral

Many of the alkane diols presented in this safety assessment were evaluated for toxicity in acute oral exposure studies in animals. An LD_{50} of 14.9 ml/kg was reported for Propanediol in rats; clinical signs were sluggishness, sedation, ataxia, and unconsciousness followed by death in some animals.[42] An approximate lethal dosage (ALD) of > 17 g/kg (70% purity) and > 25 g/kg (99.8% purity) were also reported in rats dosed with Propanediol; clinical effects noted from dosage between 2.25 g/kg and the ALD's were pallor, irregular respiration, salivation, chewing motion, and belly crawling.[60] Various animal studies reported an LD_{50} between 1.35 and 2.5 g/kg for 1,4-Butanediol administration.[14,48,57,59,61] Findings at necropsy in one rat study (animals killed 48 h post-dosing with 1.8 g/kg 1,4-Butanediol) were fluid-filled gastrointestinal tract and congestion of internal organs, histopathological changes in liver and kidneys, extensive vacuolar degeneration of hepatic parenchyma, granular clusters of desquamated cells, and interstitial infiltration of mononuclear kidney cells.[59] In another rat study, 14-days post dosing (1 to 2.5 g/kg 1,4-Butanediol), the animals that survived to necropsy showed no abnormal findings and an LD_{50} of 1.5 g/kg was reported.[57] Clinical signs observed after 1,4-Butanediol (1.35 to 2 g/kg dosage) administration in rats included irregular, decreased respiration and catalepsy, dyspnea, apathy, abnormal position, staggering, spastic gait, atony, and unusual pain reflex.[57,59,61] For the following alkane diols, LD_{50}s in rats and/or mice were reported as: 10 g/kg for 1,5-Pentanediol,[62] 3 g/kg for Hexanediol,[63] > 5 g/kg for Methylpropanediol,[58] 5 and 9 g/kg for 2,3-Butanediol,[19,64] 2.9 and 5 g/kg for Butyl Ethyl Propanediol,[56,65] > 5 g/kg for Isopentyldiol.[66] Clinical signs reported after dosing with 1,5-Pentanediol, Hexanediol, Methylpropanediol, 2,3-Butanediol, and Butyl Ethyl Propanediol included: staggering, spastic gait, salivation, exsiccosis, paresis, apathy, narcotic state, increased urination, diarrhea, chromorhinorrhea, dyspnea, piloerection, erythema, and pallor.[58,62-65] Noted at necropsy were dilation of the heart and congestive hyperemia, bloody stomach ulcerations, and abnormal bladder content in rats dosed with 1,5-Pentanediol.[62] After dosing with Methypropanediol (5 g/kg), 1 rat (n=10) showed pink bladder fluid at necropsy.[58] There were no clinical signs reported in mice dosed with Isopentyldiol;[66] at necropsy, rats and/or mice dosed with Hexanediol, Butyl Ethyl Propanediol, or Isopentyldiol showed no abnormalities.[63,65,66] In mice (n=2/sex/dosage) dosed with Butyl Ethyl Propanediol, 2 deaths were reported at 1.25 g/kg dosage; 2 deaths at 1.5 g/kg dosage; 3 deaths at 2 g/kg dosage.[65]

Inhalation

Studies evaluating the toxicity of alkane diols were conducted in rats exposed by inhalation. An approximate lethal concentration (ALC) > 5 mg/l for Propanediol (4 h exposure time, 3.2 µm mass median aerodynamic diameter) was reported; clinical signs were wet fur/perineum and ocular discharge.[42] Rats survived a 4-hour exposure to 2000 to 5000 mg/l Propanediol.[53] Rats exposed to 1,4-Butanediol (4.6 to 15 mg/l) by inhalation showed lethargy, labored breathing, red discharge in perineal area, weight loss within 24 hours post-exposure, followed by resumption of normal weight gain, and lung noise/dry nasal discharge 1 to 9 days post-dosing; 1 death (15 mg/l) occurred 1 day post-dosing.[67] In another rat study, an LC_{50} > 5.1 mg/l (4 hour exposure time) was reported; no mortality or abnormalities during gross pathology examination were reported and clinical signs, which resolved within 48 hours post-exposure, included shallow breathing, nasal discharge, ruffled fur, staggering gait, and deterioration.[57] A 1,4-Butanediol concentration of 5100 mg/l was administered and, although shallow respiration was reported during exposure (4 hours), by 24 hours post-exposure this had resolved; gross pathology revealed no abnormalities.[68] The results for other alkane diols evaluated were: no deaths occurred after 7-8 hours of exposure to concentrated vapors containing 1,5-Pentanediol,[54] Hexanediol,[54,55] or 2,3-Butanediol;[64] an LC_{50} > 5.1 g/l was reported for inhalation of Methylpropanediol.[18]

Short-Term Toxicity

Below is a summary of the short-term toxicity studies that are presented in detail in Table 9.

Oral

Short-term oral exposure studies were conducted in animals to investigate the toxicity of several alkane diols. A no-observed-effect-level (NOEL) of 1000 mg/kg/day for Propanediol was reported in a 14-day rat study.[42] A 28-day experiment in rats, evaluating the toxicity of 1,4-Butanediol, revealed liver abnormalities; NOELs of 500 mg/kg/day (females) and 50 mg/kg/day (males) were reported.[69] Another rat study (approximately 42 days exposure duration) examining 1,4-Butanediol, showed lower body weight gains and food consumption (400 and 800 mg/kg/day), a statistically significant dose-related decrease of blood glucose (male treated animals), and bladder abnormalities (400 and 800 mg/kg/day); a no-observed-adverse-effect-level (NOAEL) of 200 mg/kg/day was reported.[57] The effects of Hexanediol tested in rats (up to 1000 mg/kg/day for 28 days)[63] and rabbits (up to 2000 mg/kg for 25 doses, duration unknown)[70] resulted in a reported NOEL of 1000 mg/kg/day for rats[63] and observations of thrombosis and treatment-related effects (unspecified) on the liver and kidneys of rabbits.[70] Results of Methylpropanediol tested in rats up to 1000 mg/kg/day for 14 days were reported to be unremarkable.[58] A NOAEL of 1000 mg/kg/day for Butyl Ethyl Propanediol was reported in a 28-day rat experiment; rats exhibited liver abnormalities (in males at 1000 mg/kg/day) and kidney abnormalities (in males at 150 or 1000 mg/kg/day).[65]

Inhalation

Short-term inhalation exposure studies were conducted in animals to evaluate the toxicity of Propanediol and 1,4-Butanediol. A rat study evaluating exposure to Propanediol up to 1800 mg/l, 6 h/day for 2 weeks reported no remarkable results.[53] A study in which rats were exposed to 1,4-Butanediol (up to 5.2 mg/l), 6 h/day, 5 days/week for 2 weeks showed red nasal discharge, lower body weights, and abnormal blood chemistry parameters.[67] In other rat studies of 4-month durations (2 h/day exposure time) evaluating 1,4-Butanediol a NOAEC of 500 mg/l (or NOAEL of 23 mg/kg/day) and a lowest-observed-adverse-effect-concentration (LOAEC) of 1500 mg/l (or LOAEL of 85 mg/kg/day) were reported; observations in the study reporting the LOAEC of 1500 mg/l included a sleepy condition 20 minutes post-exposure and pulmonary abnormalities.[68]

Subchronic Toxicity

Below is a synopsis of the subchronic toxicity studies that are presented in detail in Table 9.

Oral

Several of the alkane diols were evaluated for toxicity in subchronic (approximately 3-month) studies in rats with oral exposure. A NOEL of 1000 mg/kg/day for Propanediol was reported;[71] another evaluation of 5 or 10 ml/kg of Propanediol resulted in 100% mortality (5 deaths) with the 10 ml/kg dosage and 2 deaths with the 5 ml/kg dosage.[42] NOAEL's for Hexanediol were reported to be 400 mg/kg/day (males) and 1000 mg/kg/day (females); a treatment-related decrease (in males at 1000 mg/kg/day) in mean body weights and a statistically significant increase in organ weights (in males at 1000 mg/kg/day) were observed.[63] A NOEL of 600 mg/kg/day was reported for Methylpropanediol; abnormalities seen were decreased liver enzymes and inorganic phosphate (at 1000 mg/kg/day).[58] NOAELs of 150 mg/kg/day (females) and 15 mg/kg/day (males) were reported for Butyl Ethyl Propanediol; there were 4 treatment-related deaths (males at 150 or 1000 mg/kg/day), abnormal locomotion and respiration 1 to 2 hours post-dosing (after which animals returned to normal), hunched body, urinary abnormalities (at 150 and 1000 mg/kg/day), and kidney abnormalities (at $\geq$ 15 mg/kg/day) reported.[65]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Provided below is a summary of DART studies that are presented in detail in Table 10.

Developmental and reproductive toxicity studies were conducted in animals that were orally exposed to several alkane diols reviewed in this safety assessment. In rat studies evaluating Propanediol at dose rates up to 1000 mg/kg/day, spermatogenic endpoints were unaffected (90-day exposure duration)[71] and no maternal (dosing on days 6-15 of gestation) or fetal toxic effects were observed (maternal and fetal NOAEL of 1000 mg/kg/day).[42] In a mouse study evaluating 1,4-Butanediol at up to 600 mg/kg/day, a maternal and developmental NOAEL of 100 mg/kg/day and a LOAEL of 300 mg/kg/day were reported; maternal central nervous system intoxication (300-600 mg/kg/day) and maternal and fetal body weight reduction (maternal 300-600 mg/kg/day) were observed.[72] Results were mixed in rat studies evaluating 1,4-Butanediol. For males and females dosed with up to 800 mg/kg/day (14 days prior to mating and for females through day 3 of lactation), the following were reported: a reproductive parental and developmental NOAEL of 800 mg/kg/day,[57,68] a maternal toxicity NOAEL of 200 mg/kg/day, and a developmental toxicity/ teratogenicity NOAEL of 400 mg/kg/day.[57] A maternal and developmental NOAEL of 1000 mg/kg/day was reported in animal studies on Hexanediol (rats dosed on days 6-19 of gestation)[63] and for Methylpropanediol (rats dosed on days 0-20 of gestation; rabbits dosed on days 0-29 of gestation).[18,73] In a rat study evaluating Butyl Ethyl Propanediol up to 1000 mg/kg/day (dosing on days 6-19 of gestation) a maternal NOAEL of 150 mg/kg/day (reduced activity, staggering, limb dragging, slow respiration, and reduced food consumption/body weight observed with 1000 mg/kg dose) and a developmental NOAEL of 1000 mg/kg/day were reported.[65]

GENOTOXICITY

Provided below is a summary of genotoxicity studies that are presented in detail in Table 11.

Genotoxicity data are available for most of the alkane diols presented in this safety assessment. Experiments conducted *in vitro* evaluating Propanediol were negative for genotoxicity in a mammalian cell gene mutation assay (up to 5000 µg/ml), a chromosomal aberration test (up to 5000 µg/ml), and an Ames test (up to 5000 µg/plate).[42] There was another mammalian chromosomal aberration test (2500 µg/ml) evaluating Propanediol that resulted in positive responses for genotoxicity without metabolic activation, which was negative with metabolic activation;[42] *in vitro* tests performed in rat liver and testicular homogenates from rats were fed 500 ppm Propanediol in the diet for 15 weeks, indicated that the metabolism of Propanediol produced malondialdehyde *in vivo*, which caused damage in rat DNA.[44] 1,4-Butanediol was negative for genotoxicity in a *Salmonella typhimurium* mutagenicity test (up to 10,000 µg/plate),[74] in a mammalian cell gene mutation assay (up to 5000 µg/ml),[57] and in a chromosomal aberration test (up to 5000 µg/ml).[57] In an Ames test (up to 5000 µg/plate) 1,5-Pentanediol was negative for genotoxicity.[62] Hexanediol was negative for genotoxicity in an Ames test (up to 5000 µg/plate), in a mammalian chromosomal aberration test (up to 1.2 µg/ml), and in a mammalian cell gene mutation assay (up to 5000 µg/ml).[63] Methylpropanediol was negative in an Ames II™ assay (up to 5000 µg/plate) and in a chromosomal aberration test (up to 5000 µg/ml);[58] 2,3-Butanediol was negative in an Ames test (up to 5000 µg/ml).[64] Butyl Ethyl Propanediol was negative for genotoxicity in an Ames test (up to 5000 µg/plate) and in a mammalian cell gene mutation assay (up to

7.2 mmol/l);[65] Isopentyldiol was negative for genotoxicity in an Ames test (up to 10,000 µg/plate) and in a liquid suspension assay (up to 100 mg/plate).[66] Mouse micronucleus tests conducted *in vivo* were negative for Propanediol (single dose of 2150 mg/kg)[42] and for Butyl Ethyl Propanediol (single dosage up to 1250 mg/kg).[65]

CARCINOGENICITY

1,4-Butanediol

No carcinogenicity studies for the alkane diols reviewed in this safety assessment were located in the literature. However, one review article referred to a 2-year oral bioassay evaluating the carcinogenic potential of gamma-butyrolactone in rats (males dosed up to 225 mg/kg, females dosed up to 450 mg/kg for 5 days/week for 102 weeks) and mice (both sexes dosed up to 525 mg/kg for 5 days/week for 102 weeks).[48,75,76] There were no carcinogenic responses reported in either sex of rat or in female mice; there was an increase in focal hyperplasia and a slight increase in adrenal gland pheochromocytoma in male mice, however these findings were considered to be equivocal. This study was essentially an evaluation of GHB because, in the body, 1,4-Butanediol is rapidly metabolized to form GHB, as is the cyclic lactone of GHB, gamma-butyrolactone.[75] In a two-step process, 1,4-Butanediol is metabolized to form GHB (as described previously in the Toxicokinetics Section above); in a one-step process, gamma-butyrolactone is converted to GHB through lactonase catalysis.

OTHER RELEVANT STUDIES

Neurotoxicity

1,4-Butanediol

Central nervous system effects have been reported for exposures to 1,4-Butanediol.[48] Central nervous system depression, anesthetic effect, loss of righting reflex, struggle response, and voluntary motor activity were documented in rats administered 496 mg/kg 1,4-Butanediol (no further details were specified). During oral, intraperitoneal, or intravenous exposure, neuropharmacologic responses have been reported. These effects were also observed after administration of GHB. Endogenous levels of GHB in the brain of mammals are in micromolar concentrations, while in the liver, heart, and kidneys concentrations are 5 to 10 times higher. Although 1,4-Butanediol can be converted to GHB in the brain, liver, kidney, and heart, the liver has the greatest capacity (per gram of tissue) to metabolize GHB. When GHB was administered at dosages exceeding 150 mg/kg in rats, a state of behavioral arrest was observed, with bilaterally synchronous electroencephalogram readings resembling those of humans undergoing seizures (non-epileptic).

DERMAL IRRITATION AND SENSITIZATION STUDIES

A summary of dermal irritation, sensitization, and photoirritation/photosensitization studies is provided below; details are presented in Table 12.

Irritation

Animal

Skin irritation testing of the alkane diols resulted in the following observations: Propanediol (undiluted) was mildly irritating to rabbit skin in 24-hour occlusive patch tests;[42] 1,4-Butanediol (undiluted) caused only minimal redness after application to rabbit ears and no irritation was observed in a 24-hour occlusive patch test on intact and abraded rabbit skin;[59] 1,5-Pentanediol (undiluted) was non-irritating to rabbit skin in both a 24-hour non-occlusive skin test[54] and a 20-hour occlusive patch test on intact and scarified skin;[62] Hexanediol (45% to 80%) was non-irritating to animal skin in both non-occlusive and occlusive tests performed with approximately 24-hour dermal exposure;[54,55,63,77] Methylpropanediol (concentration not specified) was non-irritating to animal skin;[18,58,58] 2,3-Butanediol (undiluted) was non-irritating to rabbit skin in a 24-hour occlusive patch test;[64] Butyl Ethyl Propanediol (undiluted) was no-to-minimally irritating to rabbit skin in 4-hour semi-occlusive patch tests;[65] Isopentyldiol (undiluted) was no-to-slightly irritating to rabbit skin in 24-hour occlusive and semi-occlusive patch tests.[66] Overall, the alkane diols were no-to-mildly irritating to animal skin.

Human

Skin irritation testing in human subjects showed the following: Propanediol (25% to 75% and undiluted) was no-to-slightly irritating in 24-hour occlusive patch tests;[78] 1,4-Butanediol (concentration not specified) was non-irritating in a patch test (no additional details provided);[68] Methylpropanediol (concentration not specified) was non-irritating to subjects with sensitive skin in a 14-day cumulative irritation study;[18] Isopentyldiol (concentration not specified) and 1,3-Butanediol (concentration not specified) were slightly irritating in a 48-hour Finn chamber skin test.[66] Generally, the alkane diols evaluated were no-to-slightly irritating in human skin.

Sensitization

Animal

Skin sensitization testing of the alkane diols resulted in the following observations: Propanediol (2.5% intradermal and 100% epicutaneous concentrations applied at induction) was non-sensitizing to guinea pig skin;[42] 1,4-Butanediol (10% intradermal and 30%

topical concentrations applied at induction) was non-sensitizing to guinea pig skin.[59] Hexanediol (5% intradermal and 50% epicutaneous concentrations applied at induction) was non-sensitizing to guinea pig skin in one test.[63] In another test, strong erythema was reported in guinea pigs with Hexanediol challenge (no concentration specified) following induction (sensitization) with another compound (0.2% hydroxyethyl methacrylate), however no Hexanediol induction (0.2%)/ Hexanediol challenge (no concentration specified) tests showed a positive sensitization reaction.[77] Methypropanediol showed mild sensitization potential in guinea pigs (10% intradermal to 100% epidermal concentrations applied at induction).[58] 2,3-Butanediol (5% intradermal and 50% epicutaneous concentrations applied at induction) was non-sensitizing to guinea pig skin, however during epicutaneous induction animals showed incrustation and confluent erythema with swelling.[64] Butyl Ethyl Propanediol (2.5% intradermal and 100% topical concentrations applied at induction) was non-sensitizing in guinea pigs.[65] Isopentyldiol (10% intradermal and 100% topical concentrations applied at induction) was non-sensitizing in guinea pigs, however during intradermal injection at induction and topical induction, moderate and confluent erythema were observed.[66] Sensitization results were mixed with no-to-mild sensitization potential and some positive skin reactions observed during induction.

Human

Skin sensitization studies of the alkane diols showed the following results: Propanediol was non-sensitizing (5% to 75% concentrations applied at induction);[78] 1,4-Butanediol (concentration not specified) was non-sensitizing;[68] Methylpropanediol (concentration not specified) was non-sensitizing in one test;[18] in another test Methylpropanediol (concentration not specified) showed mild skin sensitization potential, however other components of the test mixture may have contributed to the mild dermal reactions observed in a few subjects during induction and challenge phases of the study.[18] Generally, the alkane diols evaluated were non-sensitizing in human skin.

Photoirritation / Photosensitization

Animal

Isopentyldiol (undiluted) was neither a photo-irritant nor a photo-sensitizer (no reactions were observed during induction or challenge phases) when tested in guinea pig skin; positive controls were used in both experiments and yielded expected results.[66]

OCULAR IRRITATION

Below is a synopsis of ocular irritation studies that are presented in detail in Table 13.

Ocular irritation was evaluated in rabbit eyes for most of the alkane diols reviewed in this safety assessment; results were mixed. No-to-slight irritation (resolved within 48 hours post-application) was reported for undiluted Propanediol.[42] Undiluted 1,4-Butanediol was slightly irritating.[14,59] No-to-mild irritation was observed for undiluted 1,5-Pentanediol[54,62,79] and undiluted Hexanediol.[54,55,63] Methylpropanediol (concentration not specified)[18,58] and undiluted 2,3-Butanediol[64] were non-irritating to rabbit eyes. Butyl Ethyl Propanediol (concentration not specified) resulted in severe eye injury in one test.[56] In another experiment, undiluted Butyl Ethyl Propanediol was considered to be irritating, with corneal opacification and diffuse crimson conjunctiva coloration, swelling, and partial eyelid eversion; the rabbit eyes returned to normal by 14 days post-application.[65] Isopentyldiol (concentration not specified) was non-irritating.[66]

CLINICAL STUDIES

Occupational Exposure

International occupational inhalation exposure limits for 1,4-Butanediol are 100 mg/m^3 (Italy and Portugal) and 200 mg/m^3 (Austria and Germany); short term exposure value is 800 mg/m^3 (Austria).[39]

Case Reports

Below is a synopsis of case reports that are presented in detail in Table 14.

Information from case reports for the alkane diols included adverse effects in adults (including death) and poisoning in children from oral exposure to 1,4-Butanediol (varying doses);[57,61,68,80,81] allergic contact dermatitis as a result of dermal exposure to 1,5-Pentanediol (0.5% to 10%) in a resveratrol-containing cream;[82] precautions recommended for dental professionals exposed to Hexanediol in dentin primers because of the potential to cause contact dermatitis following repeated occupational exposure.[77]

SUMMARY

The 10 alkane diols included in this safety assessment reportedly function in cosmetics as solvents, humectants, and skin conditioning agents.

VCRP data from the FDA in 2016 indicate that the highest reported uses are for Propanediol (815 uses), Methylpropanediol (400 uses), and Isopentyldiol (127 uses). The highest maximum use concentration was 39.9% for Propanediol in leave-on products.

Several of the alkane diols are used as indirect food additives and none are GRAS food ingredients. The FDA has issued warnings about dietary supplements containing 1,4-Butanediol. 1,4-Butanediol is considered to be a Class I Health Hazard by the FDA, as well as a Schedule I Controlled Substance Analog by the DEA if potential illicit use is intended for human consumption.

A permeability coefficient of 1.50×10^{-5} cm/h was calculated for Propanediol after abdominal skin from human cadavers was exposed for 48 hours in a static diffusion cell to a 1.059 g/ml Propanediol solution (vehicle not specified).

In vitro tests of pharmaceutical cream formulations containing 0.1% mometasone furoate and 25% 1,5-Pentanediol or 1% hydrocortisone and 25% 1,5-Pentanediol showed that 1,5-Pentanediol was a penetration enhancer in human breast skin samples exposed to the formulations for 60 hours.

Rat liver homogenates metabolized Propanediol to yield malondialdehyde. 1,4-Butanediol was a competitive inhibitor of ethanol metabolism by alcohol dehydrogenase. Methylpropanediol was demonstrated to be a substrate for alcohol dehydrogenase *in vitro*. Diacetyl, acetoin, and 2,3-Butanediol were interconvertible with a molar equilibrium ratio of 0:3:7, respectively, in rat liver homogenates.

A single dose of Propanediol, 1,4-Butanediol, Hexanediol, or 2,3-Butanediol administered orally to rabbits yielded the corresponding glucuronic acid conjugates in the urine representing 2% to 26% of the administered dose. Orally administered 1,4-Butanediol and 1,5-Pentanediol produced succinic acid and phenacyl glutarate, respectively, in the urine.

Endogenous concentration of 1,4-Butanediol in rats were 30 to 165 ng/g in aqueous phase tissues and 150 to 180 ng/g in lipid phase tissues. 1,4-Butanediol concentrations were 96 µg/g, 52 µg/g, and 58 µg/g in the brain, liver, and kidney, respectively, of rats 75 minutes after oral exposure to 1 g/kg 1,4-Butanediol. In rats orally exposed to up to 400 mg/kg 1,4-Butanediol (radiolabels on C1 and C4), >75% of the radioactivity was excreted as $^{14}CO_2$ by 24 hours post-dosing; up to 6% was eliminated in feces 72 hours post-dosing. Methylpropanediol orally administered to rats was reported to be rapidly metabolized and eliminated as 3-hydroxybutyric acid in the urine and as CO_2 in exhaled breath. Experiments in rats orally administered 1M diacetyl, acetoin, or 2,3-Butanediol showed interconversion among these compounds *in vivo*.

Oral exposure to 25 mg/kg 1,4-Butanediol resulted in measurable plasma concentrations of GHB in human subjects within 5 to 30 minutes after exposure, indicating rapid conversion of 1,4-Butanediol to GHB; GHB concentrations were below the limit of quantitation within 4 hours. Clearance of 1,4-Butanediol was rapid in some subjects and relatively slow in other subjects; the latter were confirmed to have a genetic mutation of variant alleles of ADH-1B. Nearly 100% of 1,4-Butanediol was rapidly converted to GHB in a study in which 15 or 30 mg/kg 1,4-Butanediol was intravenously injected into human subjects.

The toxicity of acute dermal exposure in animals to Propanediol, 1,5-Pentanediol, Hexanediol, and Butyl Ethyl Propanediol was evaluated, and reported LD_{50}s ranged from > 2 g/kg to > 20 g/kg. A single dermal exposure to 5 g/kg 1,4-Butanediol caused dermal lesions within 48 hours and liver abnormalities within 14 days, but no mortalities in rats. In rabbits, a single 2 g/kg dermal application of Methylpropanediol caused kidney, lung, liver, and gastrointestinal tract abnormalities, among other effects, but no mortalities.

Acute oral LD_{50}s reported in multiple studies of mammalian test species included 14.9 ml/kg Propanediol, 1.35 to 2.5 g/kg 1,4-Butanediol, 10 g/kg 1,5-Pentanediol, 3 g/kg Hexanediol, 3 to 5 g/kg Butyl Ethyl Propanediol, and ≥ 5 g/kg Methylpropanediol, 2,3-Butanediol, and Isopentyldiol. Clinical signs in the affected animals included ataxia, paresis, dyspnea, and exsiccosis in these studies. Necropsy and histological examinations revealed bloody stomach ulcerations, abnormal bladder contents, congestive hyperemia, and changes in the liver and kidneys in the affected animals.

A single 4-hour inhalation exposure to 2000 to 5000 mg/l Propanediol caused moderate weight loss but no deaths in rats. A single 4.6 to 15 mg/l exposure to 1,4-Butanediol resulted in lethargy, labored breathing, and lung noise/dry nasal discharge in rats 1 to 9 days post-dosing, and 1 death at 15 mg/l 1 day post-dosing. Rats exposed for 4 hours to 5100 mg/l 1,4-Butanediol exhibited shallow respiration that resolved within 24 hours post-exposure; gross pathology examination revealed no abnormalities. No deaths were reported after a single 7- to 8- hour inhalation exposure to 1,5-Pentanediol, Hexanediol, or 2,3-Butanediol. An LC50 > 5.1 g/l for inhalation was reported for Methylpropanediol.

Reported NOELs and NOAELs for short-term oral exposures in rats included 200 mg/kg/day 1,4-Butanediol (~42 days), 500 mg/kg/day 1,4-Butanediol (28 days), and 1000 mg/kg/day Propanediol and Methylpropanediol (14 days) or Hexanediol and Butyl Ethyl Propanediol (28 days). Effects observed at dose rates exceeding the NOEL or NOAEL in these studies included decreased food consumption and body weight gains, liver and bladder abnormalities, and decrease in blood glucose concentrations. Rabbits, orally exposed to twenty-five 200 mg/kg dosages exhibited thrombosis and unspecified effects in the liver and kidneys.

Results were unremarkable in a study in which rats inhaled up to 1800 mg/l Propanediol, 6 h/day, for 2 weeks. Rats exposed to up to 5.2 mg/l 1,4-Butanediol, 6 h/day, 5 days/week, for 2 weeks, showed red nasal discharge, lower body weights, and abnormal blood chemistry parameters. Studies in which rats were exposed to 1,4-Butanediol 2 hours/day for 4 months indicated a NOAEC of 500 mg/l (equivalent to approximately 23 mg/kg/day) and a LOAEC of 1500 mg/l (equivalent to about 85 mg/kg/day). Effects at the reported LOAEC included a sleepy condition 20 minutes after each exposure and pulmonary abnormalities.

NOELs and NOAELs in subchronic, oral exposure studies ranged from 15 mg/kg/day and 150 mg/kg/day Butyl Ethyl Propanediol in male and female rats, respectively. In rats, a NOAEL of 600 mg/kg/day was reported for Methyl Propanediol and NOAELs of 1000

mg/kg/day were reported for Propanediol and Hexanediol. Effects reported in rats exposed to oral doses exceeding the NOAELs included decreased body weights, increased organ weights, decreased liver enzymes and inorganic phosphate levels, and renal and urinary abnormalities.

In rat studies evaluating oral Propanediol exposures up to 1000 mg/kg/day, spermatogenic endpoints were unaffected (90-day exposure) and no maternal or fetal toxic effects were observed (dosing on days 6-15 of gestation). A NOAEL of 100 mg/kg/day and a LOAEL of 300 mg/kg/day 1,4-Butanediol were reported for maternal and developmental toxicity in a mouse study; maternal central nervous system intoxication and maternal and fetal body weight reduction were observed at the LOAEL. NOAELs reported in male and female rats exposed to 1,4-Butanediol for 14 days before mating and, with dosing continuing in females through day 3 of lactation, included 800 mg/kg/day for parental reproductive effects, and in another study with the same dosing 400 mg/kg/day for developmental toxicity/teratogenicity, and 200 mg/kg/day for maternal toxicity. A NOAEL of 1000 mg/kg/day Hexanediol (dosing on days 6-19 of gestation) and Methylpropanediol (dosing on days 0-29 of gestation) was reported for maternal and developmental effects in animals. The NOAEL for maternal effects was 150 mg/kg/day Butyl Ethyl Propanediol in rats (dosing on days 6-19 of gestation); 1000 mg/kg/day caused staggering, slow respiration, and reduced food consumption and body weights in the dams. The NOAEL for developmental effects was 1000 mg/kg/day Butyl Ethyl Propanediol in this study.

No carcinogenicity studies of the alkane diols reviewed in this safety assessment were found in the literature. However, one review article referred to a 2-year oral bioassay of gamma-butyrolactone in rats (dosing 5 days/week for 102 weeks, 5 males at up to 225 mg/kg/day, females at up to 450 mg/kg/day) and mice (at up to 525 mg/kg/day). Both 1,4-Butanediol and gamma-butyrolactone are metabolized to produce GHB in the body. The results were generally negative for the carcinogenicity of gamma-butyrolactone. There were increased incidences of focal hyperplasia and a slight increase in adrenal gland pheochromocytoma in male mice in this study, however these findings were considered to be equivocal.

Propanediol, 1,4-Butanediol, 1,5-Pentanediol, Hexanediol, Methyl Propanediol, 2,3-Butanediol, Butyl Ethyl Propanediol, and Isopentyldiol were negative for genotoxicity in one or more of the following: mammalian cell gene mutation assay, chromosome aberration assay, Ames test, liquid suspension assay. The exception was one positive chromosome aberration test of 2500 µg/plate Propanediol without metabolic activation, which was negative with metabolic activation. *In vitro* tests performed using rat liver and testicular homogenates prepared from rats that were fed 500 ppm Propanediol in the diet, indicated that Propanediol produced malondialdehyde *in vivo*, which damaged rat DNA. Mouse micronucleus tests conducted *in vivo* were negative for Propanediol (single 2150 mg/kg dosage) and for Butyl Ethyl Propanediol (single dosages up to 1250 mg/kg).

Undiluted Propanediol, 1,4-Butanediol, 1,5-Pentanediol, 2,3-Butanediol, or Isopentyldiol was non-irritating to slightly or minimally irritating to the skin of rabbits in 20-to 24-hour patch tests. Undiluted Butyl Ethyl Propanediol was non-to-mildly irritating to rabbit skin in 4-hour semi-occlusive patch tests. Hexanediol was non-irritating to guinea pig skin (45% test substance applied) and rabbit skin (80% test substance applied) in 24-hour patch tests. Methylpropanediol (concentration not specified) was non-irritating to rabbit skin. Undiluted 1,4-Butanediol was minimally irritating when applied to rabbit ears.

Propanediol tested at concentrations ranging from 25% to 100% was non-to-slightly irritating in 24-hour occlusive patch tests in human subjects. 1,4-Butanediol was non-irritating in a patch test on human subjects and Methylpropanediol was non-irritating to subjects with sensitive skin in a 14-day cumulative irritation study; the concentrations used in these studies were not specified. Slight irritation was observed in a 48-hour Finn chamber skin test evaluating unspecified concentrations of Isopentyldiol.

The following treatments were negative in tests for the induction of dermal sensitization in guinea pigs: Propanediol (2.5% intradermal and 100% epicutaneous concentrations applied at induction), 1,4-Butanediol (10% intradermal and 30% topical concentrations applied at induction), Hexanediol (5% intradermal and 50% epicutaneous concentrations applied at induction), 2,3-Butanediol (5% intraderamal and 50% epicutaneous concentrations applied at induction), Butyl Ethyl Propanediol (2.5% intradermal and 100% topical concentrations applied at induction), and Isopentyldiol (10% intradermal and 100% topical concentrations applied at induction). In another test, strong erythema was reported in guinea pigs with Hexanediol challenge (no concentration specified) following induction (sensitization) with another compound (0.2% hydroxyethyl methacrylate); however no Hexanediol induction (0.2%)/ Hexanediol challenge (no concentration specified) tests showed a positive sensitization reaction. Methylpropanediol showed mild sensitization potential in guinea pigs (10% intradermal to 100% epidermal concentrations applied at induction).

Propanediol (5% to 75% concentrations applied at induction) and 1,4-Butanediol (concentration not specified) were non-sensitizing in human subjects. Methylpropanediol (concentration not specified) was non-sensitizing in one test and showed mild skin sensitization potential in another test. However other components of the mixture used in the latter test may have contributed to the dermal reactions observed in a few subjects during induction and challenge phases.

Undiluted Isopentyldiol was neither a photo-irritant nor a photo-sensitizer when tested in guinea pig skin.

Ocular irritation evaluated in rabbit eyes for the alkane diols reviewed in this safety assessment showed mixed results. Undiluted Propanediol, 1,4-Butanediol, 1,5-Pentanediol, Hexanediol, and 2,3-Butanediol were non-to-slightly irritating or mildly irritating in rabbit eyes. Methylpropanediol and Isopentyldiol, were also non-irritating in studies for which the concentrations of the substances tested were not specified. In contrast, undiluted Butyl Ethyl Propanediol caused severe eye injury in rabbit eyes, including irritation, corneal opacification, partial eyelid eversion, all of which were reversible.

Information from case reports for the alkane diols included the adverse effects in adults (including death) and poisoning in children from oral exposure to 1,4-Butanediol (varying doses); allergic contact dermatitis as a result of dermal exposure to 1,5-Pentanediol (0.5% to 10%) in a resveratrol-containing cream; precautions recommended for dental professionals exposed to Hexanediol in dentin primers because of the potential to cause contact dermatitis following repeated occupational exposure.

INFORMATION SOUGHT

The CIR is seeking the following information on alkane diols for use in the resulting safety assessment:

1. Impurities data;
2. Additional dermal penetration data for the larger molecular weight ingredients;
3. Sensitization testing with Methylpropanediol at maximum use concentrations;
4. Any other data relevant to the determination of safety of these ingredients as used in cosmetics.

TABLES

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment. [1;CIR Staff]

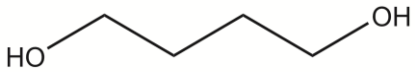
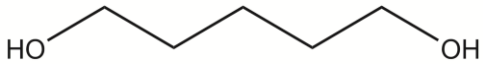
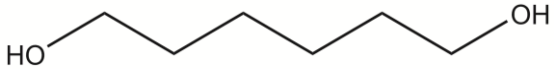
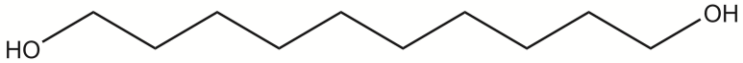
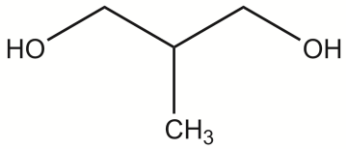
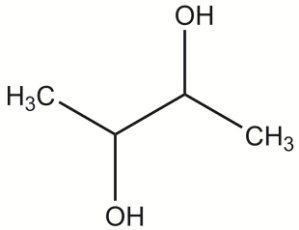
Ingredient CAS No.	Definition & Structure	Function
Propanediol 26264-14-2 504-63-2	Propanediol is the organic compound that conforms to the formula:  	Solvent; Viscosity Decreasing Agent
1,4-Butanediol 110-63-4	1,4-Butanediol is the organic compound that conforms to the formula:  	Solvent
1,5-Pentanediol 111-29-5	1,5-Pentanediol is the organic compound that conforms to the formula:  	Solvent
Hexanediol 26762-52-7 629-11-8	Hexanediol is the organic compound that conforms to the formula:  	Solvent
Octanediol 629-41-4	Octanediol is the organic compound that conforms to the formula:  	Plasticizer
1,10-Decanediol 112-47-0	1,10-Decanediol is the organic compound that conforms to the formula:  	Solvent
Methylpropanediol 2163-42-0	Methylpropanediol is the organic compound that conforms to the formula:  	Solvent
2,3-Butanediol 513-85-9	2,3-Butanediol is the organic compound that conforms to the formula:  	Fragrance Ingredient; Humectant; Skin-Conditioning Agent-Humectant; Solvent

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment. [1;CIR Staff]

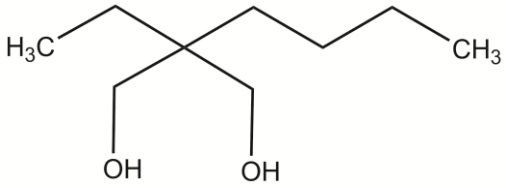
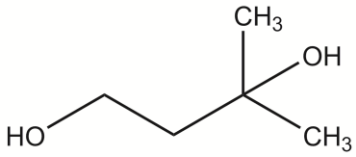
Ingredient CAS No.	Definition & Structure	Function
Butyl Ethyl Propanediol 115-84-4	Butyl Ethyl Propanediol is the organic compound that conforms to the formula:  	Skin-Conditioning Agent; Humectant
Isopentyldiol 2568-33-4	Isopentyldiol is the diol that conforms to the formula:  	Solvent

Table 2. Examples of some 1,2-alkane diols and constituent acids previously reviewed by the Panel

Ingredient	Conclusion (year issued; maximum use concentration reported)	Reference
	1,2-ALKANE DIOLS	
Propylene Glycol (same as 1,2-Propanediol)	Safe as used when formulated to be non-irritating (2012; up to 73% in leave-ons; up to 42% in rinse-offs)	3,4
1,2-Butanediol	Safe as used (2012; no reported uses)	2
Pentylene Glycol (same as 1,2-Pentanediol)	Safe as used (2012; up to 5% in leave-ons; up to 5% in rinse-offs)	2
1,2-Hexanediol	Safe as used (2012; 10% in leave-ons; 0.8% in rinse-offs)	2
Ethyl Hexanediol (same as 2-Ethyl-1,3-Hexanediol)	Safe as used (1994; no reported use concentrations, but product formulation data submitted to FDA in 1984 stated concentration of use up to 5%); reaffirmed in 2011 (no reported use concentrations)	5,6
Caprylyl Glycol (same as 1,2-Octanediol)	Safe as used (2012; up to 5% in leave-ons; up to 2% in rinse-offs)	2
Decylene Glycol (same as 1,2-Decanediol)	Safe as used (2012; no reported use concentrations; 1 reported use in leave-ons)	2,3
	ALIPHATIC DIOLS	
Butylene Glycol (same as 1,3-Butanediol)	Safe as used (1985); reaffirmed in 2006 (up to 89% in leave-ons; up to 20% in rinse-offs)	7,8
Hexylene Glycol (same as 2-Methyl-2,4-Pentanediol)	Safe as used (1985); reaffirmed in 2006 (up to 4% in leave-ons; up to 6% in rinse-offs)	7,8
	SYNTHETIC STARTING MATERIALS	
Maleic Acid (sometimes used in the synthesis of 1,4-Butanediol)	Safe for use in cosmetic formulations as a pH adjuster (2007; no reported concentrations or uses in leave-ons; 0.004% in diluted for bath use)	9
Succinic Acid (sometimes used in the synthesis of 1,4-Butanediol)	Safe as used (2012; up to 0.2% in leave-ons; up to 26% in rinse-offs)	10

Table 3. Physical and Chemical Properties

Property	Value	Reference
Propanediol		
Physical Form	Hygroscopic liquid; viscid (sticky) liquid	13,15
Color	Colorless; Colorless to pale yellow	13,15
Odor	Mild, sweet	13,15
Molecular Weight (g/mol)	76.10	15
Density (g/ml)	1.0597	15
Melting Point (°C)	146-147	83
Boiling Point (°C)	210-212	15
Water Solubility	Slightly soluble in water	13
Other Solubility	Soluble in alcohols and acetone; miscible with many polar solvents	13
Log P @ 25 °C	-1.093±0.458	84
pKa @ 25 °C	14.46±0.10	84

Table 3. Physical and Chemical Properties

Property	Value	Reference
1,4-Butanediol		
Physical Form	Viscous liquid	15
Color	Colorless	15
Molecular Weight (g/mol)	90.12	15
Density g/ml @ 20 °C	1.069	83
Melting Point (°C)	19-19.5	15
Boiling Point (°C)	230	15
Water Solubility	Soluble in water	15
Other Solubility	Soluble in DMSO, acetone, 95% ethanol	15
Log P @ 25 °C	-0.767±0.187	84
pKa @ 25 °C	14.73±0.10	84
1,5-Pentanediol		
Physical Form	Viscous, oily liquid; bitter taste	15
Molecular Weight (g/mol)	104.15	15
Density (g/ml)	0.9941	15
Melting Point (°C)	-18	15
Boiling Point (°C)	239	15
Water Solubility	Miscible with water	15
Other Solubility	Miscible with methanol, alcohol, acetone, ethyl acetate; Soluble in ether (25°C, 11% w/w); Limited solubility in benzene, trichloroethylene, methylene chloride, petr ether, heptane	15
Log P @ 25 °C	-0.559±0.185	84
pKa @ 25 °C	14.83±0.10	84
Hexanediol		
Physical Form	Crystals	15
Molecular Weight (g/mol)	118.18	15
Density (g/ml) @ 0°C	0.967	83
Melting Point (°C)	42.8	15
Boiling Point (°C) @ 760 mmHg	208	83
Water Solubility	Soluble	15
Other Solubility	Soluble in alcohol; Sparingly soluble in hot ether	15
Log P @ 25 °C	-0.049±0.185	84
pKa @ 25 °C	14.87±0.10	84
Octanediol		
Molecular Weight (g/mol)	146.23	84
Density (g/ml)	0.939±0.06	84
Melting Point (°C)	61-62	83
Boiling Point (°C)	140-150	83
Water Solubility: 4.8 (g/l) in unbuffered water (pH 7.00) @ 25 °C	Slightly Soluble	84
Log P @ 25 °C	0.970±0.186	84
pKa @ 25 °C	14.89±0.10	84
1,10-Decanediol		
Physical Form	Needles from water or diluted alcohol	15
Molecular Weight (g/mol)	174.28	15
Density (g/ml) @ 20 °C, 760 mmHg	0.923±0.06	84
Melting Point (°C)	74	15
Boiling Point (°C)	71.5	83
Water Solubility	Almost insoluble in water	15
Other Solubility	Freely soluble in alcohol, warm ether; almost insoluble in petr ether	15
Log P @ 25 °C	1.989±0.186	84
pKa @ 25 °C	14.89±0.10	84
Methylpropanediol		
Physical Form	Viscous liquid	18
Molecular Weight (g/mol)	90.12	84
Density (g/ml) @ 20 °C	1.020	83
Vapor Pressure (mmHg) @ 25 °C	0.021	18
Melting Point (°C)	-91	83
Boiling Point (°C)	195	83
Water Solubility: 215 (g/l) in unbuffered water (pH 6.88) @ 25 °C	Very Soluble	84
Log P @ 25 °C	-0.740±0.462	84
pKa @ 25 °C	14.51±0.10	84

Table 3. Physical and Chemical Properties

Property	Value	Reference
2,3-Butanediol		
Physical Form	Hygroscopic crystals (*meso*-form)	[15]
Molecular Weight (g/mol)	90.12	[15]
Density (g/ml) @ 25 °C	0.9873	[83]
Melting Point °C (meso-Form)	34.4	[15]
Boiling Point (°C)	181.7	[15]
Water Solubility: 245 (g/l) in unbuffered water (pH 6.90) @ 25 °C	Very Soluble	[84]
Other Solubility	Moderately soluble in diisopropyl ether	[15]
Log P @ 25 °C	-0.655±0.221	[84]
pKa @ 25 °C	14.67±0.20	[84]
Butyl Ethyl Propanediol		
Molecular Weight (g/mol)	160.25	[84]
Density (g/ml) @ 20 °C, 760 mmHg	0.930±0.06	[84]
Melting Point (°C)	41.4-41.9	[83]
Boiling Point (°C)	262	[83]
Water Solubility: 1.9 (g/l) in unbuffered water (pH 7.00) @ 25 °C	Slightly soluble	[84]
Log P @ 25 °C	1.709±0.470	[84]
pKa @ 25 °C	14.54±0.10	[84]
Isopentyldiol		
Molecular Weight (g/mol)	104.15	[84]
Density (g/ml) @ 20 °C	0.9867	[83]
Boiling Point (°C) @ 760 mmHg	202	[83]
Water Solubility: 122 (g/l) in unbuffered water (pH 6.96) @ 25 °C	Very Soluble	[84]
Log P @ 25 °C	-0.329±0.470	[84]
pKa @ 25 °C	14.90±0.29	[84]

Table 4. Current frequency and concentration of use of alkane diols[20,21]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Propanediol		**1,4-Butanediol**		**Hexanediol**	
Totals*	**815**	**0.0001-39.9**	**4**	**NR**	**NR**	**0.011-0.5**
Duration of Use						
Leave-On	*305*	*0.0001-39.9*	*4*	*NR*	*NR*	*0.011-0.5*
Rinse-Off	*510*	*0.005-12*	*NR*	*NR*	*NR*	*0.02-0.45*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	26	0.002-10	1	NR	NR	0.011-0.08
Incidental Ingestion	NR	3-10	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: 6 possible: 115[a]; 102[b]	spray: 0.0001-3 possible: 2-38[a]	possible: 3[a]	NR	NR	NR
Incidental Inhalation-Powder	possible: 102[b]; 3[c]	possible: 0.0071-24[c]	NR	NR	NR	possible: 0.38[c]
Dermal Contact	769	0.0001-39.9	4	NR	NR	0.011-0.45
Deodorant (underarm)	11[a]	not spray: 5-39.9	NR	NR	NR	NR
Hair - Non-Coloring	34	0.005-38	NR	NR	NR	NR
Hair-Coloring	8	0.17-12	NR	NR	NR	NR
Nail	NR	5	NR	NR	NR	NR
Mucous Membrane	451	0.5-10	NR	NR	NR	NR
Baby Products	4	NR	NR	NR	NR	NR
	1,10-Decanediol		**Methylpropanediol**		**Butyl Ethyl Propanediol**	
Totals*	**15**	**0.006**	**400**	**0.025-21.2**	**NR**	**0.29**
Duration of Use						
Leave-On	*14*	*0.006*	*249*	*0.025-21.2*	*NR*	*0.29*
Rinse-Off	*1*	*NR*	*149*	*5-12*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*2*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	42	0.71-5	NR	NR
Incidental Ingestion	NR	NR	2	NR	NR	NR
Incidental Inhalation-Spray	possible: 12[a]; 2[b]	NR	spray: 6 possible: 70[a]; 92[b]	NR	NR	possible: 0.29[a]
Incidental Inhalation-Powder	possible: 2[b]	possible: 0.006[c]	possible: 92[b]	possible: 0.8-21.2[c]	NR	NR
Dermal Contact	15	0.006	366	0.025-21.2	NR	NR
Deodorant (underarm)	NR	NR	NR	not spray: 0.025	NR	NR
Hair - Non-Coloring	NR	NR	14	NR	NR	0.29
Hair-Coloring	NR	NR	8	NR	NR	NR
Nail	NR	NR	1	0.04-12	NR	NR
Mucous Membrane	NR	NR	89	5	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Isopentyldiol	
Totals*	**127**	**0.13-15**
Duration of Use		
Leave-On	*122*	*0.13-15*
Rinse-Off	*5*	*3-15*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	25	0.13-5
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	spray: 4 possible: 67[a]; 8[b]	spray: 3-5 possible: 2-5[a]
Incidental Inhalation-Powder	powder: 3 possible: 8[b]	powder: 0.33 possible: 1-10[c]
Dermal Contact	124	0.33-10
Deodorant (underarm)	NR	spray: 1
Hair - Non-Coloring	2	3-15
Hair-Coloring	NR	5
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

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

[a]Includes products that can be sprays, but it is not known whether the reported uses are sprays

[b]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

[c]Includes products that can be powders, but it is not known whether the reported uses are powders

NR – no reported use

Table 5. Non-Cosmetic Uses

Ingredient	Non-Cosmetic Use	References
1,4-Butanediol	– Polymer component used in fabricating non-absorbable sutures for use in general and ophthalmic surgery – Indirect food additive used as a component of adhesives – Indirect food additive used as a component in polyurethane resins (no limit on amount used, but only to be used in closure gasket compositions in contact with certain food types), which are used in the manufacturing of closure-sealing gaskets for food containers – Indirect food additive used in the formation of copolyester-graft-acrylate copolymer used as a nylon modifier in nylon resins, which are used as basic components of food contact surfaces – Indirect food additive used as a reactant in the formation of polyester elastomers, which are used as basic components of food contact surfaces – Indirect food additive used as a reactant to modify polyethylene phthalate polymers used as components of plastics in contact with food – Indirect food additive used as a reactant in the formation of poly (tetramethylene terephthalate), which is used as a component in food contact surfaces – Indirect food additive used as a reactant in the formation of polyurethane resins, which are used as components of food contact surfaces – Indirect food additive used as a reactant in the formation of polyester elastomers (polybutadiene) and polyurethane resins (polyisoprene), which are rubber articles intended for repeat use in food packaging, processing, etc. – FDA estimated exposure to 1,4-Butanediol as a migrant in polyurethane resins (indirect food additive-21CFR177) would be not more than 90 µg/person/day, which FDA concluded was safe based on available toxicological data and estimated dietary exposure	21CFR74.3045; 21CFR175.105; 21CFR177.1210; 21CFR177.1500; 21CFR177.1590; 21CFR177.1630; 21CFR177.1660; 21CFR177.1680; 21CFR177.2600; [85]
Hexanediol	– Indirect food additive used as a component of adhesives – Indirect food additive used as a reactant in the formation of polyester resins and polyesterpolyurethanediol resins in adhesives, which are used in high-temperature laminate structures for food contact surfaces – Indirect food additive used as a reactant in the formation of polyurethane resins, which are used as components of food contact surfaces	21CFR175.105; 21CFR177.1390; 21CFR177.1680
Methylpropanediol	– Exemption from requirement of a tolerance for 2-Methyl-Propanediol residues (40CFR180.940a) was established when "…used as an inert ingredient component of food contact sanitizing solutions applied to all food contact surfaces in public eating places, diary-processing equipment, and food-processing equipment and utensils."-Based on EPA's review of toxicity data, especially that which showed no systemic toxicity or adverse reproductive/developmental effects at doses up to 1,000 mg/kg/day in animals, and potential for aggregate exposure – Exemption from requirement of a tolerance for 2-Methyl-Propanediol (40CFR180.910 and 40CFR180.930) when "…used as an inert ingredient in pesticide formulations applied to growing crops, raw agricultural commodities after harvest, and to animals (used for food)."	40CFR180.940(a); 40CFR180.910; 40CFR180.930;[86,87]

Table 6. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
			IN VITRO				
1,5-Pentanediol; 1,2-Propanediol	Human	Cells of a multilayer membrane system comprised 3 dodecanol collodion membranes functioning as acceptors	Test cream formulations (semisolid) containing: 0.1% tri-iodothyroacetic acid (TRIAC, a thyroid hormone analog) + 10% 1,5-Pentanediol or 0.1% TRIAC + 6% 1,2-Propanediol or 0.1% TRIAC + 10% 1,2-Propanediol	membrane area 4 cm^2; dodecanol membrane content was 2.5 mg/ 4 cm^2	10 mg test cream applied to membrane area; beaker @ 32°C used to perform experiments; penetration cells were removed from beaker at 30, 100, and 300 min; membranes separated and TRIAC extracted and analyzed by High Performance Liquid Chromatography (HPLC)	1,5-Pentanediol was a more effective penetration enhancer for TRIAC than 1,2-Propanediol; 33% TRIAC released from formulation @ 30 min, 57% released @ 100 min, 62% released @ 300 min 1,2-Propanediol (6%) was a penetration enhancer for TRIAC; 11% TRIAC released from formulation @ 30 min, 25% released @ 100 min, 37% released @ 300 min 1,2-Propanediol (10%) was a penetration enhancer for TRIAC; 14% TRIAC released from formulation @ 30 min, 37% released @ 100 min, 41% released @ 300 min	[43]
1,5-Pentanediol; 1,2-Propanediol	Human	Breast skin was surgically removed with a dermatome during reconstructive surgery; 3x6 cm; epidermal/dermal sample 400-500 µm thick; skin used immediately or stored in Eagle's minimum essential medium for up to 5 days; n=2 per formulation	Test cream formulations containing: 1% hydrocortisone + 25% 1,5-Pentanediol or 1% hydrocortisone + 25% 1,2-Propanediol or 1% hydrocortisone were prepared following Good Laboratory Practice (GLP)	Stratum corneum (1 cm^2) mounted on an *in vitro* continuous flow diffusion cell	50 mg test cream applied to top of skin in diffusion cell, receptor fluid (ethanol/phosphate buffered saline, 30:70 pumped through cell @ 2 ml/h) samples taken every 30 min between 0 and 60 h post-application; portion of test cream that was not absorbed was removed and weighed; portions of test substance that diffused through skin were assayed by HPLC; amount of test substance absorbed into skin was assayed separately; negative control (1% hydrocortisone) used in receptor fluid analysis	Absorption of hydrocortisone through skin increased by 4.4 times using 1,5-Pentanediol (has lipophilic characteristics) as compared to control (no penetration enhancer); hydrocortisone absorbed into skin was 58% (control not used in this part of experiment); the authors' speculated that 1,5-Pentanediol was potentially better absorbed into skin than 1,2-Propanediol (results below) because of the ability of 1,5-Pentanediol to bind to lipophilic structures in skin, slowing down drug transport Absorption of hydrocortisone through skin increased by 12.6 times using 1,2-Propanediol (less lipophilic than 1,5-Pentanediol) compared to control; hydrocortisone absorbed into skin was 37% (control not used)	[43]

Table 6. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
1,5-Pentanediol; 2-Methyl-Pentane-2,4-Diol (Hexylene Glycol)	Human	Breast skin was surgically removed with a dermatome during reconstructive surgery; 3x6 cm; epidermal/dermal sample 400-500 µm thick; skin used immediately or stored in Eagle's minimum essential medium for up to 5 days; n=5 per formulation	Test cream formulations containing: 0.1% mometasone furoate + 25% 1,5-Pentanediol or 0.1% mometasone furoate + 12% 2-Methyl-Pentane-2,4-Diol were prepared (GLP)	Stratum corneum (1 cm^2) mounted on an *in vitro* continuous flow diffusion cell	50 mg test cream applied to top of skin in donor chamber, receptor fluid (ethanol/phosphate buffered saline, 30:70 pumped through cell @ 2 ml/h) samples taken every 30 min between 0 and 60 h post-application; portion of test cream that was not absorbed was removed and weighed; portions of test substance that diffused through skin were assayed by HPLC; amount of test substance absorbed into skin was assayed separately	1,5-Pentanediol was a percutaneous absorption enhancer increasing the mometasone furoate absorbed through skin (4% mometasone furoate in receptor fluid) and into skin (6% mometasone furoate); 12 mg of cream remained on skin at completion of experiment 2-Methyl-Pentane-2,4-Diol was a percutaneous absorption enhancer increasing mometasone furoate absorbed through skin (5% in receptor fluid) and into skin (7%); 29 mg of cream remained on skin; the authors' speculated that the increase amount in remaining cream was possibly related to the greasiness of the formulation compared to cream containing 1,5-Pentanediol	[43]

GLP=Good Laboratory Practice; HPLC=High Performance Liquid Chromatography

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO			
Propanediol	Rat, Sprague-Dawley	Rat liver and testicular homogenates	0 or 10 mM Propanediol in 100 mg of homogenized tissue mixture	For 15 weeks rats were dosed with 500 ppm Propanediol in the diet (control rats were fed a plain diet); rats were killed and livers and testes of 2 rats/group were homogenized; a reaction mixture of either liver or testes homogenates from treated or control rats, Propanediol (without Propanediol for controls), buffer, sodium pyruvate, lactic dehydrogenase, and NAD (nicotinamide adenine dinucleotide) was prepared (in duplicate) and incubated at 37°C for 3 h; 2-thiobarbituric acid in buffer and trichloroacetic acid were added, mixture heated at 95°C for 1 h, and absorbance measured at 532 nm	Propanediol was converted to malondialdehyde (~5.6 nmol/h/100 mg of tissue) by rat liver homogenates from both the control and Propanediol-exposed rats; testicular homogenates from control and treated rats showed little to no ability to convert Propanediol to malondialdehyde This study focused on DNA cross-linking in liver and testes of rats orally administered Propanediol (data presented in the Genotoxicity Studies section of this safety assessment)	[44]
1,4-Butanediol	Not Specified	Liver alcohol dehydrogenase	0.5 mM 1,4-Butanediol and 0.5 mM ethanol (no further details provided)	1,4-Butanediol and ethanol were combined with 80 mM potassium phosphate (pH 7.6), 0.5 mM NAD, and 10 µg crystalline horse liver alcohol dehydrogenase in a mixture (3 ml total volume) and incubated at 37°C	Competitive inhibition of the metabolism of 1,4-Butanediol occurred with ethanol; oxidation of 1,4-Butanediol was inhibited in the presence of 0.5 mM ethanol; oxidation of ethanol was inhibited in the presence of 0.5 mM 1,4-Butanediol	[46]
Methylpropanediol	Rat	Rat liver cells	Not Specified	Not Specified	Metabolism studies showed that Methylpropanediol is a substrate for rat liver alcohol dehydrogenase, see reference for more information on data submitted by industry	[18]
2,3-Butanediol	Rat, Wistar	Males, rat liver homogenates	10 nmol diacetyl, 10 nmol acetoin, or 10 nmol 2,3-Butanediol were added to homogenate mixture described in Procedure column	Rat liver was homogenized in sodium phosphate buffer, centrifuged, and a mixture of 10 nmol diacetyl, acetoin or 2,3-Butanediol plus NADH, nicotinamide, 0.1 ml homogenate supernatant, and buffer were incubated for 10 min @ 37°C; reaction stopped by adding $HClO_4$, sample centrifuged, and supernatant was assayed for diacetyl, acetoin, or 2,3-Butanediol	Diacetyl, acetoin, and 2,3-Butanediol were interconvertible; they became equilibrated at a molar ratio of 0:3:7, respectively (diacetyl and acetoin were used as substrates)	[45]
			ANIMAL			

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Propanediol; 1,4-Butanediol; 1,5-Pentanediol; Hexanediol; 2,3-Butanediol	Rabbit, Chinchilla	n=variable, see Procedure column	1.0-1.5 g/kg test substances in water is specified in the reference with the total g administered listed in the Procedure column	Single doses administered via stomach tube as follows: 16 g total Propanediol fed to 4 rabbits; 9 g total 1,4-Butanediol fed to 4 rabbits; 8.5 g total 1,5-Pentanediol fed to 4 rabbits; 2.8 g total Hexanediol fed to 1 rabbit; 1.2-1.5 g total 2,3-Butanediol fed to rabbits and 2 g total 2,3-Butanediol fed to 4 rabbits; Rabbits were fed 60 g of rat cubes and 100 mL water/day; urine was treated, extracted, and assayed by various methods for metabolites 1-3 days post-dosing	Propanediol: neither malonic acid nor unchanged diol was isolated from urine 1,4-Butanediol: 0.81 g (7% of dose) of succinic acid was isolated 1,5-Pentanediol: phenacyl glutarate (0.5% of dose) was isolated from the urine Hexanediol: unchanged diol was not isolated from urine, from the carboxylic acid fraction of urine adipic acid was isolated 2,3-Butanediol: neither diacetyl nor acetoin were detected in urine or breath of rabbits (1.2-1.5 g dose); a glucuronide (triacetyl methyl ester) was isolated from urine of 2-g dosed rabbits	[47]
Propanediol; 1,4-Butanediol; 1,5-Pentanediol; Hexanediol; 2,3-Butanediol	Rabbit, Chinchilla	n=3	4 mmoles/kg Propanediol 4 mmoles/kg 1,4-Butanediol 2 mmoles/kg 1,5-Pentanediol 2 mmoles/kg Hexanediol 4 mmoles/kg 2,3-Butanediol	Single dose administered via stomach tube; rabbits were fed 60 g of rat cubes and 100 mL water/day; 1-3 days post-dosing urine was treated, extracted, and assayed by various methods for metabolites of glycols and glucuronic acid conjugation	Propanediol glucuronic acid conjugation was 0-2% of dose, no other urinary metabolites were reported; the authors' surmised that Propanediol is likely oxidized completely to CO_2 in body; 1,4-Butanediol glucuronic acid conjugation was 0-2% of dose, urinary metabolite identified was succinic acid; 1,5-Pentanediol had no glucuronic acid conjugation reported, urinary metabolite identified was glutaric acid (glutaric acid is metabolized to CO_2 in body); Hexanediol glucuronic acid conjugation was 4%-9% of dose, urinary metabolite identified was adipic acid; 2,3-Butanediol glucuronic acid conjugation was 20%-26% of dose, glucuronide of the glycol (triacetyl methyl ester) was the urinary metabolite identified	[47]
1,4-Butanediol	Rat	Not specified	1 g/kg (no further details specified)	Animals were dosed via stomach tube and the concentrations of 1,4-Butanediol in brain, liver, kidney, stomach, and pancreas were determined by Gas Chromatography/ Mass Spectrometry (GC/MS) analysis 75 min post-dosing; the same organ concentrations of 1,4-Butanediol in control rats (naïve) were determined similarly	In naive rats concentrations were 165 ng/g (stomach) and 30 ng/g (liver) in aqueous phase tissues; in lipid phase tissues concentrations ranged from 150 to 180 ng/g in all organs tested; at 75 min post-dosing 1,4-Butanediol was distributed through all organ systems evenly; 1,4-Butanediol is ubiquitous in lipid membranes and aqueous phase fractions of the organs analyzed, implying 1,4-Butanediol may be an extraneuronal source for gamma-hydroxybutyrate (GHB); 1,4-Butanediol is an endogenous hepatoxin relevant to alcohol induced liver damage	[46,49]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, F344/N	Male, n=4 per dosage level	4, 40, 120, or 400 mg/kg ^{14}C-1,4-Butanediol (C1 and C4 labeled)	Single doses administered via gavage; rats housed individually in metabolism chambers; urine and feces collected @ 8, 24, 48, and 72 h post-dosing; breath samples were collected by various traps and analyzed 2, 4, 8, 12, 24, 32, 48, 56, and 72 h post-dosing; blood drawn by cardiac puncture from anesthetized rats at completion of experiment (72 h); adipose tissue, muscle, skin, liver, and brain were removed from rats dosed with 40 mg/kg ^{14}C-1,4-Butanediol and assayed for ^{14}C; the carcasses of 2 rats each dosed with 4 or 400 mg/kg ^{14}C-1,4-Butandiol were assayed for ^{14}C; no controls used	>75% of dosed radioactivity was excreted as $^{14}CO_2$ 24 h post-dosing; with 400 mg/kg capacity-limited metabolism observed at 26-30% lower $^{14}CO_2$ production 2 h post-dosing compared to other dose levels but differences decreased over time; by 72 h post-administration 3%-6% of dosed radioactivity was excreted in urine and 0.04%-0.6% of dosed radioactivity excreted in feces; ≤1% of C^{14} were recovered in volatile compounds in breath after 4 or 400 mg/kg exposures so volatile compounds were not collected at remaining dosages; accumulation of C^{14} after the 40 mg/kg exposures was 0.9% of dosed radioactivity in muscle tissue, 0.5% of dosed radioactivity in liver tissue, 0.1% of dosed radioactivity in blood, 0.01% of dosed radioactivity in brain, 0.15% of dosed radioactivity in adipose tissue; C^{14} in carcass was 2.2% of 4 mg/kg dosed radioactivity and 2.8% of 400 mg/kg dosed radioactivity	[48]
1,4-Butanediol	Rat, Sprague-Dawley	n=4/cage (no further details specified)	1 g/kg 1,4-Butanediol and/or 3 g/kg ethanol (in 38% v/v water)	Single doses of 1,4-Butanediol (intragastrically) and ethanol (intraperitoneally) administered; food and water available *ad libitum*; rats were killed 75 min after dosing with ethanol and/or 1,4-Butanediol (maximal behavioral effects of drugs were observed at this time)	Blood ethanol levels were no different between 1,4-Butanediol and ethanol administered together compared to ethanol administered alone; concentrations of 1,4-Butanediol in brain (338 µg/g), liver (315 µg/g), and kidney (347 µg/g) tissues of rats dosed with both 1,4-Butanediol and ethanol together were statistically significantly higher than in rats administered 1,4-Butanediol alone in brain (96 µg/g), liver (52 µg/g), and kidney tissues (58 µg/g); endogenous 1,4-Butanediol in animals dosed only with ethanol was 0.02-0.05 µg/g of tissue (type of tissue not specified); liver 1,4-Butanediol concentrations were maximal 1.5-3 h post-administration of 1,4-Butanediol alone (50 µg/g) or when administered together with ethanol (>300 µg/g); by 30 min post-dosing with 1,4-Butanediol alone sedation and ataxia were observed and by 60 min catalepsy was noted, these types of effects were intensified with administration of 1,4-Butanediol and ethanol together	[46]
1,4-Butanediol	Rat, Sprague-Dawley	n=10	1 g/kg 1,4-Butanediol and 20% ethanol (v/v) in water	Ethanol administered intragastrically 6x/day for 4 days, then 10-11 h after last ethanol exposure 1,4-Butanediol was administered to 5 rats and 5 rats received saline	1,4-Butanediol had no effect on ethanol elimination	[46]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, Sprague-Dawley	No further details specified	1 g/kg 1,4-Butanediol or 3 g/kg ethanol or both together	A single dose of 1,4-Butanediol, ethanol, or both together were administered	Mortality rate 24 h post-administration of 1,4-Butanediol was 1 of 18 rats, for ethanol was 0 of 18 rats, and for both administered together was 9 of 18 rats; 1,4-Butandiol concentrations in liver tissues of 2 of 9 animals (dosed with both compounds) that died 1.5 to 2.5 h after dosing were 1450-1600 µg/g shortly after death; the remaining 7 of 9 died 12 to 24 h post-dosing when liver concentrations of 1,4-Butanediol were low	[46]
1,4-Butanediol	Rat, Sprague-Dawley	n=5 per group	1 g/kg 1,4-Butanediol or 3 g/kg ethanol or both together	A single dose of 1,4-Butanediol (intragastrically), ethanol (intraperitoneally), or both together were administered; rats killed 24 h post-dosing; gross and microscopic studies of brain, liver and kidney were conducted	No histological changes were noted in kidney, liver, or brain 24 h post-dosing with ethanol only; 1,4-Butanediol dosed rats showed hyperemia in all organs examined; in rats dosed with ethanol and 1,4-Butanediol the following results were observed: ascites and liver congestion, microscopic liver (fatty infiltration and necrosis) and kidney changes (medullary necrosis)	[46]
Methylpropanediol	Rat	Not Specified	Not Specified	Gavage administration (no further details provided)	Rapid metabolism and elimination in the urine as 3-hydroxybutyric acid and exhaled air as CO_2 were observed, see reference for more information on data submitted by industry	[18]
Methylpropanediol	Rat	Not Specified	Not Specified	Not Specified	Rapid metabolism and elimination; 31%-45% of dose eliminated by renal excretion and cage wash; 42%-57% of dose eliminated in exhaled air; <1% of dose excreted in feces; half-life was calculated to be 3.57 h (high dose) and 3.87 h (low dose); alcohol dehydrogenase catalyzed metabolism to S- and R- stereoisomers of 3-hydrobutyric acid and CO_2	[73]
2,3-Butanediol	Rat, Wistar	Male	1 M diacetyl, acetoin, or 2,3-Butanediol dissolved in saline administered at 5 mmol/kg	Single dose administered orally (control rats administered saline); 1 h post-dosing rats were intraperitoneally injected with pentobarbital and liver, kidney, and brain were removed and perfused with ice-cold saline; organs homogenized @ 4°C, centrifuged, and supernatants analyzed for diacetyl, acetoin, and 2,3-Butanediol	Diacetyl, acetoin, and 2,3-Butanediol interconvert; reduced 2,3-Butanediol was found in liver, kidney, and brain at a total of 2.3% of the administered dose of diacetyl; reduced 2,3-Butanediol was found in liver, kidney, and brain at a total of 2.6% of the administered dose of acetoin; small amounts of 2,3-Butanediol were oxidized to diacetyl and acetoin (these accumulated in liver) and 2,3-Butanediol was located in liver, kidney, and brain tissues at a total of 3% of administered dose	[45]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Wistar	Male	1 mM diacetyl, acetoin, or 2,3-Butanediol	Rats were administered pentobarbital, liver perfusion performed through portal vein to inferior vena cava @ 37°C; substrate added to buffer 30 min after perfusion began; perfusion was conducted without recirculation; perfusates collected every 10 min for 1 h, then liver was removed, homogenized, deproteinized, and assayed for diacetyl, acetoin, and 2,3-Butanediol	Diacetyl was reduced to acetoin and 2,3-Butanediol in liver (mole ratio diacetyl: acetoin: 2,3-Butanediol was 5:39:100; perfusate showed 45, 15, and 10% of diacetyl dose, respectively); diacetyl in perfused liver was 0.1% of perfused diacetyl dose so ~30% was metabolized or underwent glucuronidation in liver Acetoin was reduced to 2,3-Butanediol and small amount oxidized to diacetyl in liver (mole ratio diacetyl: acetoin: 2,3-Butanediol was 1:38:100; perfusate showed 1:15:45 of acetoin dose, respectively); acetoin in perfused liver was 0.1% of perfused acetoin dose, therefore ~30% was metabolized or conjugated in liver 2,3-Butanediol was oxidized in small amounts to diacetyl and acetoin; ~33% of perfused 2,3-Butanediol was metabolized or conjugated in liver; when only buffer was perfused none of the test compounds were detected in the perfusate	[45]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Sprague-Dawley	Male Exp. 1, n=6 livers/substrate Exp. 2, n=2 Exp. 3, n=1	Exp. 1: 2 mM 2R,3R-Butanediol or 2 mM 2S,3S-Butanediol or Racemic 2,3-Butanediol (0.8 mM RR-,SS-forms and 1.2 mM *meso*-forms); 2 mM 2R,3R-[2-^{14}C]Butanediol or 1 mM *meso*-[2-^{14}C]2,3-Butanediol	Exp. 1-Rats were fed *ad libitum.* Livers were perfused with 150 ml of bicarbonate buffer containing bovine serum albumin and 15 mM glucose for 30 min, then various forms of labeled, unlabeled, or racemic 2,3-Butanediol were added to perfusate Exp. 2-To determine if isomer interconversion occurred, buffer (in deuterium oxide, 99.9% ^{2}H) solution containing 15 mM glucose and 2 mM 2R,3R-Butanediol or 2 mM 2S,3S-Butanediol was perfused through the liver Exp. 3-To examine whether the liver would convert ethanol to 2,3-Butanediol, 15 mM glucose and 20 mM ethanol were perfused through the liver for 2 h; 5 mM pyruvate was added to perfusate after 1 h (no exogenous 2,3-Butanediol was added) In a control experiment the livers of fed rats were perfused with 15 mM glucose	Exp. 1-In unlabeled 2,3-Butanediol experiments, the uptake rate (linear) of the RR- form was greater than for the SS- form; uptake rate for either labeled or unlabeled RR- form was double that of the labeled *meso*- form; rate of formation of *meso*- form from labeled RR- form was approx. double the rate of formation of labeled RR-, SS- forms produced from *meso*-form; uptake of labeled RR- and meso- forms resulted in formation of $^{14}CO_2$, acetate, ketone bodies, acetoin, and isomers of 2,3-Butanediol, which is attributed to approx. 1/3 of label uptake; results indicate the oxidation of 2,3-Butanediol to acetyl-CoA via acetoin Exp. 2-10 µM *meso*-[$^{2}H_1$]2,3-Butanediol and 3 µM of RR,SS-[$^{2}H_1$]2,3-Butanediol were produced 60 min after start of perfusion of RR-form; no *meso*-[$^{2}H_1$]2,3-Butanediol was detected and no RR,SS-2,3-Butanediol showed deuterium present in the perfusion of the SS-form Exp. 3-No 2,3-Butanediol or acetoin were produced from ethanol perfusion 1 h after the start of perfusion, but during the 2nd h 2,3-Butanediol and acetoin were reported to be 15 µM Controls did not show any detectable 2,3-Butanediol (<1 µM) after the start of the perfusion	[88]
HUMAN						
1,4-Butanediol	Human	Not Specified	15 or 30 mg/kg (no further details specified)	Either dose level was administered by IV, additionally gamma-hydroxybutyric acid was administered for comparison (1,4-Butanediol converts to gamma-hydroxybutyric acid or GHB in the body); no further details provided	Within 2 min post-administration of 1,4-Butanediol, GHB blood levels peaked and began to decay; 1,4-Butanediol and GHB had nearly identical decay curves when equal doses of each were administered, showing a rapid and almost 100% conversion of 1,4-Butanediol to GHB (no further details provided)	[48]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Human	n=5 males, 3 females (22 to 35 yrs old)	25 mg/kg in orange or cranberry juice	Subjects were not GHB-naïve (GHB-naïve= not once ingested GHB, 1,4-Butanediol, or gamma-butyrolactone) or illicit drug or prescription drug (except for oral contraceptives) users; they were not heavy alcohol consumers (not > 3 drinks/week) and consumed no alcohol 3 days prior to the study and only light users of GHB (no more than 2 x in 6 months); design of study was randomized double-blinded, placebo-controlled, two arm, crossover; subjects were orally administered a single dose of placebo (plain juice) or 1,4-Butanediol after fasting overnight; subjects allowed to eat 3 h post-dosing; 2 day washout period between treatments; heart rate, blood pressure, respiratory rate, and skin temperature were measured 30 and 15 min prior to and every 15 min for the first 2 h after dosing; blood samples collected prior to and at 5, 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 12, and 24 h after dosing; blood sample analysis done by GC/MS; subjects completed a visual analog scale questionnaire and a computerized cognitive battery to evaluate drug effects prior to and 1, 2, and 4 h after dosing; subjects' DNA was tested for the G143A single-nucleotide polymorphism of ADH-IB (non-synonymous mutation of an amino acid 48 substitution from arginine to histidine, R48H, associated with 40-fold increase in ethanol metabolism)	Extensive conversion of 1,4-Butanediol to GHB was observed ; average C_{max} (maximum concentration) for GHB was 45.6 mg/l and for 1,4-Butanediol was 3.8 mg/l in blood plasma; 5 of 8 subjects had measurable plasma GHB levels 5 min post-dosing, the 3 other subjects did not, potentially because of slower gastrointestinal absorption; at 30 min post-dosing all subjects had measurable plasma GHB levels; elimination half-life for GHB was 32 min and for 1,4-Butanediol was 39 min; at 4 h post-dosing plasma levels were below the limit of quantitation (1 mg/l); 4 subjects showed rapid clearance and 4 showed relatively slower clearance (3 of 4 subjects with slower metabolism had variant alleles for G143A and 3 of 4 with faster metabolism had normal wild-type ADH-IB); 2 subjects experienced lightheadedness and 2 had headaches; blood pressure increased 15 min post-dosing compared to placebo; O_2 saturation was statistically significantly decreased compared to placebo, but only by 1%; heart rate or rhythm and body temperature were unaffected; some subjects reported feeling less awake and alert, less able to concentrate, more lightheaded or dizzy up to 4 h post-dosing with effects at a max 60-90 min post-dosing	[50]
GHB sodium salt (a metabolite of 1,4-Butanediol)	Human	n=4 males, 4 females (27 to 47 yrs old); subjects were GHB naive	25 mg/kg in water	Single dose of freshly prepared solution administered orally through a drinking straw on an empty stomach; subjects not allowed to consume medication, alcohol, or drugs 48 h prior to and 24 h after study; blood samples were collected just before dosing and at 10, 15, 20, 25, 30, 45, 60, 69, 90, 120, 150, 180, 240, and 360 min post-dosing; urine samples were collected 10 min pre- and 120, 240, 360, 480, 720, and 1440 min post-dosing; oral fluid was collected up to 360 min post-dosing; above samples were assayed and quantitative analysis performed using GC/MS; blood pressure, heart rate, and hemoglobin oxygen saturation were measured when blood was drawn	GHB plasma levels ranged from < limit of detection (LOD) to 76.3 µg/ml with C_{max} between 4.70 and 76.3 µg/ml occurring 20-45 min post-dosing; terminal plasma elimination half-lives were 17.4 to 42.5 min indicating oral absorption and elimination of GHB were rapid; mean residence time was 43.7 to 194 min; total clearance was 476 to 2520 ml/min; linear elimination kinetics were observed; GHB in oral fluid ranged from < LOD to 778 µg/ml (mean highest values of 203 to 101 µg/ml observed 10 to 15 min post-dosing, respectively); GHB in urine ranged from <LOD to 840 µg/ml (most subjects excreted highest GHB concentrations 60 min post-dosing, no GHB was detected in baseline urine or in urine samples collected 1440 min post-dosing; total urine recovered within 24 h was 0.2%-2.1% of dose; no severe psychotropic side effects noted or vital functions substantially affected; confusion, sleepiness, and some dizziness were observed; substantial inter-individual variation noted	[51]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference

C_{max}=maximum concentration; GC/MS=Gas Chromatography/Mass Spectrometry; GHB=gamma-hydroxybutyric acid or gamma-hydroxybutyrate; LOD=limit of detection; NAD= nicotinamide adenine dinucleotide

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
ANIMAL						
Dermal						
Propanediol	Rat, Wistar	n=2/sex/group	1.0, 2.0, or 4.0 ml/kg (undiluted, no vehicle)	Dorso-lumbar skin shaved free of hair; test substance applied to dorso-lumbar skin and occlusively covered for 24 h (rats fasted during exposure); at 24 h post-application covering removed and skin washed with detergent; rats observed for 9 days post-application	LD_{50} > 4ml/kg (or 4.2 g/kg); no mortalities reported	[42]
Propanediol	Rabbit	Not specified	20 g/kg	No details specified	LD_{50}> 20 g/kg	[53]
1,4-Butanediol	Rat, Wistar Imp: DAK	Female, n=12	5 g/kg (undiluted liquid)	Food and water were available *ad libitum*; sides and dorsum clipped free of hair; single application of test substance to dorsum and occlusively covered for 24 h, then covering was removed; rats were observed for 48 h (n=4) or daily for 14 days (n=8) post-application and then killed	No mortality; 48 h post-application dermal lesions (segmentary acanthosis, single microcrusts with granulocytes infiltrations, slight collagen edema, monomuclear cell infiltrations in hypodermis) were observed in 2 of 4 rats and in the liver of all 4 rats extensive vacuolar degeneration of hepatocyte cytoplasm was noted; 14 days post-application rats showed small, single desquarmating crusts on skin and focal granulocyte infiltrations in epidermis and in the liver moderate periportal vacuolization of hepatocytes cytoplasm was noted; the pathological lesions observed were similar to those noted following acute oral doses	[59]
1,4-Butanediol	Rat, Sprague-Dawley	n=5/sex	2 g/kg (vehicle=water)	Test substance applied (whether skin was shaved or not was not specified) to a 50 cm^2 area and skin occlusively covered for 24 h post-dosing, at that time skin washed with warm water; animals observed for 14 days post-dosing	LD_{50} > 2g/kg for males and females; no mortalities; animals gained weight; gross pathology revealed no abnormalities; clinical signs: dyspnea, poor general state within 2 h post-exposure, slight erythema after removing test substance	[57]
1,5-Pentanediol	Rabbit, New Zealand (albino)	Male, n=4	>20 ml/kg	Rabbit trunk was clipped free of hair; single application of test substance to hairless skin and covered with occlusive plastic film for 24 h, at which point plastic film was removed; rabbits were observed for 14 days; researchers noted that doses >20 ml/kg could not be "retained in contact with the skin"	LD_{50} >20 ml/kg was reported	[54]
Hexanediol	Rabbit, New Zealand (albino)	Male, n=4	>10 g/kg in a "suitable vehicle"	Rabbit trunk was clipped free of hair; single application of test substance to hairless skin and covered with occlusive plastic film for 24 h, at which point plastic film was removed; rabbits were observed for 14 days	LD_{50}>10 g/kg was reported	[54,55]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Hexanediol	Rabbit, Vienna White	n=5/sex	2.5 g/kg vehicle = 0.5% carboxymethyl cellulose)	Procedures followed were in accordance with OECD Test Guideline (TG) 402 (Acute Dermal Toxicity); rabbit dorsal and lateral back area and flanks were clipped free of hair; single application of test substance to hairless skin and occlusively covered for 24 h then skin was washed with warm water; animals observed for 8 days post-application; necropsy performed	LD_{50} > 2.5 g/kg for males and females; no mortalities; gross pathology revealed no abnormalities; clinical signs: within 20-30 min slight apathy in 1 male and 1 female, slight skin irritation in 1 male (resolved after 5 days) and in 1 female (cleared within 48 h)	63
Methylpropanediol	Rabbit, New Zealand	n=5/sex	2 g/kg	Procedure followed was in accordance with OECD TG for Testing Chemicals; single application of test substance (semi-occlusive) for 24 h; animals observed for 14 days post-application; necropsy performed	LD_{50} > 2 g/kg; 1 death on day 12 (deemed not treatment-related because there were no signs observed previously); no-to-slight dermal reaction in 2 rabbits on day 1, but cleared by day 7; 5 of 9 animals showed abnormal kidneys and gastrointestinal tract at necropsy; a tissue mass and hemorrhagic areas on dorsal abdominal cavity of 1 animal were noted; weight loss in 2 animals observed; clinical signs: slight erythema, diarrhea, yellow nasal discharge, few feces, bloated abdomen and soiling of anogenital area; abnormalities in lungs, pleural cavity, liver and gastrointestinal tract	58
Methylpropanediol	Rabbit	Not Specified	2 g/kg	Not Specified	LD_{50} > 2 g/kg	18
Butyl Ethyl Propanediol	Rat, CD(SD)BR VAF/Plus	n=5/sex	2 g/kg (no vehicle, test substance in powder form and moistened with distilled water before application)	Procedures followed (non-GLP) were in accordance with OECD TG 402 (Acute Dermal Toxicity); rat skin was clipped free of hair; a single application of test substance to hairless skin and occlusively covered for 24 h then skin was washed with water; animals were observed for 14 days post-application; necropsy performed	LD_{50} > 2 g/kg for males and females; no mortalities; no abnormal clinical signs; rats gained weight; gross pathology revealed no treatment-related observations	65
Butyl Ethyl Propanediol	Rabbit	Not Specified	3.81 ml/kg	Single application of test substance to skin (no further details provided)	LD_{50}=3.81 ml/kg	56
				Oral		
Propanediol	Rat, Wistar (albino)	n=5/sex/dose	9.0, 10.8, 13.0, 15.6, 18.7 ml/kg (no vehicle was used)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity) but no controls; animals were fasted overnight; single doses administered by gavage; animals observed for 14 days post-dosing, necropsy performed on survivors	LD_{50} was calculated (Weil method) to be 14.9 ml/kg; clinical signs within a few hours post-dosing were sluggishness, sedation, ataxia, and unconsciousness preceding death; animals that survived recovered to good health by 14 days post-dosing; no gross pathology changes in survivors were reported; mortality was as follows: 1 female (10.8 mg/kg), 2 males (13.0 ml/kg), 3 males and 2 females (15.6 ml/kg); 5 males and 5 females (18.7 ml/kg)	42

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Propanediol	Rat	n=at least 5/dose	1-9, 11, 12, 13, 14, 15, 16, 17, 18, 19 ml/kg (no vehicle specified)	Dose administered by gavage (no further details provided)	Mortality rates were as follows: 10%-18% (11-14 ml/kg); 64% (15 ml/kg); 50% (16 ml/kg); 40% (17 ml/kg); 100% (18-19 ml/kg) Authors' speculated that the variable mortality was potentially related to gastrointestinal absorption variability No mortality observed with 1-9 ml/kg	[42]
Propanediol	Cat	n=3	3 ml/kg	Dose administered by gavage (no further details provided)	At 48 h post-dosing no effects observed; by 72 h post-dosing cats vomited after drinking water and would not eat; weight loss and death reported within 1 week post-dosing	[42]
Propanediol	Rat, Wistar	n=8/sex	10.5 g/kg equivalent to 10 ml/kg (no vehicle used)	Dose administered by gavage (no further details provided)	LD_{50}=10 ml/kg; piloerection noted 24 h post-dosing in some animals; 4 of 16 animals died	[42]
Propanediol	Rat, ChR-CD	n=1 male/dose	2.25, 3.4, 5, 7.5, 11, 17, 25 g/kg; two different grades of Propanediol were evaluated undiluted at the above dosages (refined 99.8% and crude 70%)	Single dose administered by intragastric intubation; rats observed for 14 days post-dosing	Approximate lethal dose (ALD) > 25 g/kg for 99.8% purity; no mortalities at any dosages; clinical signs observed at all dosages 1-2 days post-dosing included pallor, irregular respiration, belly-crawling, chewing motion, and salivation ALD = 17 g/kg for 70% purity; rats died within 24 h of dosing with 17 or 25 g/kg; no mortalities at remaining dosages; clinical signs at dosages below 17 g/kg observed on days 1-6 post-dosing were pallor, irregular respiration, salivation, chewing motions, belly-crawling, and diuresis	[60]
Propanediol	Rat	Preliminary Test: n=1/sex/group Definitive Test: n=4/sex	Preliminary Test: 0.63, 1.25, 2.5, 5, 10 ml/kg Definitive Test: 10 ml/kg	Preliminary Test: Single dose administered by gavage; animals observed through 9 days post-dosing (no further details provided) Definitive Test: Single dose administered by gavage (no further details provided)	Preliminary Test: 2 deaths (females) by 2 days post-dosing (no details as to which dose was lethal), other animals survived until 9 days post-dosing; piloerection noted 24 h post-dosing Definitive Test: LD_{50}=10 ml/kg (or 10.5 g/kg)	[31]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, Wistar Imp: DAK	n=4/sex/dose group; n=5/sex/dose group	1.5 to 2.5 g/kg at increasing doses; 1.8 g/kg	Food and water were available *ad libitum*; animals fasted for 16 h prior to dosing; single doses of 1.5 to 2.5 g/kg were administered by gavage and rats observed daily for 14 days; single doses of 1.8 g/kg administered, rats killed 48 h (n=8) or 14 days (n=8) post-dosing and examined for pathological lesions	Estimated LD_{50} = 1.83 g/kg (1.7-1.98 g/kg range) for males and 2.00 g/kg (1.8-2.22 g/kg range) for females 48 h post-dosing: unspecified number of deaths were reported (pathological findings were fluid-filled gastrointestinal tract and congestion of internal organs); in both sexes irregular, decreased respiration and catalepsy were observed; histopathological changes in liver and kidneys were noted (1.8 g/kg dose); extensive vacuolar degeneration of hepatic parenchyma noted in liver of all rats; 1 male showed periportal fatty changes in liver; hyaline or granular casts/clusters of desquamated cells (renal tubule lumen of subcortical zone and outer medulla), tubules with regeneration, and interstitial infiltration of mononuclear cells in kidneys were noted 14 days post-dosing: periportal vacuolization of hepatocytes cytoplasm and cells in mitosis were observed in liver; in 3 of 3 males and 2 of 5 females hyaline casts, single tubules regenerations, and dispersed interstitial infiltration with lymphocytes were seen in kidneys; liver and kidney changes were reversible	[59]
1,4-Butanediol	Rat, Sprague-Dawley	n=5/sex/dose	1, 1.3, 1.5, 2, 2.5 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401(Acute Oral Toxicity); single dose administered by gavage and animals observed for 14 days post-dosing; necropsy was performed	LD_{50} estimated to be 1.5 g/kg for males and females; at 24 h post-dosing 27 animals dead (≥1.3 g/kg); deaths attributed to congestive hyperemia; animals killed after 14 days showed no abnormalities; clinical signs reported: dyspnea, apathy, abnormal position, staggering, atony, unusual pain reflex, unusual cornea reflex, narcotic-like state, tremor, spastic gait, scrubby fur, hair loss, exsiccosis, exophthalamus, poor general state; animals that survived to 14 days gained weight	[57]
1,4-Butanediol	Rat	n=5/sex	1.35 and 1.67 g/kg	Single dose administered by gavage; animals observed for 14 days post-dosing; necropsy performed	LD_{50} = 1.67 g/kg (females) and 1.35 g/kg (males); clinical signs included: dyspnea, apathy, abnormal position, staggering, atony, unusual pain reflex, unusual cornea reflex, narcotic-like state, tremor, spastic gait, scrubby fur, loss of hair, exsiccosis, exophthalamus, poor general state	[61]
1,4-Butanediol	Rat, albino	n=25/sex	1.55 g/kg	Not Specified	LD_{50}= 1.55 g/kg	[48]
1,4-Butanediol	Rat	Not Specified	1.78 g/kg	Not Specified	LD_{50}=1.78 g/kg	[14]
1,4-Butanediol	Rat, Wistar	Not Specified	1.525 g/kg	Not Specified	LD_{50}=1.5 g/kg	[14]
1,4-Butanediol	Mouse	Not Specified	2.1 g/kg	Not Specified	LD_{50}=2.1 g/kg	[14]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Mouse	Not Specified	2.2 g/kg	Not Specified	LD_{50}=2.2 g/kg (24 h post-dosing)	[14]
1,4-Butanediol	Guinea Pig	Not Specified	1.2 g/kg	Not Specified	LD_{50}=1.2 g/kg	[14]
1,4-Butanediol	Rabbit	Not Specified	2.5 g/kg	Not Specified	LD_{50}=2.5 g/kg	[14]
1,5-Pentanediol	Rat, Carworth-Wistar	n=5	Dose not specified, a "suitable vehicle" (e.g. water, corn oil, or semi-sold agar suspension) was used	Single dose administered by gastric intubation to non-fasted rats; rats observed for 14 days post-dosing	An estimated LD_{50}= 5.89 g/kg ±1.96 standard deviations was reported, LD_{50} range reported was 5.38 to 6.44 g/kg	[54]
1,5-Pentanediol	Rat, Sprague-Dawley	n=12 total (males and females)	1, 4.64, 6.81, 10 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity); single dose administered by gavage; animals observed for 14 days post-dosing	LD_{50} = 10 g/kg for males and females; 1 death in 24 h (6.81 g/kg dose), 3 deaths in 24 h (10 g/kg dose), no deaths at two lower doses; reduced weight gain early in study; gross pathology revealed acute dilation of the heart and congestive hyperemia, bloody stomach ulcerations, diarrhetic and hematonic gut content, and abnormal bladder content; clinical signs: reduced state, staggering, paresis, spastic gait, salivation, exsiccosis	[62]
Hexanediol	Rat, Carworth-Wistar	n=5	Dose not specified, a "suitable vehicle" (e.g. water, corn oil, or semi-sold agar suspension) was used	Single oral dose administered by gastric intubation to non-fasted rats; rats observed for 14 days post-dosing	An estimated LD_{50}=3.73 g/kg was reported, LD_{50} range reported was 2.68 to 5.21 g/kg	[54,55]
Hexanediol	Rat	n= 20 total (males and females)	2.5, 3.2, 6.4 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity); dose administered by gavage; animals observed for 7 days (2.5 and 6.4 g/kg dose) or 14 days (3.2 g/kg dose); necropsy performed	LD_{50} = 3 g/kg for males and females; mortality as follows: none in 7 days (2.5 g/kg dose), 7 deaths in 24 h (3.2 g/kg dose), 4 deaths in 24 h and 5 deaths in 7 days (6.4 g/kg dose); gross pathology revealed no abnormalities; clinical signs: staggering (within 24 h of 2.5 g/kg dose); apathy (within 1 h of 3.2 g/kg dose), lateral position, narcotic state, and atonia, constant urination (within 3 h of 3.2 g/kg dose); apathy and atonia (within 1 h of 6.4 g/kg dose), lateral position, increased urination (within 3 h of 6.4 g/kg dose), piloerection (within 24 h of 6.4 g/kg dose)	[63]
Methylpropanediol	Rat, Wistar	n=5/sex	5 g/kg	Procedures followed were in accordance with OECD TG for Testing of Chemicals; dose administered orally by a syringe and animals observed for 14 days post-dosing; negative controls used; necropsy performed	LD_{50} > 5 g/kg; no mortality; body weight not different from controls; 1 male had pink fluid in bladder at necropsy; clinical signs: diarrhea and chromorhinorrhea observed in 3 animals	[58]
Methylpropanediol	Rat	Not Specified	5 g/kg	Not Specified	LD_{50} > 5g/kg	[18]
2,3-Butanediol	Mouse	Not Specified	9 g/kg	Oral administration details were not provided	LD_{50}=9 g/kg	[19]
2,3-Butanediol	Rat, Sprague-Dawley	n=5/sex	5 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity)	LD_{50}= 5 g/kg for males and females; no mortality; clinical signs: dyspnea, apathy, staggering, piloerection, erythema, exophthalmos, poor general state	[64]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Butyl Ethyl Propanediol	Rat, Sprague-Dawley	n=5/sex/dose	2, 3.2, and 5 g/kg (vehicle=aqueous methylcellulose 1% w/v)	Procedures followed were in accordance with (Good Laboratory Practice-GLP), and similar to European Union Method B.1 (Acute Toxicity Oral); single dose administered by gavage; animals observed for 15 days post-dosing; necropsy performed	LD_{50} calculated to be 2.9 g/kg for males and females; mortality as follows (most within 2 h post-dosing): 1 male (2 g/kg dose), 2 males and 5 females (3.2 g/kg dose), 5 males and 4 females (5 g/kg dose); gross pathology revealed no abnormalities; normal weight gain for rats except for 2 females with low weight gain; clinical signs (all dose levels): piloerection, hunched posture, waddling, lethargy, decreased respiration, ptosis, pallor-these resolved within 48 h post-dosing	[65]
Butyl Ethyl Propanediol	Rat	Not Specified	5.04 g/kg	Single oral dose administered (no further details provided)	LD_{50}=5.04 g/kg	[56]
Butyl Ethyl Propanediol	Mouse, NMRI	n=2/sex/dose	0.313, 0.625, 1.25 g/kg (vehicle=PEG 400)	Single dose administered by gavage; animals were observed for toxicity 1, 2-4, 6, 24, 30, and 48 h post-dosing (this acute study was performed in conjunction with a genotoxicity study; summary data from the genotoxicity study is presented in the Genotoxicity Table 11)	No mortality below 1.25 g/kg; 2 male deaths (4 h post-dosing) with 1.25 g/kg dose; clinical signs at all dose levels included reduced activity, eyelid closure, ruffled fur-these resolved by 24 h post-dosing	[65]
Butyl Ethyl Propanediol	Mouse	n=2/sex/dose	1, 1.25, 1.5, 2 g/kg	Single dose administered by gavage; animals were observed for up to 48 h post-dosing for toxicity; this was a range-finding study used to determine dosages for a genotoxicity study (summary data is presented in Genotoxicity Table 11)	No mortality below 1.5 g/kg; 1 male death (4 h post-dosing) and 1 female death (6 h post-dosing) with 1.5 g/kg; 1 male death (6 h post-dosing) and 2 female deaths (4 h post-dosing) with 2 g/kg; clinical signs observed throughout all dosages included reduced activity, abdominal position, ruffled fur, closed eyelids (most signs resolved within 24 h or less post-dosing)	[65]
Isopentyldiol	Mouse, CD-1	n=5/sex/dose	2 g/kg and 5 g/kg (vehicle= water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity); necropsy performed	LD_{50} > 5 g/kg; no mortality; gross necropsy revealed no abnormalities; no signs of toxicity reported	[66]
				Inhalation		
Propanediol	Rat, Crl:CD (SD)BR	n= 6 males	5 mg/l mean aerosol concentration (vehicle=air)	Animals were restrained in test chamber with conical nose pieces; airflow rate 15 L/min; mass median aerodynamic diameter/ geometric standard deviation = 3.2 µm/ 2.1µm; animals exposed for 4 h and observed for 14 days post-exposure	Approximate Lethal Concentration (ALC) > 5.0 mg/l; no mortalities reported; after animals were removed from chamber all had wet fur/ perineum and 1 animal had ocular discharge; 24 h post-exposure weight loss observed in all rats, but all rats gained weight by 14 days post-exposure	[42]
Propanediol	Rat	Not specified	2000 to 5000 mg/l	Animals were exposed to concentration for 4 hours (no further details provided)	Rats survived; slight-to-moderate weight loss observed the day following exposure	[53]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, Crl:CD (SD) BR	Male, n=10/group (3 groups total)	4.6 (± 0.4), 9.4 (± 1.1), or 15.0 (± 4.2) mg/l	Food and water were available to rats *ad libitum* except during exposure; animal noses were positioned in a chamber where aerosolized liquid was present for inhalation of a single, 4 h duration; chamber samples were collected every 30 min; particle size (mass median diameter) was evaluated; rats were observed and weighed daily for 14 days post-exposure and then killed	Particle sizes were 3.0 to 3.6 µm mass median diameter; 1 rat died 1 day after exposure to 15.0 (±4.2) mg/l; lethargy and labored breathing were reported with 4.6 and 9.4 mg/l concentrations; red discharge was observed in perineal area with 15.0 mg/l concentration; slight (seen with 4.6 mg/l concentration) to severe (seen with 15.0 mg/l concentration) weight loss noted 24 h post-exposure, but then normal weight gain resumed; with 9.4 and 15.0 mg/l concentrations rats exhibited lung noise and dry, red nasal discharge 1 to 9 days post-exposure	[67]
1,4-Butanediol	Rat, Wistar	n=5/sex	5.1 mg/l (no vehicle)	Animals were restrained in test chamber with conical nose pieces; animals were exposed to a single concentration for 4 h; rate of air 1500 l/h; mass median aerodynamic diameter 1.9 µm; animals were observed for 14 days post-exposure; necropsy performed	LC_{50} > 5.1 mg/l (in air) for 4 h for males and females; no mortality; animals gained weight; gross pathology revealed no abnormalities; clinical signs: during exposure and on test day shallow breathing reported; on test day nasal discharge, ruffled fur, staggering gait, and deterioration observed; by 48 h post-exposure all animals were symptom free	[57]
1,4-Butanediol	Rat, Wistar	Not Specified	5100 mg/l	GLP procedures were followed in accordance with OECD TG 403 (Acute Inhalation Toxicity); concentration administered for 4 h; animals observed for 14 days post-exposure; necropsy performed	Accelerated and shallow respiration were reported during exposure, but by day 1 post-exposure these signs had resolved; gross pathology revealed no abnormalities	[68]
1,5-Pentanediol	Rat, albino	n=6/sex	Concentrated vapor (concentration in air not specified)	Rats were exposed to a stream of air containing the concentrated vapor; vapor was produced by passing dried air (2.5 liters/min) through a glass disc immersed in 1 inch of 50 ml 1,5-Pentanediol; duration of inhalation exposure was up to 8 h; rats observed for 14 days post-exposure	No deaths were reported for up to 8 h of inhalation exposure	[54]
1,5-Pentanediol	Rat, Sprague-Dawley	n=6/sex	0.11 g (no vehicle)	Procedures followed were in accordance with OECD TG 403 (Acute Inhalation Toxicity); animals exposed for 7 h; animals observed for 14 days post-exposure; necropsy performed	LC_0 = 0.078 mg/l air for 7 h for males and females; no mortality; gross pathology revealed no findings	[62]
Hexanediol	Rat, albino	n=6/sex	Concentrated vapor (concentration in air not specified)	Rats were exposed to a stream of air containing the concentrated vapor; vapor was produced by passing dried air (2.5 liters/min) through a glass disc immersed in 1 inch of 50 ml Hexanediol; duration of inhalation exposure was up to 8 h; rats observed for 14 days post-exposure	No deaths were reported for up to 8 h of inhalation exposure	[54,55]
Hexanediol	Rat, Fischer 344	n=3/sex	3.3 mg/l (no vehicle used)	Procedures followed were in accordance with OECD TG 403 (Acute Inhalation Toxicity); animals exposed for 8 h; animals observed for 14 days post-exposure; necropsy performed	LC_{50}= 3.3 mg/l (in air) for 8 h for males and females; no mortality; gross pathology revealed no abnormalities; no clinical signs reported	[63]
Methylpropanediol	Rat	Not Specified	5.1 g/l	Not Specified	LC_{50}> 5.1 g/l	[18]
2,3-Butanediol	Rat	n=12 total	Saturated atmosphere @ 20°C (up to 0.85 mg/l in air)	Animals exposed for 7 h (no further details specified)	LC_{50} > 0.85 mg/l (in air) for males and females; no mortality	[64]
Other Routes						

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Propanediol	Rabbit	n=3/dose	3, 4, 5, 6, 7, ml/kg (vehicle=water)	Dose was injected by IV into marginal ear vein (no further details provided)	LD_{50}=4-5 ml/kg; mortality rate as follows: 40% (4 ml/kg), 60% (5 ml/kg), 100% (6-7 ml/kg); no mortality reported at 3 ml/kg	[42]

ALC=Approximate Lethal Concentration; ALD=Approximate Lethal Dose; GLP=Good Laboratory Practice; NOAEL=No Observed Adverse Effect Level; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
SHORT-TERM (< 3 MONTHS)							
ANIMAL							
Oral							
Propanediol	Rat, Crl:CD(SD)BR	n=5/sex/dose	0, 100, 250, 500, 1000 mg/kg (vehicle=deionized water)	14 days	Animals were dosed daily by gavage as indicated; necropsy performed at study termination	NOEL = 1000 mg/kg/day; no mortality; no clinical signs; body weight, food consumption, organ weights were no different than control group; neither gross necropsy nor microscopic examination revealed any treatment-related findings different from control group	[42]
1,4-Butanediol	Rat, Wistar Imp: DAK	n=8/sex/group	0, 5, 50, 500 mg/kg/day (control group received distilled water)	28 days	Food and water were available *ad libitum*; dose administered by gavage 1 time per day for 28 consecutive days; blood samples (fasting) were collected just prior to necropsy	NOEL 500 mg/kg/day (females) and NOEL 50 mg/kg/day (males) for clinical chemistry parameters; NOEL 50 mg/kg/day and lowest-observed-effect-level (LOEL) 500 mg/kg/day for histopathological changes; no mortality; unremarkable clinical observations; body weight, food consumption, and organ weights were unaffected; hematology parameters showed statistically significant differences compared to controls as follows: decrease in red blood cells and elevated hemoglobin (in various treatment groups, not dose dependent), lower hematocrit (males with 500 mg/kg dose), other parameters were statistically significantly different from controls (erythrocytic mean corpuscular volume, mean corpuscular hemoglobin, platelets, thrombocytes) but were not dose dependent; statistically significant increase in alanine aminotransferase and sorbitol dehydrogenase and decrease in total protein (males with 500 mg/kg dose); pronounced proliferation of bile ducts with 500 mg/kg dose (statistically significant compared to controls) and periportal infiltrations in the liver were noted in treated animals	[69]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
1,4-Butanediol	Rat, Sprague-Dawley	n=13/sex/dose	200, 400, 800 mg/kg/day (vehicle=water); controls received water	42 days (males), from 14 days prior to mating until day 3 of lactation (females)	Food and water were available *ad libitum*; procedures followed were in accordance with OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test); dose administered by gavage daily as indicated; hematology and clinical chemistry samples were collected at study termination; necropsy performed	NOAEL=200 mg/kg/day for males and females; dose dependent toxic central nervous system signs observed in both sexes; hyperactivity immediately following administration (200 mg/kg/day); hyperactivity observed after a few 400 mg/kg/day doses; some animals exhibited hypoactivity or were recumbent prior to becoming comatose (800 mg/kg/day) but this resolved 5 h post-dosing and animals recovered to normal; lower body weight gains and food consumption earlier in study (at 400 and 800 mg/kg/day) that remained through study termination; statistically significant (dose-related) decrease of blood glucose in treated animals (males); gross pathology revealed no treatment-related lesions; diffuse transitional epithelial hyperplasia and fibrosis in lamina propria of bladder (400 and 800 mg/kg/day) were noted	[57]
1,4-Butanediol and Hexanediol	Rat, Sprague-Dawley	n=4 (1,4-Butanediol), n=6 (Hexanediol)	0.5% 1,4-Butanediol or 0.5% Hexanediol (control animals received untreated water)	10 weeks (1,4-Butanediol) and 12 weeks (Hexanediol)	Food and water were available *ad libitum* for test and control animals; each test substance was dissolved in the treated animals' drinking water; at study termination 2 to 4 animals/group were necropsied	1,4-Butanediol: animals lost weight 6 weeks into the study, but gradually resumed weight gain; histology results revealed no changes in tissues compared to controls Hexanediol: weight gain and clinical signs were unaffected; histology results revealed no changes in tissues compared to controls	[12]
Hexanediol	Rabbit	Not specified	50 to 2000 mg/kg	Not specified	Up to 25 doses were administered by gavage as indicated (no further details provided)	Increase in clotting observed leading to thrombosis; liver and kidney were affected by treatment (no further details provided)	[70]
Hexanediol	Rat, Wistar	n=5/sex/dose	100, 400, 1000 mg/kg/day (controls were dosed with water vehicle only)	28 days	Procedures followed were in accordance with GLP and OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents); animals were dosed daily by gavage as indicated; blood and urine samples were collected throughout study	NOEL = 1000 mg/kg/day for males and females was reported; statistically significant decrease in female body weights was not considered to be treatment-related because of the lack of dose-response relationship and was consistent with historical controls (food consumption was similarly affected); clinical observations, clinical chemistry, gross pathology, and histopathology were unaffected by treatment	[63]
Methylpropanediol	Rat, Wistar	n=5/sex/dose	0, 300, 600, 1000 mg/kg/day	14 days	Procedures followed were in accordance with OECD Guidelines for Testing Chemicals; doses administered daily by gavage as indicated	There were no treatment-related clinical signs and histopathology; clinical chemistry and hematology parameters were unaffected	[58]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Butyl Ethyl Propanediol	Rat, Sprague-Dawley (CD)	n=5/sex/dose	15, 150, 1000 mg/kg/day (controls were dosed with methylcellulose vehicle only, 1% w/v aqueous)	28 days	Procedures followed were in accordance with OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents); animals were dosed daily by gavage as indicated; blood samples collected; necropsy performed	NOAEL=1000 mg/kg/day (males and females); NOEL=15 mg/kg/day (males and females); no mortalities; no treatment-related effects were correlated with clinical signs, body weight and weight gain, food/water consumption, hematology, clinical chemistry, and organ weights; gross pathology revealed liver and kidney enlargement (males with 1000 mg/kg/day) and pale, mottled kidneys (males with 150 or 1000 mg/kg/day); an adaptive liver effect noted (males with 1000 mg/kg/day); dose-related increase in renal cortical tubular eosinophilic inclusions (males with 150 or 1000 mg/kg/day)	[65]
				Inhalation			
Propane diol	Rat, CRl:CD(SD)BR	n=10 males/group	0, 41, 650, 1800 mg/l (analytical concentrations verified the nominal concentrations 0, 60, 600, 1800 mg/l)	6 h/day for 2 weeks (9 exposures total)	Rats were restrained and fitted with conical nose pieces extending into a chamber during exposure; mass median aerodynamic diameter 2.2-2.4 µm at 2 higher concentrations and vapor at lower concentration; concluding the 2- week exposure period urine and fasting blood samples were collected, 5 rats/group were killed and pathological exam performed; concluding the 2-week exposure an 18-day recovery was allowed for remainder of animals prior to urine and fasting blood analysis and pathological exams	No mortalities during exposure and/or recovery period; no treatment-related clinical signs or clinical chemistry or hematology changes were reported; no abnormalities during microscopic or gross pathological exam (other than incidental or typical of occurring in this strain); no-observed-effect level (NOEL) for body weights was 1800 mg/l; vapor phase concentration achieved at 41 mg/l	[53]
1,4-Butanediol	Rat, Crl:CD BR	n=10 males/group (4 groups total including a control group)	0.2, 1.1, 5.2 mg/l (control group was exposed to air only); particle size was 2.5 to 3.6 µm (mass median diameter)	6 h/day, 5 days/wk for 2 weeks (10 exposures total)	Food and water were available to rats *ad libitum* except during exposure; animal noses were positioned in a chamber where aerosolized liquid was present for inhalation; chamber samples were collected every 30 min; particle size (mass median diameter) was evaluated; rats were observed and weighed daily for 14 days post-exposure; 5 rats/group were killed and necropsied at the end of the 2-week exposure period; the remainder were killed and necropsied concluding the 14-day post-exposure recovery period; clinical laboratory and urine analysis were performed on all rats (both after 2-wk exposure period and after 14-day post exposure period)	NOAEC reported for 0.2 and 1.1 mg/l; no mortality at any level; only clinical sign noted for some rats in all groups was slight, red nasal discharge during inhalation exposure; body weights (5.2 mg/l) were statistically significantly lower than controls; serum cholesterol concentrations (5.2 mg/l) were statistically significantly lower in rats killed after 10^{th} exposure compared to controls (not seen in 14-day post-exposure rats at 5.2 mg/l); statistically significantly higher erythrocyte counts and hematocrits (5.2 mg/l) in rats killed after 10^{th} exposure compared to controls (not seen in 14-day post-exposure rats at 5.2 mg/l); urine analysis and organ weights were unaffected by treatment; in lymphoid cells from thymus slight atrophy was noted (5.2 mg/l), but was not present in the 14-day post exposure rats with 5.2 mg/l	[67]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
1,4-Butanediol	Rat	Males	1500 to 2000 mg/l	2 h/day each day for 4 months	Animals were exposed daily as indicated (no further details provided)	Lowest Observed Adverse Effect Concentration (LOAEC)=1500 mg/l (or LOAEL 85 mg/kg/day); around 3-4 weeks into the study a sleepy condition was induced 10-20 min post-exposure; noted on histopathological exam were pulmonary emphysema, mild lung edema, treatment-related inflammatory changes of single alveolar cell and weak hyperplasia of alveolar septum (lymphocytes and histiocytes were present)	[68]
1,4-Butanediol	Rat	Males	300 to 500 mg/l	2 h/day for 6 days/week for 4 months	Animals were exposed as indicated (no further details provided)	NOAEC=500 mg/l (or 23 mg/kg/day); body weight, neuromuscular response, hemogenesis, liver and kidney function were unaffected	[68]
SUBCHRONIC (3-6 MONTHS)							
ANIMAL							
Oral							
Propanediol	Rat, Crl:CD(SD)BR	n=10/sex/group	0, 100, 300, 1000 mg/kg/day (control group received water)	90 days	Procedures followed (GLP) were in accordance with EPA Toxic Substances Control Act Health Effects Testing Guidelines (40CFR1989); single doses were administered daily by gastric intubation for 91-92 days; food and water were available *ad libitum*; blood samples (fasting) were collected for clinical pathology analysis (evaluated at 4 weeks post-dosing and at study termination); necropsy performed	NOEL=1000 mg/kg/day for males and females; no mortality; no treatment-related clinical signs; no treatment-related hematology or chemistry parameter changes; neither microscopic nor gross pathology change related to treatment were observed (only incidental lesions typically seen in laboratory rats were noted)	[71]
Propanediol	Rat	n=5/group (7 groups total)	5% or 12% in diet; 5 ml/kg or 10 ml/kg (gavage); control diet; control diet + 10 ml water (gavage); control diet + 10 ml 1,2-Propanediol (gavage)	15 weeks	Animals were dosed by gavage or in the diet as indicated (no further details provided)	100% mortality prior to study termination for animals dosed with 10 ml/kg Propanediol; 2 rats died (5 ml/kg group); reduced growth weights were noted in groups dosed with Propanediol	[42]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Hexanediol	Rat, Wistar	n =10/sex/dose	100, 400, 1000 mg/kg/day (controls were dosed with water vehicle only)	91-92 days	Procedures followed were in accordance with GLP and OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); animals were dosed daily by gavage as indicated; blood and urine samples were collected	NOAEL=400 mg/kg/day (males) and NOAEL=1000 mg/kg/day (females); no mortality; treatment-related decrease with 1000 mg/kg/day (males only) in mean body weight (-10.5%) and mean body weight change (-18.7%); no treatment-related effects were reported for food/water consumption, ophthalmoscopic exam, hematology, clinical chemistry, histopathology, estrous cycle, sperm parameters, gross pathology; non-adverse treatment-related effects for urinalysis (decreased urine volume and pH and increased specific gravity in males with 1000 mg/kg/day); non-adverse treatment-related decrease in grip strength of hindlimbs (males with 1000 mg/kg/day); statistically significant increase (compared to controls) in relative organ weights (males-multiple organs with 1000 mg/kg/day; male adrenal glands with 400 mg/kg/day) were observed	[63]
Methylpropanediol	Rat, Wistar	n=10/sex/dose	0, 300, 600, 1000 mg/kg/day	90 days	Procedures followed were in accordance with OECD Guidelines for Testing Chemicals; doses administered daily by gavage as indicated	NOEL=600 mg/kg/day; no treatment-related clinical signs or histopathology were reported; small increase in partial thromboplastin time (females with 1000 mg/kg/day); decrease (10%-14%) in alanine transaminase (ALT) and aspartate aminotransferase (AST) in males with 1000 mg/kg/day; decrease in inorganic phosphate (males and females with 1000 mg/kg/day)	[58]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Butyl Ethyl Propanediol	Rat, Wistar	n=10/sex/dose	15, 150, 1000 mg/kg/day (controls received hydroxypropyl methylcellulose vehicle only)	90 days	Procedures (GLP) followed were in accordance with OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); dose administered daily by gavage as indicated; blood and urine samples collected; necropsy performed	NOAEL=15 mg/kg/day (males) and NOAEL=150 mg/kg/day (females); treatment-related deaths of 3 males (1000 mg/kg/day) and 1 male (150 mg/kg/day); the following were unaffected by treatment: body weight and weight gain, food/water consumption, ophthalmoscopic exam, hematology, and gross pathology; clinical signs (with 1000 mg/kg/day) were reduced activity, abnormal locomotion and respiration up to 1-2 hours post-dosing after which animals returned to normal, piloerection, hunched body posture, and partially closed eyes were observed; compared to controls a statistically significant increase in urea (males with 150 or 1000 mg/kg/day) and protein and globulin levels (males with 1000 mg/kg/day); statistically significant decrease in urinary pH (males and females with 1000 mg/kg/day); statistically significant increase in urinary specific gravity (males with 1000 mg/kg/day); higher kidney weights (males with ≥ 150 mg/kg/day) and corresponding tubular dilation (males with ≥ 150 ng/kg/day) and nephropathy (males with ≥ 15 mg/kg/day)	[63]

ALT=alanine transaminase; AST=aspartate aminotransferase; GLP=Good Laboratory Practice; LOAEC=Lowest Observed Adverse Effect Concentration; LOAEL=Lowest Observed Adverse Effect Level; LOEL=Lowest Observed Effect Level; NOAEC=No Observed Adverse Effect Concentration; NOAEL=No Observed Adverse Effect Level; NOEL=No Observed Effect Level; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 10. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Dosage (Vehicle)	Procedure	Results	Reference
			Oral			
Propanediol	Rat, Crl:CD(SD)BR	n=10 males/group	0, 100, 300, 1000 mg/kg/day (control group received water)	Procedures followed were in accordance with GLP and EPA Toxic Substances Control Act Health Effects Testing Guidelines (40CFR1989); single doses were administered daily by gastric intubation for about 90 days; food and water were available *ad libitum*; at study termination the animals were killed and epididymis excised and weighed; sperm motility was measured; sperm assessed for morphology; testis and epididymis were homogenized and examined for sperm production rates	Spermatogenic endpoints (mean testicular and epididymal sperm counts, sperm production rate, sperm motility and morphology) were unaffected by treatment at all dose rates	[71]
Propanediol	Rat, Sprague-Dawley	n=20 females	0, 250 or 1000 mg/kg/day (vehicle=0.8% aqueous hydroxypropyl-methylcellulose gel)	Procedures followed (GLP) were in accordance with OECD TG 414 (Prenatal Developmental Toxicity Study); females were dosed by gavage on days 6 through 15 of gestation	Maternal and fetal toxicity NOAEL=1000 mg/kg/day; no maternal toxic effects from treatment (fertility rate was 91% for all dose rates); no embryotoxic or teratogenic effects on fetuses from treatment	[42]
1,4-Butanediol	Mouse, Swill (CD-1)	n=28-32/group	0, 100, 300, 600 mg/kg/day	Pregnant mice were dosed by gavage during days 6 through 15 of gestation	Maternal and developmental NOAEL=100 mg/kg/day; maternal and developmental LOAEL=300 mg/kg/day ; no maternal mortality; maternal central nervous system intoxication was observed (300-600 mg/kg/day) 4 h after daily dosing; reduced food consumption and body weight/weight gain noted (maternal with 300-600 mg/kg/day); developmental toxicity observed was reduced fetal body weight (300-600 mg/kg/day maternal dose)	[72]
1,4-Butanediol	Rat, Sprague-Dawley	n=13/sex/dose	200, 400, 800 mg/kg/day (vehicle=water); controls received water	Food and water were available *ad libitum*; procedures followed were in accordance with GLP and OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test); dose administered daily by gavage for 42 days (males) and from 14 days prior to mating until day 3 of lactation (females); non-fasting blood samples collected after final exposure	Reproduction (parental) NOAEL=800 mg/kg/day; offspring (male/female) NOAEL=800 mg/kg/day (absence of developmental effects); male/female (parents) NOEL=400 mg/kg/day (no toxic effects on reproduction during repeated dose administration); offspring male/female NOEL=400 mg/kg/day (pup weight decreased on lactation day 4 at 800 mg/kg/day, effect was secondary to maternal reduced food consumption and body weight)	[57]
1,4-Butanediol	Rat, Sprague-Dawley	n=13/sex/dose	200, 400, 800 mg/kg/day (controls received water vehicle only)	Procedures followed were in accordance with GLP and OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test); dose administered daily by gavage; duration of exposure was 42 days for males and 14 days before mating to lactation day 3 for females	Maternal toxicity NOAEL=200 mg/kg/day (hypoactivity noted at ≥ 400 mg/kg/day); Developmental toxicity/ teratogenicity NOAEL=400 mg/kg/day (small, but substantial decrease in pup body weights on lactation day 4 at maternal 800 mg/kg/day)	[57]

Table 10. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, CD(SD)	Not Specified	200, 400, 800, mg/kg/day (controls received water vehicle only)	Procedures followed were in accordance with OECD TG 422 (Combined Repeat Dose and Reproductive Toxicity Screening Test); dose administered daily by gavage; duration of exposure was for 2 weeks prior to mating and 2 weeks of mating (males and females) and for females exposure through pregnancy until postpartum day 3	Reproductive NOAEL for parents and offspring was reported as 800 mg/kg; maternal toxicity of reduced food consumption and body weight gain was reported; offspring body weight was slightly, but statistically-significantly decreased (800 mg/kg maternal dose) and considered to be a secondary effect relative to maternal toxicity; no parental reproductive parameters were changed by treatment; offspring viability and morphological abnormalities were unaffected by treatment	[68]
Hexanediol	Rat, Wistar	n=10/sex/dose	0, 100, 400, or 1000 mg/kg/day, controls received water vehicle only	Food and water available *ad libitum*; procedures followed were in accordance with GLP and OECD TG 421 (Reproduction/Developmental Toxicity Screening Test; animals dosed daily by gavage; duration of treatment for males was approximately 4 weeks (2 weeks premating); duration of treatment for females was about 6 weeks (2 weeks premating); study termination was post-partum day 4; animals killed at study conclusion and necropsy performed	Parental (female) NOAEL=1000 mg/kg/day; parental (male) NOAEL=400 mg/kg/day; offspring (male/female) NOAEL=1000 mg/kg/day; male parents (1000 mg/kg/day) showed treatment-related (stat. sig) decrease in food consumption and body weight; male fertility index was 90%-100%; female mating index was 90%-100% and fertility index was 100%; offspring exhibited no treatment-related effects	[63]
Hexanediol	Rat, Wistar	n=25 females	0, 100, 400,1000 mg/kg/day (controls received water vehicle only)	Food and water were available *ad libitum*; procedures followed were in accordance with GLP and OECD TG 414 (Prenatal Developmental Toxicity Study); animals were dosed by gavage during days 6 through 19 of gestation; on day 20 of gestation females were killed and necropsies performed	Maternal and developmental NOAEL=1000 mg/kg/day; no maternal mortalities or clinical signs; maternal body weight and food consumption unaffected; maternal necropsies revealed no findings; conception rate 96%-100%; female fetus weight (1000 mg/kg dose) was slightly but statistically-significantly decreased, and still within historical control range; a few external malformation were reported in test groups and the control group, but agreed with historical control data; 2 fetal soft tissue malformations (1000 mg/kg) and skeletal malformations (all test groups) occurred, but data were not significantly different from controls and agreed with historical control data	[63]
Hexanediol	Rat, Wistar	n=10/sex/dose	0, 100, 400, 1000 mg/kg/day (controls received water vehicle)	Food and water were available *ad libitum*: procedures were in accordance with GLP and OECD TG 421 (Reproduction/Developmental Toxicity Screening Test); animals were dosed by gavage; duration of treatment for males was approximately 4 weeks (2 weeks premating); duration of treatment for females was about 6 weeks (2 weeks premating); at study termination uterus, ovaries, and fetuses were examined	Maternal and developmental NOAEL=1000 mg/kg/day; no maternal toxic or embryotoxic effects were observed	[63]
Methylpropanediol	Rat, Sprague-Dawley	n=10/sex/dose	0, 100, 300, 1000 mg/kg/day	A 2-generation reproduction study was conducted; animals were dosed by gavage (no further details provided)	Maternal and neonatal NOAEL=1000 mg/kg/day	[73]

Table 10. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Dosage (Vehicle)	Procedure	Results	Reference
Methylpropanediol	Rat, Wistar	Females	Up to 1000 mg/kg, negative controls were used (no further details specified)	Animals were dosed by gavage on days 0 through 20 of gestation (no further details specified); this study was repeated due to possibly skewed results (outcomes of both studies are summarized in the Results column)	No maternal toxicity or changes in fetal development were reported; potential embryotoxicity reported because of a statistically significant increase (compared to controls) in early absorptions (maternal 600 and 1000 g/kg/day doses), but results may have been skewed by 1 female at those dose levels with atypically high incidences so the study was repeated; the follow-up study results were unremarkable and indicated that interuterine growth and survival were unaffected by treatment (with up to 1000 mg/kg/day maternal dose)	[18]
Methylpropanediol	Rabbit, New Zealand White	Not Specified	0, 250, 500, 1000 mg/kg	Animals were dosed by gavage on days 0 through 29 of gestation (no further details provided)	Maternal toxicity, fetotoxicity, and teratogenic effects NOAEL=1000 mg/kg/day; intrauterine growth and survival was not affected by treatment, no treatment-related effects were observed for malformations or changes in soft or skeletal tissues	[73]
Butyl Ethyl Propanediol	Rat, Sprague-Dawley	n=24 females	0, 15, 150, 1000 mg/kg/day (controls received the aqueous hydroxypropyl methylcellulose vehicle only)	Food and water were available *ad libitum*; procedures followed were in accordance with GLP and OECD TG 414 (Prenatal Development Toxicity Study); dose administered by gavage on days 6 through 19 of gestation; animals were killed on gestation day 20; necropsy performed	Maternal NOAEL=150 mg/kg/day; Developmental NOAEL=1000 mg/kg/day; maternal clinical signs included subdued behavior, reduced activity, staggering, limb dragging, slow/wheezing respiration, excess salivation, piloerection, partially closed eyes (1000 mg/kg); small decrease in maternal body weights/food consumption (day 7-8 of gestation, 1000 mg/kg) which returned to normal by gestation days 9-12; no embryotoxic/teratogenic effects were observed	[65]

GLP=good laboratory practice; LOAEL=lowest observed adverse effect level; NOAEL=no observed adverse effect level; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type/ Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO			
Propanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100, TA102	33.3, 100, 333.3, 1000, 2500, 5000 µg/plate (vehicle=water)	Bacterial reverse mutation assay (Ames Test) was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[42]
Propanediol	Rat, Sprague-Dawley	Rat liver and testicular homogenates	500 ppm Propanediol in the diet	Rats were orally exposed prior to killing and performing *in vitro* tests For up to 15 weeks, rats were dosed in the diet (control rats were fed a plain diet); 3 rats/group were killed at 5, 10, and 15 weeks; tissues from the liver and one testicle from each rat were homogenized and assayed to isolate the DNA; bound tryptophan was measured (effect of DNA concentration on fluorescence was evaluated); DNA template activity was determined; hepatic and testicular DNA was assayed for cross-linking	The metabolism results from the homogenized liver and testes are summarized in the Toxicokinetics Section of this safety assessment. No substantial difference in control vs. treated rats was observed in the evaluation of lipid-soluble testicular fluorophores; tryptophan bound to testicular DNA of treated rats was not different from the controls; tryptophan bound to hepatic DNA in treated rats killed at 5 and 15 weeks was statistically significantly higher than in corresponding controls; treated rats showed a statistically significantly lower template activity in hepatic DNA in rats killed at 10 and 15 weeks compared to controls; template activities of testicular DNA showed no difference from controls; in treated rats the hepatic DNA-protein and DNA-crosslinking at 10 and 15 weeks were higher than controls; testicular DNA-protein and DNA-crosslinking of treated rats were slightly higher than controls at 15 weeks; given the above results and the toxicokinetics results presented in Table 8 (rat liver homogenates converted Propanediol to malondialdehyde) there are indications that Propanediol produced malondialdehyde *in vivo*, resulting in damage to rat DNA	[44]
Propanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)/ Hypoxanthine-guanine phosphoribosyl transferase (HPRT)	0, 250, 1000, 2500, 5000 µg/ml	Mammalian cell gene mutation assay was performed, with and without metabolic activation, in accordance with GLP and OECD TG 476 (*In vitro* Mammalian Cell Gene Mutation Test); 2 independent experiments using the same test conditions were performed; negative, vehicle, and positive controls were used	Negative; controls performed as expected; cytotoxicity was reported (low survival) at 5000 µg/ml without using metabolic activation	[42]
Propanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)	625, 1250, 2500, 5000 µg/ml (vehicle=water)	Mammalian chromosomal aberration test was performed, with (4 h exposure) and without (4 or 20 h exposure) metabolic activation, in accordance with GLP and OECD TG 473 (*In vitro* Mammalian Chromosome Aberration Test); vehicle and positive controls were used	Negative; controls performed as expected; cytotoxicity was noted at 5000 µg/ml without metabolic activation (20 h exposure)	[42]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type/ Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Propanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)	250, 1000, 2500 µg/ml (18 h, without activation); 500, 2500, 5000 µg/ml (18 h, with activation); 375, 1250, 2500 µg/ml (18 h, without activation); 1250 µg/ml (28 h, without activation); 2500, 3750, 5000 µg/ml (18 h, with activation); 5000 µg/ml (28 h, with activation)	Mammalian chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG for Testing of Chemicals, section 4, No. 473); vehicle and positive controls were used	Positive for genotoxicity (18 h interval with 2500 µg/ml concentration) without metabolic activation (controls performed as expected); negative for genotoxicity with metabolic activation (controls performed as expected)	[42]
1,4-Butanediol	*Salmonella typhimurium* and *Escherichia coli*	*S. typhimurium*: TA98, TA100, TA1535, TA1537; *E. coli*: WP2 uvrA	0, 313, 625, 1250, 2500, 5000 µg/plate	Ames Test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay) and 472 (Genetic Toxicology: *E. coli*, Reverse Mutation Assay); vehicle and positive controls were used	Negative; controls performed as expected	[57]
1,4-Butanediol	*Salmonella typhimurium*	TA1535, TA1537, TA1538, TA98, TA100	500, 1000, 2500, 5000, 7500, and 10,000 µg/plate (vehicle=distilled water)	Ames Test was performed with and without metabolic activation; negative, vehicle, and positive controls were used	Negative: controls performed as expected	[57]
1,4-Butanediol	*Salmonella typhimurium*	TA98, TA100, TA1535, TA97	0, 1, 3, 10, 33, 100, 333, 1000, 3333, and 10,000 µg/plate	Mutagenicity test performed; 0.05 ml of test compound was incubated @ 37°C with *S. typhimurium* and a buffer; tests were performed with and without metabolic activation; negative and positive controls were used	Negative	[74]
1,4-Butanediol	Hamster	Chinese Hamster Ovary cells	20, 60, 200, 600, 2000, 5000 µg/ml (vehicle=Ham's F12 cell culture medium)	Mammalian cell gene mutation assay was performed, with and without metabolic activation in accordance with GLP and OECD TG 476 (*In vitro* Mammalian Cell Gene Mutation Test); vehicle, negative, and positive controls were used	Negative; controls were validated	[57]
1,4-Butanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)	400, 3000, 5000 µg/ml (vehicle=MEM cell culture medium)	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 473 (*In vitro* Mammalian Chromosome Aberration Test); vehicle and positive controls were used	Negative; controls performed as expected	[57]
1,4-Butanediol	Hamster	Chinese Hamster Lung (CHL/IU) cells	0, 230, 450, 900 µg/ml (vehicle=distilled water)	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 473 (*In vitro* Mammalian Chromosome Aberration Test); vehicle and positive controls were used	Negative; controls performed as expected	[57]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type/ Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,5-Pentanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	0, 20, 100, 500, 2500, 5000 µg/plate (vehicle=water; application by agar plate incorporation)	Ames Test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[62]
1,5-Pentanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	0, 20, 100, 500, 2500, 5000 µg/plate (vehicle=water; application by preincubation @ 37°C for 20 min)	Ames Test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[62]
Hexanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	20, 100, 500, 2500, 5000 µg/plate (vehicle=dimethyl sulfoxide or DMSO; application by agar plate incorporation)	Ames Test was performed (non-GLP), with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[63]
Hexanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	20, 100, 500, 2500, 5000 µg/plate (vehicle=DMSO; application by preincubation @ 37°C for 20 min)	Ames Test was performed (non-GLP), with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[63]
Hexanediol	Hamster	Chinese Hamster V79 cells	0.3, 0.6, 1.2 µg/ml (vehicle=MEM; application by agar plate incorporation and preincubation in suspension)	Mammalian chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 473 (*In vitro* Mammalian Chromosome Aberration Test); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[63]
Hexanediol	Hamster	Chinese Hamster (V79)/ Hypoxanthine-guanine phosphoribosyl transferase (HPRT)	500, 1000, 2500, 5000 µg/ml	Mammalian cell gene mutation assay was performed, with and without metabolic activation, in accordance with GLP and OECD TG 476 (*In vitro* Mammalian Cell Gene Mutation Test); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[63]
Methylpropanediol	*Salmonella typhimurium*	TA98, TA100, TA1535, TA1537	100 to 5000 µg/plate	Reverse mutation assay was performed, with and without metabolic activation, in accordance with OECD Guidelines for Testing of Chemicals (no further details)	Negative	[58]
Methylpropanediol	Hamster	Chinese Hamster V79 cells	333 to 5000 µg/plate	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with OECD Guidelines for Testing Chemicals; positive controls were used	Negative; controls performed as expected	[58]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type/ Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Methylpropanediol	Human	Human lymphocytes	333 to 5000 µg/plate (3 h, with metabolic activation); 10 to 5000 µg/plate (24 and 48 h, without metabolic activation) Vehicle=F10 medium buffered with 20 mM HEPES	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with OECD Guidelines for Testing Chemicals; positive controls were used	Negative; controls performed as expected	[58]
2,3-Butanediol	*Salmonella typhimurium*	TA98 and TA mix (TA7001-7006)	4 to 5000 µg/ml	Ames II Assay test was performed (GLP), with and without metabolic activation; negative, vehicle, and positive controls were used	Negative; controls performed as expected	[64]
Butyl Ethyl Propanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	0, 50, 150, 500, 1500, 5000 µg/plate (vehicle=ethanol; application by plate incorporation)	Ames Test was performed (non-GLP), with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Assay); Ames Test was conducted independently 2x (for initial assessment and then for confirmation); vehicle, and positive controls were used	Negative; controls performed as expected; cytotoxicity was reported at 5000 µg/plate with TA98 without activation in both initial and confirmatory experiments	[65]
Butyl Ethyl Propanediol	Mouse	Thymidine kinase locus in mouse lymphoma L5178Y cells	0.03, 0.06, 0.11, 0.22, 0.45, 0.90, 1.3, 1.8, 2.6, 3.1, 3.6, 4.2, 5.0 mMol/l (24 h, without activation); 0.06, 0.11, 0.22, 0.45, 0.9, 1.8, 2.6, 3.7, 5.2, 6.1, 7.2, 8.5, 10 mMol/l (4 h, with activation); 0.06, 0.11, 0.22, 0.45, .9, 1.8, 2.6, 3.7, 5.2, 6.1, 7.2, 8.5, 10 mMol/l (4 h in a confirmatory assay with and without activation)	Mammalian cell gene mutation assay was performed, with and without metabolic activation, in accordance with GLP and OECD TG 476 (*In vitro* Mammalian Cell Gene Mutation Test); negative and positive controls were used	Negative for genotoxicity; cytotoxicity (with and without activation) limited the confirmation assay to a maximum concentration of 7.2 mMol/l; controls performed as expected	[65]
Isopentyldiol	*Salmonella typhimurium* and *Escherichia coli*	*S. typhimurium*: TA98, TA100, TA1535, TA1537; *E. coli*: WP2 uvrA (pKM101)	33 to 10,000 µg/plate (vehicle=DMSO)	Bacterial reverse mutation assay was performed , with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Test) and EC Directive 2000/32/EC B.12/14 Mutagenicity-Reverse Mutation Test using Bacteria; 10,000 µg/plate exceeds the 5000 µg/plate limit recommended for non-cytotoxic substances; positive controls were used	Negative; controls performed as expected	[66]
Isopentyldiol	*Bacillus subtilis*	M45, H17	6.25, 12.5, 25, 50, 100 mg/plate (vehicle=DMSO)	Preliminary rapid streak test was conducted to determine dose levels; liquid suspension assay was performed with and without metabolic activation; negative, vehicle, and positive controls were used	No toxicity reported in preliminary test; liquid suspension assay was negative for genotoxicity; controls performed as expected	[66]
IN VIVO						
Oral						

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type/ Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Propanediol	Mouse, Hsd/Win: NMRI	n=14/sex/dose (main test), n=6/sex/dose (repeated test)	Main Test: single dose of 2150 mg/kg Repeated Test: single dose of 1000, 1470, or 2150 mg/kg (vehicle=water)	Micronucleus assay to test for chromosomal aberrations was performed in accordance with GLP and European Commission ECC Directive 92/69/EEC Part B: Methods for the Determination of Toxicity, B.12. Micronucleus Test); single dose administered orally; positive controls were used for each test; mice were killed 24 or 48 h post-exposure	Genotoxicity results were negative (non-mutagenic) for males and females; controls performed as expected; in the main test a statistically significant increase in micronucleated polychromatic erythrocytes at 48 h sampling was reported. Therefore, as per the method, a repeat test was performed; repeat test did not verify findings from the main test (findings were considered incidental)	[42]
Butyl Ethyl Propanediol	Mouse, NMRI	n=6/sex/dose (1250 mg/kg dose was performed 2x, reason why not specified); only n=5/sex/dose were evaluated (no further details)	312.5, 625, 1250 mg/kg (controls received PEG 400 vehicle only)	Micronucleus assay was performed in accordance with GLP and OECD TG 474 (Mammalian Erythrocyte Micronucleus Test); single dose administered by oral gavage; negative, vehicle, and positive controls were used; bone marrow smears were prepared from each femur	Negative for genotoxicity; controls performed as expected; clinical signs of toxicity were observed (summary data is presented in the Acute Toxicity Table 8)	[65]

DMSO=dimethyl sulfoxide; GLP (or non-GLP)=good laboratory practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
IRRITATION						
Animal						
Propanediol	Rabbit, New Zealand White	n=6 (abraded skin), n=6 (intact skin)	Undiluted	Procedures followed were in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); 0.5 ml test compound was applied (1 x1 cm patch) to shaved back skin (abraded and intact) and occlusively covered for 24 h; at 24 h post-application patch was removed; skin examined immediately and 48 h after patch removal (72 h post-application); no controls were used	Slightly irritating (well-defined erythema); mean Draize scores for intact skin at 24 h post-application was 1.3 and at 72 h was 0.3; mean Draize score for abraded skin at 24 h post-application was 1.3 and at 72 h was 0.8; these effects were reversible and cleared up in 48 h	[42]
Propanediol	Rabbit	n=8	Undiluted	Procedures followed (non-GLP) were in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); test substance was applied to shaved skin (abraded and non-abraded) and occlusively covered for 24 h; skin was observed for 7 days post-application	Mild erythema and edema were reported on abraded and non-abraded skin for 7 of 8 rabbits; this cleared by 3 days post-exposure	[42]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rabbit, Vienna White	n=4	Undiluted; control areas of skin were untreated and treated with water	Food and water were available *ad libitum*; fur was clipped and shaved from sides of trunk; 0.3 ml test substance was applied to hair-free skin (intact on right side and abraded on left side) and occlusively covered with a 2 x 2 cm patch for 24 h; at 24 h post-exposure the patch was removed and skin examined at 1, 24, 48, and 72 h following patch removal Additionally, the rabbits' right ears (internal area) were coated with undiluted or 50% (water dilution) 1,4-Butanediol for 10 days; controls used were left ears coated with water; the 1st day after applying coating the ears were examined	No reactions were observed on the intact or abraded trunk skin test sites; minimal redness was noted 10 days post-application of undiluted 1,4-Butanediol to the right ears of 2 of 4 rabbits; no reaction in rabbit ears was observed with 50% test solution	[59]
1,4-Butanediol	Rabbit	Unknown	Unknown	Repeated treatments were applied to abraded and intact skin (no further details provided)	No irritation observed; no signs of absorption of toxic quantities of 1,4-Butanediol	[14]
1,5-Pentanediol	Rabbit, albino	n=5	Undiluted or in solutions of water, propylene glycol, or acetone (no further specifications provided)	Fur was clipped from skin; 0.1 ml test substance was applied and left uncovered for 24 h, at which point skin was examined	Non-irritating (rated grade 1 on a scale from 1-non-irritating to 10-necrosis)	[54]
1,5-Pentanediol	Rabbit, Vienna White	n= 6 total (1 male, 5 females); no controls	Undiluted	Procedures followed (non-GLP) were in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); 1 ml of test substance saturated on a cotton patch (2.5 x 2.5 cm area) was applied to intact or scarified back skin and occlusively covered for 20 h, then patch was removed and skin was washed with 50% polyethylenglycol in water; skin was examined for irritation 24, 48, and 72 h post-application and also 7 days post-application	Non-irritating: For the 24, 48, and 72 h post-application time points the mean erythema score was 0.5 (very slight effect) and mean edema score was 0.1 (very slight effect); this erythema and edema were reversible within 48 h; additional findings were at 48 h spotted appearance (scarified skin of 2 animals), at 72 h desquamation (scarified skin of 3 animals), and at 7 days observation desquamation (scarified skin of 4 animal)	[62]
Hexanediol	Rabbit, albino	n=5	Test substance was applied in an appropriate vehicle (no further specifications provided)	Fur was clipped from skin; 0.1 ml test substance was applied and left uncovered for 24 h, at which point skin was examined	Estimated reaction was a grade 2 on a scale from 1-non-irritating to 10-necrosis	[54,55]
Hexanediol	Rabbit, Vienna White	n=2	80% solution; vehicle=water	A non-GLP irritation test was performed; 1 ml of test substance was applied to intact back skin and occlusively covered (2.5 x 2.5 cm) for 1 min, 5 min, 15 min, or 20 h, then the patch was removed and test substance washed off with a Lutrol®-water mixture; skin was examined at various points over a 3 day period	Non-irritating; mean erythema and edema scores were 0 out of 4	[63]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Hexanediol; Ethylene Glycol	Guinea Pig; Hartley	Primary Skin Irritation Test: n=3/test concentration Cumulative Skin Irritation Test: n=3/test concentration	62.5 wt % (Ethylene Glycol); 45 wt % (Hexanediol)	Primary Skin Irritation Test: To the shaved flank skin of animals, 200 µl of test solutions soaked into filter paper were applied and occlusively covered for 24 h; at 24, 48, and 72 h post-application the skin was examined and rated based on criteria of the ICDRG Cumulative Skin Irritation Test: To the shaved flank skin of animals, 200 µl of test solutions soaked into filter paper were applied and left uncovered; 1x/day for 5 days the test solution was reapplied; 5 days post-application the skin was examined and rated based on criteria of the ICDRG	No irritation for primary or cumulative skin irritation test for either compound	[77]
Methylpropanediol	Rabbit, New Zealand White	n=6	Not specified	0.5 ml test substance was applied and semi-occlusively covered for 24 h for each of 4 sites/animal (2 abraded and 2 intact); period of observation was 72 h (no further details provided); procedures followed were in accordance with OECD Guidelines for Testing Chemicals	Non-irritating (no erythema or edema reported)	[58]
Methylpropanediol	Animal	Unknown	Not specified	Irritation testing was conducted (no further details were provided)	Non-irritating	[18]
2,3-Butanediol	Rabbit, Vienna White	n=6 (no controls)	Undiluted	An irritation/ corrosion test (non-GLP) was performed; test substance was applied to skin and covered occlusively (no further details provided); skin was examined at 24 h post-application and for up to 8 days	Non-irritating; erythema and edema reactions were reported, but were reversible within 8 days	[64]
Butyl Ethyl Propanediol	Rabbit, New Zealand White	n=3 (no controls)	Undiluted	To the shaved dorsum skin, 0.5 ml of heated (44°C) test substance was applied (6 cm^2 area) and covered with a bandage (semi-occluded) for 4 h then covering was removed, skin was washed with water and dried; skin was examined at 24, 48, and 72 h post-application	Non-irritating; mild erythema was reported up to 48 h post- application but cleared within 72 h; no edema observed	[65]
Butyl Ethyl Propanediol	Rabbit, New Zealand White	n=3 (no controls)	Undiluted	An irritation test was performed in accordance with GLP and OECD TG 404 (Acute Dermal Irritation/ Corrosion); to the shaved dorsal skin 0.5 g of crystalline test substance moistened with water was applied and covered with a bandage (semi-occlusively) for 4 h; covering was removed after 4 h and skin washed; skin was examined at 24, 48, and 72 h post-application	Minimally irritating; very slight, transient reactions (erythema and edema) were noted in all animals 30 min after removing covering, but skin cleared by 48 to 72 h post-application	[65]
Butyl Ethyl Propanediol	Rabbit	Unknown	Unknown	Ingredient was tested on rabbit skin (no further details provided)	Non-irritating	[56]
Isopentyldiol	Rabbit, New Zealand White	n=3/sex	Undiluted	Procedures followed were a variation of OECD TG 404 (Acute Dermal Irritation/Corrosion); test substance was applied and occlusively covered for 24 h, then the patch was removed; skin was examined at 24 and 72 h post-application	Non-irritating	[66]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Isopentyldiol	Rabbit, New Zealand White	n=9 males	Not specified	15 µl of test substance was applied to dorsal trunk area (clipped) while another site in the vicinity was used as a control; sites were covered (semi-occlusively) for 24 h, then patches were removed and skin examined; another treatment of test substance was applied to the same site and procedures used during the first application were repeated each day for 28 days; at the completion of the study the animals were killed and skin cells examined	No substantial irritation with repeated skin application On day 10 of study an animal died (cause was gastrointestinal disease and unrelated to treatment) and another was added to test group; an animal died on day 22, but cause was unknown On days 15, 18, and 27 slight erythema and/or edema was observed in 4 animals, but by the following day irritation had resolved At the treatment site of 4 animals, mild inflammatory cell infiltration was reported, but in 2 of those 4 animals the control sites yielded similar results	[66]
				Human		
Propanediol	Human	n=40	Undiluted	Single treatment of test substance was applied (no further details provided)	No substantial irritation	[78]
Propanediol	Human	n=100	5%, 25%, 50%; controls used water vehicle only	For the induction phase 0.1 ml of test solution was applied to pad (1 inch),covered with clear adhesive, and pressed onto left arm; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the other arm, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	No skin reactions or irritation at any concentration levels nor with controls were observed	[78]
Propanediol; 1,2-Propanediol	Human	n=200	Propanediol: 25% (pH 7), 50% (pH 7), and 75% (pH 4, 7, 9); 1,2-Propanediol: 25% (pH 7); 50% (pH 7); 75% (pH 7); vehicle=water; negative controls were used at pH 4, 7, and 9	For the induction phase, 0.1 ml of test solution was applied to pad (1 inch), covered with clear adhesive, and pressed onto the upper back; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the back, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	Propanediol: Very slight erythema at test sites was noted 24 or 72 h post-challenge application in a few subjects (at all concentration levels), however these findings were considered clinically insignificant; during induction 4 subjects showed mild erythema after the 1st of 9 applications (with 75% only) 1,2-Propanediol: During 9 applications of induction phase and 24 and 72 h post-challenge, mild to moderate skin irritation and cumulative skin irritation were observed in 8.2% of subjects treated with 25%, 21.7% of subjects with 50%, and 22.7% of subjects with 75%	[78]
1,4-Butanediol	Human	n=200	Unknown	A patch test was performed (no further details provided)	Non-irritating	[68]
Methylpropanediol	Human	n=25 (sensitive skin subjects)	Unknown	A cumulative irritation study was conducted for 14 days (no further details provided)	Non-irritating	[18]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Isopentyldiol; 1,3-Butanediol	Human	n= 13 males and 17 females (20 to 66 yrs old)	Not specified	An unspecified concentration of Isopentyldiol, 1,3-Butanediol, and water (control) were soaked into filter paper and applied to medial brachium area of skin and covered with a Finn chamber; 48 h post-application the test substance/Finn chamber were removed and skin examined at 30 min, 24 h, and up to 7 days	Slightly irritating; slight erythema reported 30 min after Finn chamber removal (in 66 yr old female and in 49 yr old female), but this resolved within 24 h	[66]
SENSITIZATION						
Animal						
Propanediol	Guinea Pig, SPF albino	Males, n=8/ concentration	Induction Phases 1 & 2: 25%; Challenge: 10% (vehicle=water for all dilutions)	A Landsteiner/ Draize test was performed (time lapse between induction and challenge was not specified) Induction Phase 1: 0.05 ml of test substance was intradermally injected (1st injection) Induction Phase 2: 0.01 ml of test substance was intradermally injected (2nd through 10th injections) Challenge: 0.05 ml of test substance was intradermally injected skin examined 24 h post-challenge Negative controls were used (0.05 ml of 10% at challenge with no treatment during induction)	Non-sensitizing; reactions at challenge were very mild or mild and were not considered to vary substantially from controls; during repeated induction phase exposures mild to severe reactions were reported	[42]
Propanediol	Guinea Pig	n=2/sex (preliminary test); n=10/sex (test animals); n=5/sex (controls used at induction and challenge)	Induction: 2.5% (intradermal) and undiluted (epicutaneous) Challenge: 50% (epicutaneous and semi-occlusive) vehicle=water	A guinea pig maximization test was performed (non-GLP) in accordance with OECD TG 406 (Skin Sensitization) Preliminary Test: conducted to find the concentrations for intradermal and topical challenge Induction: 6 intradermal injections (within a 4 x 4 cm area) were made on shaved back of each animal; 1 week later, to the same back skin site (freshly shaved), a test substance (undiluted) soaked filter paper patch was applied and occlusively covered for 48 h Challenge: 2 weeks after induction,50% test substance soaked filter paper patch (2.5 x 2.5 cm) was applied to shaved flanks and covered by adhesive tape and a bandage for 24 h; at 24 h post-application bandage was removed and skin was examined immediately and 24 h (site shaved 3 h prior to 24 h reading) and 48 h after patch removal	Non-sensitizing; no reactions in any tests	[42]
1,4-Butanediol	Guinea Pig, Hartley albino	n=30 (male and female) total: 10 used for controls and 20 used for test substance evaluation	Both induction and challenge phase concentrations were 10% (intradermal injection) and 30% (topical application)	Food and water (containing 400 mg/l vitamin C) were available *ad libitum*; a Magnusson and Kligman guinea pig maximization test was performed	Non-sensitizing	[59]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Hexanediol	Guinea Pig, Pirbright-Hartley	Range-finding study n=4; in main study n=10 females, n=5 controls	Intradermal Induction: 5% Hexanediol in 0.9% aqueous sodium chloride solution containing Freund's adjuvant Epicutaneous Induction: 50% Hexanediol in aqua bidest. solution Challenge: 25% Hexanediol in aqua bidest. solution	Food and water were available *ad libitum*; A guinea pig maximization test was performed (GLP) in accordance with European Union (EU) Method B.6 (Skin Sensitization) Range-finding study was conducted (2 x 2 cm filter paper soaked in approximately 0.15 g of test substance was applied 2x to flank skin and occlusively covered for 24 h; skin was examined at 24 and 48 h post-application) Intradermal Induction: 6 injections total (2 injections/animal) as follows: 2 injections each of 0.1 ml Freund's adjuvant emulsified with 0.9% sodium chloride (1:1) not containing test substance; 2 injections each of 0.1 ml Freund's adjuvant emulsified with 0.9% sodium chloride (1:1) containing test substance; 2 injections each of 0.1 ml test substance only Epicutaneous Induction: 1 week following intradermal induction; 2 x 4 cm filter paper soaked in 0.3 g of test substance was applied to shoulder skin and occlusively covered for 48 h Challenge: 21 days following induction; 2 x2 cm filter paper soaked in 0.15 g of test substance was applied to flank skin (hair clipped) and occlusively covered for 24 h; then patch was removed and skin was examined at 24 and 48 h post-application	Non-sensitizing	[63]
Hexanediol; Ethylene Glycol	Guinea Pig, Hartley	n=19 total	Induction Phases 1 & 2: Test solutions (% by wt) were experimental dentin primers: 0.2% 2-HEMA; 0.2% Ethylene Glycol; or 0.2% Hexanediol (vehicle=7:3, v/v, olive oil: acetone)	A Magnusson and Kligman guinea pig maximization test was performed; below are the compounds used as the sensitizer followed by test substance used at challenge (neither time lapse between induction and challenge nor challenge concentrations were specified): 2-HEMA sensitizer/ Ethylene Glycol challenge (n=5) 2-HEMA sensitizer/ Hexanediol challenge (n=5) Ethylene Glycol sensitizer/ Ethylene Glycol challenge (n=2) Hexanediol sensitizer/ Hexanediol challenge (n=2) 2-HEMA sensitizer/ 2-HEMA challenge (n=5) Induction Phase 1: 50 µl of each test solution was intradermally injected (also injected was 50:50 Freund's complete adjuvant: distilled water) into back skin Induction Phase 2: 1 week after Phase 1, 0.2 ml (100%) of test solution soaked into filter paper was applied to shaved back; 0.1 ml (100%) test solution soaked into filter paper was applied to 2 skin sites and occlusively covered for 24 h	There were positive results for 2-HEMA sensitizer/ Hexanediol challenge with a mean response of 1.5 (24 h) and 0.8 (48 h) indicating strong erythema (no vesicles present); positive responses were also noted with 2-HEMA sensitizer/ 2-HEMA challenge; the results for Hexanediol sensitizer/ Hexanediol challenge were negative	[77]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Methylpropanediol	Guinea Pig, Himalayan	n=20 test animals, n=10 controls	Intradermal Induction: 10% test substance in saline; 50:50 Freund's Complete Adjuvant (FCA)/distilled water; and 20% test substance emulsified in FCA Epidermal Induction: 100% test substance Challenge: 0, 25, 50, or 100% test substance in distilled water	Guinea pig maximization test was conducted in accordance with OECD Guidelines for Testing Chemicals Induction Phases: 0.1 ml intradermal injections were performed at the indicated concentrations; on the 6th day following intradermal inductions a treatment of 10% sodium-dodecyl-sulfate in petrolatum was applied; on the 7th day, 0.5 ml of the test substance (100%) was applied to injection sites and covered with a patch for 48 h Challenge: 2 weeks following the epidermal induction phase the test material was applied at the indicated concentrations and covered with a patch for up to 48 h	Mild sensitization potential was reported; 24 h after the patch from the challenge treatment was removed positive responses were noted in 1 animal with 25% and 1 animal with 50% challenge concentrations, but not at 100%; by 48 h after the patch was removed following challenge, 1 animal with 25%, 3 animals with 50%, and 1 animal with 100% challenge concentrations showed positive reactions; controls performed as expected	[58]
2,3-Butanediol	Guinea Pig	n=10 females	Intradermal Induction: 5% test substance in Freund's adjuvant/0.9% aqueous sodium chloride solution Epicutaneous Induction: 50% test substance in distilled water Topical Challenge: 25% test substance in distilled water	A guinea pig maximization test was performed (GLP) in accordance with OECD TG 406 (Skin Sensitization); controls were used Intradermal Induction: injections were as follows (no volumes provided): Freund's adjuvant/ 0.9% aqueous sodium chloride; 0.9% aqueous sodium chloride; test substance in Freund's adjuvant/0.9% aqueous sodium chloride solution; test substance in 0.9% aqueous sodium chloride solution Epicutaneous Induction: no further details were provided explaining this induction other than concentration Challenge: no further details were provided explaining challenge other than concentration	Non-sensitizing The following reactions were reported: -All animals injected with only Freund's adjuvant/ 0.9% aqueous sodium chloride showed erythema and swelling at injection sites -Animals injected with only 0.9% aqueous sodium chloride had no skin reactions -Test group animals injected with 5% test substance in Freund's adjuvant/ 0.9% aqueous sodium chloride showed erythema and swelling at injection sites -Test group animals injected with 5% test substance in 0.9% aqueous sodium chloride showed moderate and confluent erythema and swelling -Test group animals epicutaneously exposed to 50% test substance during induction showed incrustation and confluent erythema with swelling -Test group animals exposed to 25% test substance at challenge showed no reactions	[64]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Butyl Ethyl Propanediol	Guinea Pig, Dunkin-Hartley	Males, n=10 test animals, n=5 controls	Intradermal Induction: 2.5% (v/v) Topical Induction: 100% Topical Challenge: 100% and 50% (v/v) (vehicle=Alembicol D)	A guinea pig maximization test was performed (GLP) in accordance with EU Method B.6 (Skin Sensitization) Intradermal Induction: 3 pairs of injections as follows: 2 injections of 0.1 ml Freund's adjuvant diluted with water (1:1); 2 injections of 0.1 ml test substance in Alembicol D; 2 injections of 0.1 ml test substance in 50:50 of Freund's adjuvant/Alembicol D Epicutaneous Induction: 6 days following intradermal induction; shaved skin (same site as injection) was pretreated with 0.5 ml 10% sodium lauryl sulfate in petroleum (w/w); after 24 h a patch soaked with 0.4 ml of test substance was applied to same skin area and occlusively covered for 48 h Challenge: 0.2 ml of test substance was applied to anterior site and 50% test substance (diluted in Alembicol D) was applied to posterior site; both sites were occlusively covered for 24 h; then patches were removed and skin was examined at 24, 48, and 72 h post-application	Non-sensitizing; no reaction were observed	[65]
Isopentyldiol	Guinea Pig, Dunkin-Hartley	n=20 test animals, n=10 controls	*Main Study:* Intradermal Induction: 10% in distilled water Topical Induction: 100% undiluted Challenge: 50% in distilled water	Guinea pig maximization test was performed in accordance with OECD TG 406 (Skin Sensitization-Magnusson & Kligman) Preliminary study was conducted using an intradermal concentration of 10% test substance in distilled water and a topical induction concentration of 50% test substance in distilled water; these were the maximum non-irritating concentrations Induction Phases: test substance was applied at indicated concentrations (volumes were not specified) Challenge: test substance was applied at indicated concentration (volumes were not specified); skin was examined 24 and 48 h post-challenge application; positive and negative controls were used	Induction Phases: moderate and confluent erythema was reported 24 h post-application at intradermal injection sites and topical application sites; controls showed slight or discrete erythema Challenge: Non-sensitizing; no reactions in test group or negative controls; positive controls performed as expected	[66]
				Human		
Propanediol	Human	n=100	5%, 25%, 50%; controls used water vehicle only	For the induction phase 0.1 ml of test solution was applied to pad (1 inch), covered with clear adhesive, and pressed onto left arm; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the other arm, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	Propanediol was non-sensitizing	[78]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Propanediol; 1,2-Propanediol	Human	n=200	25% (pH 4), 50% (pH 7), and 75% (pH 9), vehicle=water	For the induction phase 0.1 ml of test solution was applied to pad (1 inch), covered with clear adhesive, and pressed onto the upper back; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the back, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	Propanediol and 1,2-Propanediol were non-sensitizing	[78]
1,4-Butanediol	Human	n=200	Unknown	Sensitization test was performed (no further details provided)	Non-sensitizing	[68]
Methylpropanediol	Human	n=104	Unknown	4 patch tests were conducted; they included 9 induction applications (occlusive and semi-occlusive); no further details provided	Non-sensitizing	[18]
Methylpropanediol	Human	n=110	Unknown	A patch test with induction and challenge phases was conducted (no further details provided)	During induction phase "mild dermal responses" were observed in 4 subjects; at challenge 5 subjects showed "mild dermal responses"; 1 subject's reaction was described as an atopic state indicating the reaction was caused by Methylpropanediol and to propylene glycol and butylene glycol (no details of how these two latter compounds were incorporated into the testing were mentioned); for the other subjects who had reactions it is unclear as to whether irritation, allergy, or an unrecognizable atopic condition were the cause; Methylpropanediol was not considered to be a strong irritant or potent sensitizer	[18]
PHOTOIRRITATION/ PHOTOSENSITIZATION						
Animal						
Isopentyldiol	Guinea Pig, Dunkin-Hartley	n=10 test animals, n=10 controls	Undiluted	To the shaved back of each animal 0.025 ml of test substance and a positive control (8-methoxysporalen or 8-MOP) were applied epicutaneously to test animals; animals were exposed to 20 J/cm^2 of UVA radiation (320-400 nm); when exposure of UVA radiation reached 2.5 J/cm^2 the positive control site was concealed with lightproof tape; control animals were not exposed to UVA radiation; skin of all animals examined 24, 48, and 72 h post-application	Isopentyldiol was a not a photoirritant; positive control performed as expected	[66]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Isopentyldiol	Guinea Pig, Dunkin-Hartley	n=10 test animals, n=10 controls, n=10 positive controls	Undiluted (test animals); distilled water (controls); 0.1% tetrachlorosalicylanilide in petrolatum (positive controls)	Induction: to the shaved and chemically depilated back of each test animal, 0.025 ml of test substance was epicutaneously applied; animals were exposed to 485 mJ/cm^2 of UVA radiation and 185 mJ/cm^2 of UVB radiation for 10 min; this procedure was repeated 5x every 48 h for a total of 6 applications in 2 weeks (animals were shaved/depilated as needed); control and positive control animals were similarly treated except with distilled water and tetrachlorosalicylanilide, respectively; skin was examined 24, 48, and 72 h post-application Challenge: 12 days after induction phase was complete, test substance was applied epicutaneously (open) to the backs (shaved/depilated) of test and control animals following the same procedures used in the induction phase; 30 min post-application test and control animals were exposed to 10 J/cm^2 of UVA radiation, then test substance was applied to a nearby skin site of the test and control animals and no radiation exposure applied to those sites; skin of all animals was examined 24, 48, and 72 h post-application of test substance, distilled water, or positive control substance	Isopentyldiol was non-photosensitizing; 1 animal was killed before challenge because of probable pneumonia; no skin reactions post-application of treatment during induction or challenge phases; positive controls performed as expected	[66]

2-HEMA=2-hydroxyethyl methacrylate; EU=European Union; FCA=Freund's Complete Adjuvant; GLP=Good Laboratory Practice; HRIPT=Human Repeat Insult Patch Test; ICDRG=International Contact Dermatitis Research Group; non-GLP=non-Good Laboratory Practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 13. Ocular Irritation Studies

Test Substance	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Propanediol	Rabbit, New Zealand White	n=6	Undiluted	Procedures followed were in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion); 0.1 ml of test substance was applied to the everted lower lid of one eye (remaining eye was the control), upper and lower lid were held together for 1 second, no eye washing occurred; eyes were examined 24, 48, and 72 h and 7 days post-application	Slight conjunctivae redness was observed in 4 of 6 rabbits, but had cleared by 48 h post-application; results were considered to be non-irritating	[42]
Propanediol	Rabbit	n=4	Undiluted	Procedures followed (non-GLP) were in accordance with Federal Register 28 (110), 1963 para 191.12 Test for eye irritants; 0.2 ml of test substance was instilled into the conjunctival sac of one eye (remaining eye served as control); 2 treated eyes were rinsed and 2 treated eyes were unrinsed; eyes were examined 30 min and 1, 2, 3, and 7 days post-application	Transient, mild conjunctival reddening/swelling was reported in 3 rabbits, 2 of the eyes had been rinsed and 1 was not rinsed, however all symptoms had resolved by 48 h post-application	[42]
1,4-Butanediol	Rabbit, New Zealand White	n=4	Undiluted	A single application (0.1 ml) of test substance was instilled into the conjunctival sac of the right eye (left eyes were used as controls); eyes were examined at 1, 24, 48 and 72 h post-application	Slightly irritating; all rabbits showed small discharge and slight redness of conjunctives at 1 h post-application, however these symptoms lessened by 48 h post-application	[59]
1,4-Butanediol	Rabbit	Not specified	Not specified	Test substance was instilled into the conjunctival sac of rabbit eyes (no further details specified)	Slight conjunctival irritation without corneal damage was reported	[14]

Table 13. Ocular Irritation Studies

Test Substance	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
1,5-Pentanediol	Rabbit	Unknown	Unknown	Test substance was instilled into the conjunctival sac (no further details specified)	On a scale of 1 (very small area of necrosis) to 10 (a severe burn) 1,5-Pentanediol application resulted in a rating of 2, suggesting mild irritation	[54]
1,5-Pentanediol	Rabbit	Not specified	Not specified	Not specified	Mildly irritating	[79]
1,5-Pentanediol	Rabbit, Vienna White	n=2 male, 4 female	Undiluted	Procedures followed (non-GLP) were in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion); 0.1 ml test substance was instilled into the conjunctival sac of one eye (remaining eye served as control); eye were unwashed; examination of eyes occurred 24 to 72 h post-application and for up to 8 days post-application	Results were considered to be non-irritating; average eye ratings were: slight irritation, fully reversible by 72 h for cornea, iris, conjunctivae, chemosis	[62]
Hexanediol	Rabbit	Unknown	Concentration unknown, a suitable vehicle was used	Test substance was instilled into the conjunctival sac (no further details specified)	On a scale of 1 (very small area of necrosis) to 10 (a severe burn) 1,5-Pentanediol application resulted in a rating of 3, suggesting it is mildly irritating	[54,55]
Hexanediol	Rabbit, Vienna White	n=2	Undiluted	Non-GLP study; 50 mg of test substance was instilled into the conjunctival sac of the eye (the other eye was talcum-treated and served as control); eyes were at 1, 3, 24, 48, 72 h post-application and at 5 days post-application; eyes were washed with Lutrol® and Lutrol®/water (1:1) mixture 20 h post-application	Results were considered to be non-irritating; average eye ratings were: cornea=slightly irritating, fully reversible by 72 h; chemosis=slightly irritating, fully reversible by 48 h; conjunctivae=slightly irritating, fully reversible by 72 h; discharge was noted in 1 eye 1 h post-dosing	[63]
Methylpropanediol	Rabbit, New Zealand White	n=6	Unknown	Procedures followed were in accordance with OECD Guidelines for Testing Chemicals; 0.1 ml was instilled into the conjunctival sac of one eye of each rabbit; eyes were observed up to 72 h post-application	Non-irritating	[58]
Methylpropanediol	Rabbit	Not specified	Not specified	Not specified	Non-irritating	[18]
2,3-Butanediol	Rabbit, Vienna White	n=6	Undiluted	This non-GLP study evaluated the effect of the test substance on rabbit eyes (no mention of controls used); the eyes were observed for 72 h post-application (no further details specified)	Non-irritating	[64]
Butyl Ethyl Propanediol	Rabbit	Unknown	Not specified	Test substance was instilled into rabbit eye, but the method used was not described	Results indicate severe eye injury	[56]
Butyl Ethyl Propanediol	Rabbit, New Zealand White	n=3	Undiluted	Procedures followed were in accordance with GLP and European Union Method B.5 (Acute Toxicity: Eye Irritation/ Corrosion); 0.1 ml of warm liquid test substance was applied to the lower everted lid of one eye of each rabbit (other eye served as control); eyes were not washed; eyes examined at 1 h and at 1, 2, 3, 4, 7, and 14 days post-application	Irritating; all 3 rabbits showed corneal opacification and diffuse crimson conjunctiva coloration with swelling and partial eyelid eversion or eyelids half-closed, 1 rabbit exhibited iridial inflammation; eyes returned to normal 7 to 14 days post-application; no toxic signs in rabbits during observation period	[65]
Isopentyldiol	Rabbit, New Zealand White	n=6	Not specified	Procedures followed were in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion); eyes were examined at 1, 24, 48, and 72 h and up to 7 days post-application	Non-irritating	[66]

GLP=Good Laboratory Practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 14. Case Reports

Test Substances(s)	Species	Test Population	Concentration/ Dosage (Vehicle)	Exposure Route	Investigation and Method (when available)	Results	Reference
1,4-Butanediol	Human	Report of n >100	Unknown	Oral	US FDA reported more than 100 people were ill and 3 died as a result of taking unregulated 'party drugs', also sold as dietary supplements to induce sleep, containing 1,4-Butanediol	Side effects reported by FDA were dangerously low respiratory rates, unconsciousness, vomiting, seizures, and death; effects were amplified when consumed with alcohol or depressant drugs	[61]
1,4-Butanediol	Human	n ≥ 8 (14 months to 10 yrs old)	Approximately 14% of extractable 1,4-Butanediol by weight	Oral	Children developed vomiting, ataxia, self-limited coma after swallowing small, colored plastic beads (sold in toy craft kits); in biological samples collected from some of the children gamma-hydroxybutyrate (GHB) was found; in 2007 a voluntary recall of the beads was issued by the US Consumer Product Safety Commission; investigation determined that 1,4-Butanediol had been substituted for the more expensive 1,5-Pentanediol (used in glues) in the plastic beads; 1,4-Butanediol converts to GHB in the body	Small, plastic toy beads were found to have 14% 1,4-Butanediol and no 1,5-Pentanediol or GHB; clinical signs reported were consistent with ingestion of several dozen of the plastic toy beads containing 1,4-Butanediol (approximately 9-12 mg of 1,4-Butanediol per bead)	[80]
1,4-Butanediol	Human	n=8 patients (22 to 51 yrs old)	Non-fatal cases of 1,4-Butanediol ingestion were 1 to 14 g; Fatalities occurred at doses between 5.4 to 20 g	Oral	Patients having toxic effects from oral ingestion of 1,4-Butanediol were identified (from emergency room department visits and/or from public health officials and family members); analysis of 1,4-Butanediol and/or GHB in urine, serum, or blood was performed and/or hospital records or autopsy reports were examined	Patients ingested 1,4-Butanediol for recreational use, enhancement during body building, or for the treatment of depression or insomnia; evidence of addiction and withdrawal were seen in some cases; clinical signs included vomiting, urinary and fecal incontinence, agitation, combativeness, labile level of consciousness, respiratory depression, and death; in 6 patients (2 of whom died) no additional toxicants were detected; the 2 other patients reported that they did not ingest other toxicants; GHB was detected in blood, serum, and urine at levels exceeding normal concentrations; 1,4-Butanediol was not detected in non-fatal cases potentially because ingested doses were smaller, conversion to GHB in the body is rapid, and there were limits on detection of the assay used	[81]
1,4-Butanediol	Human	n=1 male (44 yrs old)	Unknown	Oral	A 44-year-old man was taken to the emergency room with signs of intoxication, agitation, loss of consciousness, vomiting, and myoclonic jerking (heart rate 40 and respiration rate 8); negative blood ethanol; man was awake and alert after 3 h	Man reported ingesting nine yohimbine tablets and pine needle oil; 3 oz spray bottle reported to contain 'pine needle oil' was determined to contain 1,4-Butanediol	[57]

Table 14. Case Reports

Test Substances(s)	Species	Test Population	Concentration/ Dosage (Vehicle)	Exposure Route	Investigation and Method (when available)	Results	Reference
1,4-Butanediol	Human	n=1	Unknown	Oral	A patient ingested an illicit product called 'liquid ecstasy'; blood, urine, and gastric content were analyzed for 1,4-Butanediol and GHB by immunoassay and gas chromatography-mass spectrometry (GC-MS); identification of the 'liquid ecstasy' substance was determined by GC-MS	The 'liquid ecstasy' substance was found to contain 1,4-Butanediol; in the patient 1,4-Butanediol was found at 82 µg/ml (in blood), 401 µg/ml (in urine), and 7.4 µg/ml (in gastric content); GHB was found at 103 µg/ml (in blood) and 430 µg/ml (in urine); other drugs detected were methylenedioxymethylamphetamine (0.23 µg/ml in blood) and its metabolite methylenedioxyphenylamphetamine (0.1 µg/ml in blood); benzoylecgonine (0.1 µg/ml in urine)	[57]
1,4-Butanediol	Human	n=7	15 or 30 g (0.21 or 0.43 g/kg, assumed body weight of 70 kg)	Rectal	Single dose rectally administered (no further details specified)	Clinical signs observed 10 to 20 min post-administration included coma, miosis and areflexia (sustained for 1 to 16 h); 2 deaths within 72 h post-administration (both found to have renal disorder); 5 remaining patients were given analeptic and recovered	[57]
1,4-Butanediol	Human	Unknown	30 mg/kg (intravenous) or 15 to 22 mg/kg/h (by infusion) for 38 to 68 h (initial dose 30 mg/kg)	Intravenous	No further information specified about administration of dose	Clinical signs after dosing included sleep, restlessness, clonic spasms of muscles of the extremities	[68]
1,5-Pentanediol	Human	n=1 (39 yr old male); n=10 controls for each of Test 2 and Test 3	Test 2: 0.5%, 5%, and 10% 1,5-Pentanediol (in water); 0.1%, 1%, and 10% resveratrol (in 70% ethanol); 10 controls were patch tested with the doses of test substances above Test 3: 0.1%, 1%, and 5% resveratrol (in petrolatum); 10 more control subjects were patch tested with same doses of resveratrol in Test 3	Dermal	A 39-yr-old patient was prescribed a resveratrol-containing cream (also contained 1,5-Pentanediol, concentration not specified) for recurrent scaling erythematous dermatitis; dermatitis intensified after 2 weeks of cream application; after use of cream was discontinued eczema eventually cleared Patient underwent patch testing (Test 1: propylene glycol and the resveratrol cream unchanged were applied) 4 months later an additional patch test (Test 2) was performed on the patient and controls using the ingredients in the resveratrol cream A final patch test (Test 3) was performed on the patient and controls using resveratrol diluted in petrolatum	Test 1 on patient: the resveratrol cream produced +/++ reactions by days 2 and 3 Test 2 on patient and controls: patient had strong reaction to 1,5-Pentanediol (++ with 5% and 10% doses and +/++ with 0.5% dose); patient had slight reactions to resveratrol showing erythema on days 2 and 3 with all dose levels; 9 of 10 controls were negative and 1 control subject developed slight erythema with all doses levels of 1,5-Pentanediol and resveratrol (this control subject had not been previously exposed to resveratrol and had no prior reactions to cosmetics, but did report hyperirritable skin type) Test 3 on patient and controls: patient reacted to 5% resveratrol only (+ by days 2 and 3); controls were negative Final conclusion: patient was diagnosed with allergic contact dermatitis from resveratrol containing cream attributed to sensitization to 1,5-Pentanediol and potential co-sensitization to resveratrol	[82]

Table 14. Case Reports

Test Substances(s)	Species	Test Population	Concentration/ Dosage (Vehicle)	Exposure Route	Investigation and Method (when available)	Results	Reference
Hexanediol; ethylene glycol	Human	n=1 (32 yr old female)	Test compounds used were experimental dentin primers (by wt %): 62.5% Ethylene Glycol; 45% Hexanediol; 35% Hydroxyethyl methacrylate	Dermal	A 32-yr-old dentist worked with ethylene glycol dentin primer for a year, which required repeated dermal contact with the compound; this dermal contact resulted in 2 months of symptoms including cracked fingertip skin, reddening desquamation, desiccation and inflammatory dolorific sclerosis; she was diagnosed with (irritant) contact dermatitis; a patch test was performed on the dentist with the test compounds indicated; test compounds were soaked into a cotton patch and occlusively applied to healthy brachial skin for 48 h; 48 h post-application the patches were removed and skin was examined immediately, 24, and 48 h after patch removal	Slight erythema was noted with ethylene glycol 48 h after patch removal; dental professionals sensitized to hydroxyethyl methacrylate should take precautions if using Hexanediol in a dentin primer (no further patch test results specified); other supporting tests in animals were conducted in conjunction with this case report (results presented in Table 12)	[77]

GC-MS=Gas Chromatography-Mass Spectrometry; GHB=Gamma-Hydroxybutyric Acid

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