Safety Assessment of Monoalkylglycol Dialkyl Acid Esters as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 28 monoalkylglycol dialkyl acid esters as used in cosmetics. The most common cosmetic function reported for this group of ingredients is as a skin conditioning agent; other reported functions film former, hair conditioning agent, opacifying agent, plasticizer, slip modifier, solvent, surface modifier, and viscosity increasing agent. The Panel reviewed the relevant data for these ingredients and concluded that these monoalkylglycol dialkyl acid esters are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a safety assessment of 28 monoalkylglycol dialkyl acid esters as used in cosmetics (Table 1). The ingredients in this report are structurally related to each other as alkyl esters of monoalkyl diols (i.e. not *poly*alkyldiols such as polyethylene glycols (PEGs)) that vary by type of diol and lengths of the fatty acid residues. The ingredients in this report include:

- Butylene Glycol Dicaprylate/Dicaprate
- Butylene Glycol Diisononanoate
- Diethylpentanediol Dineopentanoate
- Dioctadecanyl Didecyltetradecanoate
- Dioctadecanyl Ditetradecyloctadecanoate
- Glycol Dibehenate
- Glycol Diethylhexanoate
- Glycol Dilaurate
- Glycol Dioleate
- Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate
- Glycol Dipalmate/Rapeseedate/Soyate
- Glycol Dipivalate
- Glycol Distearate
- Glycol Ditallowate
- Hexanediol Distearate
- Neopentyl Glycol Dicaprate
- Neopentyl Glycol Dicaprylate/Dicaprate
- Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate
- Neopentyl Glycol Diethylhexanoate
- Neopentyl Glycol Diheptanoate
- Neopentyl Glycol Diisononanoate
- Neopentyl Glycol Diisostearate
- Neopentyl Glycol Dilaurate
- Propanediol Dicaprylate
- Propanediol Dicaprylate/Caprate
- Propanediol Diisostearate
- Propanediol Dipelargonate
- Trimethyl Pentanyl Diisobutyrate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI *Dictionary*), the most common cosmetic function reported for this group of ingredients is as a skin conditioning agent; other the reported functions of these ingredients include film former, hair conditioning agent, opacifying agent, plasticizer, slip modifier, solvent, surface modifier, and viscosity increasing agent – nonaqueous (Table 1).[1]

Some of these ingredients have been previously assessed for safety by the Panel. Glycol Distearate has been previously reviewed by the Panel and was found to be safe as used; the conclusion was reaffirmed in 2001 (Table 2).[2,3] Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate and Neopentyl Glycol Diisononanoate have also been reviewed by the Panel and were found to be safe as used in 2011.[4]

The Panel has reviewed related ingredients, moieties, and component parts of these ingredients (Table 2). These CIR safety assessments have been utilized herein, in part, to inform the safety of the monoalkylglycol dialkyl acid esters. Please see the original reports for further details (http://www.cir-safety.org/ingredients).

Data on the molecular weight and log P are useful in determining if these ingredients may penetrate the skin and are provided in the chemical and physical properties table (Table 3). If it is possible that monoalkylglycol dialkyl acid esters penetrate the skin and/or toxicity data are lacking, data on the hydrolysis products of these ingredients are also useful in determining safety. Data on neopentanoic acid, a hydrolysis product of Diethylpentanediol Dineopentanoate, are provided in Table 4. There were no data for the other hydrolysis product of Diethylpentanediol Dineopentanoate, i.e., 2,4-diethyl-1,5-pentanediol. However, data on 1,5-Pentanediol and Isopentyldiol, which may be used as surrogates for 2,4-diethyl-1,5-pentanediol due to their similar chemical structures, are available from the CIR report on alkane diols. These data are also summarized in Table 4.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Pertinent data were discovered in the European Chemicals Agency (ECHA) database for Glycol Distearate, Neopentyl Glycol Dicaprylate/Dicaprate, Neopentyl Glycol Diethylhexanoate, Neopentyl Glycol Diheptanoate, and Trimethyl Pentanyl Diisobutyrate.[5-9] Data were also discovered in this database for neopentanoic acid, a hydrolysis product of Diethylpentanediol Dineopentanoate.[10] The ECHA website provides summaries of information submitted by industry. ECHA is cited in this assessment to identify the source of the data obtained from these summaries.

Summaries from the original reports on Glycol Distearate, Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate, and Neopentyl Glycol Diisononanoate are included in the appropriate sections in *italics*.[3,4] Please see the original reports for further

details (http://www.cir-safety.org/ingredients).

CHEMISTRY

Definition and Structure

The ingredients in this report are structurally related to each other as alkyl diesters of monoalkane diols. These ingredients vary by the type of diol and the size of the carboxylic acid residues (Figure 1). For example, Neopentyl Glycol Dicaprate is a diol (neopentyl glycol) esterified at both hydroxyl groups with a carboxylic acid (capric acid) (Figure 2).

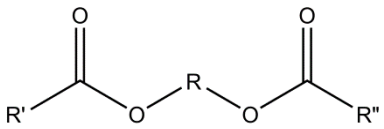


Figure 1. Monoalkylglycol Dialkyl Acid Esters in which "ORO" is the residue of a diol and "R'C(O)" and "R"C(O)" are the residues of a fatty acids.

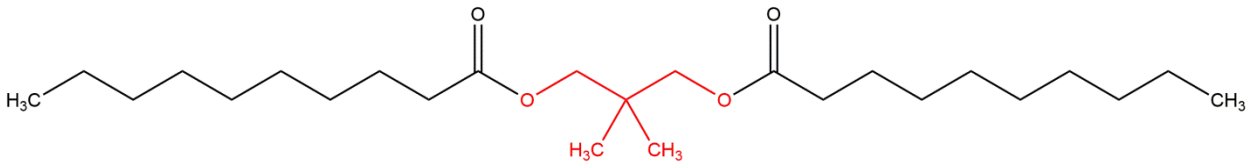


Figure 2. Neopentyl Glycol Dicaprate, wherein "ORO" from Figure 1 is the residue of neopentyl glycol, and both R'C(O)" and "R"C(O)" are the residues of capric acid.

Physical and Chemical Properties

Physical and chemical properties for the monoalkylglycol dialkyl acid esters in this safety assessment are presented in Table 3.

Some of the monoalkylglycol dialkyl acid esters (e.g., Neopentyl Glycol Diethylhexanoate and Propanediol Dicaprylate) are clear or yellow liquids that are insoluble in water.[8,11-13] However, longer-chain diesters, such as Glycol Distearate, can be white to cream-colored waxy solids.[3] Estimated and experimental log P values range from 4.91 (for Trimethyl Pentanyl Diisobutyrate) to 46.27 (for Dioctadecanyl Ditetradecyloctadecanoate), supporting the statements that these ingredients are quite lipophilic and thus poorly water-soluble.[4-6,8,9,14,15] The physical properties of these ingredients may vary within specified limits according to the proportions of mono- and di-esters, and other components (e.g., variations in how many of the glycol residues in Glycol Distearate are mono- or di-substituted with stearic acid). Depending on the intended use, these variations can be set during manufacturing to achieve the desired physical characteristics.

Diethylpentanediol Dineopentanoate is reported to be stable at 25°C under storage conditions.[16]

The average residual ash on ignition reported by one vendor for Neopentyl Glycol Dicaprate is 0.05%.[17]

Trimethyl Pentanyl Diisobutyrate is stable at pH 4.0 and 7.0.[18] The half-life in water at pH 9 is 178 days.

UV Absorption

Data provided by a manufacturer indicated that Neopentyl Glycol Diisononanoate did not significantly absorb light in the 250 to 400 nm range.[4] The structures of these ingredients lack chromophores that would result in UV absorption above 210 nm.

Method of Manufacture

In general, alkyl esters can be produced via the esterification of carboxylic acids with the corresponding glycols (with or without a metal catalyst).[19] These carboxylic acids and glycols are often derived from plant or animal sources (e.g., Glycol Dipalmate/Rapeseedate/Soyate and Glycol Ditallowate). Acids from these sources are often mixtures; accordingly, the resulting esters are also mixtures (e.g., Glycol Dipalmate/Palm Kernelate/Olivate/ Macadamiate and Glycol Dipalmate/Rapeseedate/ Soyate).

Impurities/Constituents

Ethylene glycol and/or ethylene oxide are used as starting material for the synthesis of Glycol Stearate. These starting materials are expected to also be used as starting materials for Glycol Distearate, a related ingredient. Because the former is known to be contaminated with traces of 1,4-dioxane, it is possible that such traces could also appear in the final synthesized material.[20] A safety data sheet on a product mixture containing Glycol Distearate recited that 1,4-dioxane was not detected.[21]

A batch of Neopentyl Glycol Diheptanoate was reported to be > 99% pure; the impurities were not named.[6]

One batch of Trimethyl Pentanyl Diisobutyrate was reported to be > 99% pure, and another batch was reported to be 98.95% pure.[7] The impurities were not named. Another source also reported that Trimethyl Pentanyl Diisobutyrate was > 99% pure and the major impurity was 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate.[18]

A product data sheet for a product mixture containing Glycol Distearate (88% to 95%), ethylene glycol monostearate (5% to 15%), and ethylene glycol (< 4%), reported that this product contained < 0.0000001% toluene.[21,22] According to this product data sheet, this product mixture contains < 0.001% of the following: cadmium, mercury, antimony, arsenic, chromium, cobalt, nickel, lead, or silver. It was also reported to not contain ethylene oxide or propylene oxide.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetic industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys conducted by the Council, of maximum reported use concentration by product category.

According to VCRP survey data received in 2017, Glycol Distearate was reported to be used in 1663 formulations, mostly in hair products (1041 formulations); this is an increase from 28 uses in 2001.[2,4,23] Trimethyl Pentanyl Diisobutyrate and Neopentyl Glycol Diheptanoate are used in 399 (all nail products) and 415 (mostly in skin care products) formulations, respectively. The rest of the ingredients with reported uses were used in 102 or fewer formulations. As for the other ingredients that were previously reviewed by CIR, Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate and Neopentyl Glycol Diisononanoate had no uses reported to the VCRP in 2001 or 2017 (Table 5, Table 6, and Table 7).

The results of the concentration of use survey conducted by the Council in 2016 indicate Neopentyl Glycol Diethylhexanoate had the highest reported maximum concentration of use; it is used at up to 57% (face and neck products and body and hand products).[24] Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use in a leave-on formulation; it is used at up to 40% (in lipsticks).

In 2001, Glycol Distearate was reported to be used at up to 9% in rinse-off products (non-coloring hair products) and at up to 6% in leave-on products (body and hand products); in 2016, the maximum concentrations of use for rinse-off and leave-on formulations were reported to have increased to 10% (non-coloring hair products) and 13.1% (products used around the eye), respectively.[2,4,24] In 2009, Neopentyl Glycol Diisononanoate was reported to be used at up to 1% in rinse-off products (skin cleansing products); in 2016, the maximum concentrations of use have increased to 1.3% in leave-on products (body and hand products) and 5% in rinse-off products (skin cleansing products). There were no reported maximum concentrations of use for Neopentyl Glycol Dicaprylate/Dipelargonate/ Dicaprate in 2009 or 2016.

In some cases, no uses were reported in the VCRP, but concentration of use data were reported in the industry survey. For example, Glycol Diethylhexanoate had no reported uses in the VCRP, but a maximum use concentration in a foundation (5%) was provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

The ingredients not in use according to 2017 VCRP data and the Council survey are listed in Table 7.

Several of the monoalkylglycol dialkyl acid esters are reported to be used in products applied near the eye (e.g., Neopentyl Glycol Dicaprate is used at the highest reported concentration at up to 50% in eye makeup removers). Several of these ingredients are reported to be used in products (lipsticks) that may be ingested and come in contact with mucus membranes (e.g., Neopentyl Glycol Dicaprate is used at the highest reported concentration at up to 40%). According to VCRP data, Glycol Distearate, Neopentyl Glycol Dicaprylate/Dicaprate and Neopentyl Glycol Diheptanoate are reported to be used in baby products; industry only reported a concentration of use for Neopentyl Glycol Diheptanoate (up to 2.2% in the category of baby lotions, oils and creams).

Additionally, some of the monoalkylglycol dialkyl acid esters are used in cosmetic sprays and could possibly be inhaled. For example, Neopentyl Glycol Diheptanoate was reported to be used in a pump hair spray at up to 19.5%. 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.[25-29] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[25,27] Neopentyl Glycol Dicaprate is reported to be used in spray deodorants at up to 4%. 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.[25] 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. Neopentyl Glycol Dicaprate was reported to be used in face powders at up to 16.8%. Conservative estimates of inhalation exposures to respirable particles during the use of loose-powder cosmetic products are 400- to 1000-fold less than protective regulatory guidance limits for inert airborne respirable particles in the workplace.[30]

None of the monoalkylglycol dialkyl acid esters recited in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[31]

Non-Cosmetic

Trimethyl Pentanyl Diisobutyrate is a secondary plasticizer, used in combination with other plasticizers, and is used in products like weather stripping, furniture, wall paper, vinyl flooring, sporting goods, traffic cones, vinyl gloves, inks, water-based paints, and toys.[32]

Relevant regulations in the Code of Federal Regulations that indicate how Trimethyl Pentanyl Diisobutyrate, Glycol Distearate, and Glycol Ditallowate may be used in foods or food packaging are provided in Table 8.

The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) rates Trimethyl Pentanyl Diisobutyrate as Tier 1.[33] Chemicals identified based on the Tier I assessment do not pose an unreasonable risk to workers, public health, and/or the environment.

TOXICOKINETICS STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

ORAL EXPOSURE

Trimethyl Pentanyl Diisobutyrate

In an oral metabolic fate and disposition study of radio-labeled 3-[^{14}C]-Trimethyl Pentanyl Diisobutyrate, the test substance was administered in corn oil to male Sprague-Dawley rats (n = 3) by gavage at a dosage of approximately 250 mg/kg.[7,34] An additional set of rats was administered approximately 186.7 mg/kg of radio-labeled 2,2,4-trimethyl-1,3-pentanediol (3-[^{14}C]-TMPD), a potential metabolite of Trimethyl Pentanyl Diisobutyrate. The rats were killed and examined on days 8, 15, and 22 post-dosing. Trimethyl Pentanyl Diisobutyrate was rapidly absorbed and excreted, with renal excretion accounting for 47% to 72% of the dose within 5 to 10 days of dosing; the greatest portion of the urinary radioactivity was eliminated in the first 72 h. Radioactivity in the feces accounted for 14% to 31% of the dose; fecal elimination was virtually complete by 7 days after dosing. Measurements of radioactivity in expired CO_2 did not differ from controls. Excretions accounted for 95% to 99% of the administered dose. About half of the urinary radioactivity was identified as 3-[^{14}C]-TMPD or its metabolites. Less than 1% of the administered radioactivity was retained in the tissues and carcass. In the rats administered 3-[^{14}C]-TMPD, urinary excretion accounted for 94% of the dose with 93% being excreted within the first 48 h. Expired air contained no detectable [^{14}C]-CO_2 in excess of background, accounting for less than 0.01% of the dose. The feces accounted for 2.4% of the dose, with most of the fecal radioactivity being excreted within 48 h of dosing. Four major urinary metabolites were identified for Trimethyl Pentanyl Diisobutyrate: 75% of the dose was present as an *O*-glucuronide of 3-[^{14}C]-TMPD, approximately 1.5% was excreted unchanged, approximately 7% was present as 2,2,4-trimethyl-3-hydroxyvaleric acid and its glucuronides, and < 4% was present as a further breakdown product, 2-methylmalonic acid.

In a similar oral metabolic fate and disposition study of radio-labeled Trimethyl Pentanyl Diisobutyrate (236, 250, 283, 350, or 895 mg/kg; as diisobutyrate ester of 3-[^{14}C]-2,2,4-trimethyl-1,3-pentanediol), the test substance was administered to Sprague-Dawley rats (n = 5/group) by gavage.[34] Urine, feces, and cage washes were collected every 24 h. Air samples were analyzed for [^{14}C]. One rat was killed and necropsied on Day 8 after administration, two on Day 14, and one on Day 22. Trimethyl Pentanyl Diisobutyrate was rapidly absorbed and excreted, with renal excretion accounting for 47% to 72% of the dose within 5 to 10 days of dosing; the greatest portion of the urinary radioactivity was eliminated in the first 72 h. Radioactivity in the feces accounted for 14% to 31% of the dose; fecal elimination was virtually complete by 7 days after dosing with the majority isolated after 48 h. No radio-labeled CO_2 was detected. Total excretion was 95% to 99% of the dose. The majority of the recovered Trimethyl Pentanyl Diisobutyrate was in the form of metabolites. The amount of residual radioactivity in the tissues was similar to controls.

Rats (strain and n not specified) were orally administered unlabeled Trimethyl Pentanyl Diisobutyrate (475 mg/kg) and fecal samples were collected and extracted with acetone after 24 h (method of administration not specified).[35] Analysis of the extract showed that 8% to 36% of the dose remained as Trimethyl Pentanyl Diisobutyrate, 18% to 27% was the monoester, and trace amounts of TMPD were detected. In urine, Trimethyl Pentanyl Diisobutyrate, TMPD, the monoester of TMPD, and conjugates of TMPD and 2,2,4-trimethyl-3-hydroxyvaleric acid were detected. Concentrations were not quantified.

Rats (strain and n not specified) were orally administered unlabeled Trimethyl Pentanyl Diisobutyrate (196 or 208 mg/kg).[35] At 48 h after dosing, the major urinary metabolite was the *O*-glucuronide of TMPD (72% to 73% of the dose). Other compounds detected in the urine were the sulfate (6.4% to 6.5%) and free forms of TMPD (1% to 1.7%), and free 2,2,4-trimethyl-3-hydroxyvaleric acid (3%) and its glucuronide (4.3% to 4.4%).

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

Dermal

Neopentyl Glycol Diisononanoate

The acute dermal toxicity of undiluted [Neopentyl Glycol Diisononanoate] was evaluated using 10 SD CD strain rats (5 males and 5 females).[4] A dose of 2000 mg/kg body was applied…. None of the animals died and there were no signs of systemic toxicity or dermal irritation. Necropsy findings were not indicative of any abnormalities and an LD_{50} of > 2000 mg/kg was reported.

Acute dermal toxicity studies are summarized in Table 9.

The dermal LD_{50} of Trimethyl Pentanyl Diisobutyrate was reported to be > 20 mL/kg in guinea pigs and > 2000 mg/kg in rabbits.[7,18,34] Clinical signs were: instances of diarrhea, few feces, and soiling of the anogenital area. Glycol Distearate was not toxic to rabbits at 100%.[5]

Oral

Neopentyl Glycol Diisononanoate

The acute oral toxicity of undiluted [Neopentyl Glycol Diisononanoate] was evaluated using groups of 4 SD CD rats.[4] One group was dosed orally with 300 mg/kg and the remaining 2 groups were dosed with 2000 mg/kg. None of the animals died, and there were no signs of systemic toxicity in any of the 3 groups. Necropsy did not reveal any abnormal findings and an LD_{50} of > 2000 mg/kg body weight was reported.

Glycol Distearate

Glycol Distearate [has] been tested in [four] studies for acute oral toxicity in rats….[3] During the various studies, doses of 13 or more g/kg body weight [13,000 mg/kg] in corn oil produced effects which included diarrhea, wet oily coats, and nasal hemorrhage; the symptoms appeared within four days following administration, but disappeared within the next six days. No animals were dosed with high levels of corn oil alone. One study on Glycol Distearate reported that at the 14-day gross autopsy [necropsy], the stomach contained residues which appeared to be the test material.

Acute oral toxicity studies are summarized in Table 9.

The oral LD_{50} of Trimethyl Pentanyl Diisobutyrate was reported to be > 2000 mg/kg in rats.[7,18,34] Clinical signs included moderate weakness and some vasodilatation. No clinical abnormalities were observed in mice administered up to 6400 mg/kg by gavage.[7,18,34] The oral LD_{50} of Diethylpentanediol Dineopentanoate was estimated to be ≥ 2500 mg/kg in rats.[16,36] The oral LD_{50} of Glycol Distearate for mice was reported to be > 5000 mg/kg.[5,37] The oral LD_{50} of Neopentyl Glycol Dicaprate was reported to be > 2000 mg/kg in rats.[17] The oral LD_{50} of Neopentyl Glycol Diethylhexanoate was reported to be > 2000 mg/kg in rats and > 1880 mg/kg in mice.[9] No mortalities or clinical signs of toxicity were observed when rats were orally administered a single dose of Neopentyl Glycol Diheptanoate (2000 mg/kg).[8]

Inhalation

Acute inhalation toxicity studies are summarized in Table 9.

In rats, the lowest lethal concentration (LC_{lo}) of Trimethyl Pentanyl Diisobutyrate was reported to be > 0.12 mg/L in one 4-h inhalation toxicity test and 5.30 mg/L in another.[7,18,34] The acute inhalation LC_{50} of Neopentyl Glycol Diheptanoate was reported to be > 5.22 mg/L in rats exposed to the test substance for 4 h; clinical signs included hunched posture, increased respiratory rate, and piloerection.[6,8]

Short-Term Toxicity Studies

Dermal

Glycol Distearate

Two formulations [containing Glycol Distearate] were tested for 28 days.[3] The concentration of Glycol Distearate ranged from 0.05% to 0.5%. Following complete gross and microscopic examination, including hematology, there was no evidence of systemic toxic effects.

A separate but similar 28-day study reported on two formulations containing Glycol Distearate at a concentration in the range of 0.05-0.4%. … The report noted no "gross necropsy or microscopic alterations" in the tissue related to the test.

A shampoo containing 1-3% Glycol Distearate was applied at concentrations of 0.05% and 0.3% to 10 animals [rabbits] (five male and five female) at each concentration. After four weeks, there were no systemic effects or deaths resulting from the application of the test compound….

Oral

Trimethyl Pentanyl Diisobutyrate

In a preliminary combined repeated dose/reproductive and developmental toxicity study, male and female Sprague-Dawley rats (n not specified) were exposed by gavage to Trimethyl Pentanyl Diisobutyrate (0, 500, 750, or 1000 mg/kg/day; 0.5 mL/100g body weight) for 2 weeks.[7,34] There were increases in the liver weights of both sexes in the 500, 750, and 1000 mg/kg/day groups and in the kidney and adrenal gland weights of both sexes in the 750 and 1000 mg/kg/day groups.

In three feeding experiments conducted concurrently, Trimethyl Pentanyl Diisobutyrate (0.0, 0.1% and 1.0%) was administered to albino Holtzman rats (n = 10/sex/group) for 51 to 99 days.[7] Experiment 1: three groups were given diets containing Trimethyl Pentanyl Diisobutyrate (0, 0.1% and 1.0%) together with 5.0% corn oil for 51 days; these rats were killed and necropsied without further treatment. Experiment 2: three groups were given diets containing Trimethyl Pentanyl Diisobutyrate (0, 0.1% and 1.0%) for 99 days [See Subchronic Toxicity Studies.]. Experiment 3: four groups, with the first two of the groups fed diets containing Trimethyl Pentanyl Diisobutyrate (0.1% and 1.0%) for 52 days, followed by a 47-day recovery period; the next two groups were given the control diet for 52 days, followed by 47 days in which the rats were fed diets containing Trimethyl Pentanyl Diisobutyrate (0.1% and 1.0%). The control group from Experiment 2 was used as a control group for Experiment 3.

There were no test-substance related mortalities, and all rats exhibited normal appearance and behavior throughout the study. Feed consumption and utilization were not affected. In Experiment 1, the minimal reduction (< 10%) in body weight gain in the groups administered Trimethyl Pentanyl Diisobutyrate at 1.0% was not statistically significantly different compared with controls. Liver weights, relative to body weight, were slightly increased in rats consuming all of the 1.0% Trimethyl Pentanyl Diisobutyrate diets, but much of the increase was attributed to the slightly lower body weights of the treated rats. Relative kidney weights were increased only for rats on the 52-day feeding regimen, and the increase was considered to have no toxicological significance. No biologically significant differences were observed among groups in hematology or clinical chemistry determinations. No morphologic evidence of toxicity was observed in any of the rats at necropsy or on microscopic examination of tissues from multiple organ systems. The authors considered 1.0% Trimethyl Pentanyl Diisobutyrate administered in the diet to be the no-observed-adverse-effect-level (NOAEL) in both male and female rats under all conditions in this study.

In the livers of the male and female rats fed 1.0% Trimethyl Pentanyl Diisobutyrate in the diet for 51 days, there was an increase in *p*-nitroanisole demethylase, uridine phosphorylase (UDP)-aminophenol, and UDP-bilirubin glucuronyl transferase activities, while glucose-6-phosphatase activity remained at control levels. When both sexes were treated with 1.0% Trimethyl Pentanyl Diisobutyrate in the diet for 52 days and then returned to the control diet for 47 days, *p*-nitroanisole demethylase and bilirubin glucuronyl transferase activities returned to control levels. It was concluded that the repeated exposure to high doses of Trimethyl Pentanyl Diisobutyrate caused reversible adaptive changes in the livers of male and female rats. Increases in enzymatic activity observed at high oral doses were reversed and returned to control levels when Trimethyl Pentanyl Diisobutyrate was removed from the diet.[7]

In a combined repeated dose and reproductive/developmental toxicity study, Trimethyl Pentanyl Diisobutyrate (0, 30, 150 and 750 mg/kg/day in corn oil) was administered to Sprague-Dawley rats (n = 12/sex) by gavage for 44 (males) or 40 to 53 (females) consecutive days.[7,18,34] The control group received corn oil. [See the Developmental and Reproductive Toxicity section for results related to reproduction.] All rats survived and there were no treatment-related clinical signs. Slight decreases in body weight gain were observed in the 750 mg/kg/day males, but no changes in feed consumption were identified. Slight increases in feed consumption were observed in females, but the relationship to the test substance was not clear. Hematology and serum clinical chemistry parameters, evaluated in the males, showed no hematological effects. Serum clinical chemistry changes (including increased serum protein, creatinine, and bilirubin) in the 150 and 750 mg/kg/day males suggested an effect on the liver and kidneys. Other serum chemistry changes in males of one or more groups included increased albumin, calcium, and inorganic phosphorus, and decreased serum glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), chloride, and *gamma*-glutamyl transpeptidase. These latter findings were not considered to be suggestive of a toxic effect on any particular organ system. Organ weight differences that were considered to be related to the test substance included increased relative liver weights in 150 and 750 mg/kg/day males, increased absolute liver weights in 750 mg/kg/day males, increased absolute and relative kidney weights in 150 and 750 mg/kg/day males, and increased absolute and relative liver weights in 750 mg/kg/day females. Histopathological examination revealed necrosis of the proximal tubules, dilatation of distal tubules, and fibrosis in the kidneys and centrilobular swelling of hepatocytes in the livers of males in the 750 mg/kg/day group. Basophilic tubules and hyaline dilatation were present in kidneys of males from all dose groups, were enhanced in a dose-dependent manner in the 150 and 750 mg/kg/day groups, and were considered related to the test substance. The NOAEL for repeat oral administration of Trimethyl Pentanyl Diisobutyrate under the conditions of this study was reported to be 30 mg/kg/day for males and 150 mg/kg/day for females.

Subchronic Toxicity Studies

Dermal

Glycol Distearate

Two formulations [containing Glycol Distearate] were tested [on rats] for 91 days.[3] The concentration of Glycol Distearate applied to the animals ranged from 0.05% to 0.5%. No evidence of treatment-induced systemic effects was observed.

Oral

Trimethyl Pentanyl Diisobutyrate

In a feeding study, CD[Crl:CD(SD)] rats (n = 20/sex) were exposed to Trimethyl Pentanyl Diisobutyrate (0, 30, 150 or 750 mg/kg/day) in feed for 90 days.[7,34] The rats were then killed and necropsied. There were no test substance-related mortalities, clinical signs, or neurobehavioral abnormalities. In the high-dose male group, kidney weights were increased along with an increased presence of hyaline droplets and an increased incidence of chronic progressive nephropathy. Other observed effects that were not considered to be adverse included: hyaline droplets in all groups of treated males, minimal decreases in body weight gain, and clinical chemistries indicative of a possible effect on the liver in both high-dose males and females (these were not found to be correlated with microscopic examination). In male rats, the lowest-observed-effect-level (LOEL) was reported to be 750 mg/kg/day, and the NOAEL was reported to be 150 mg/kg/day. The NOAEL in female rats was reported to be 750 mg/kg/day.

In three feeding experiments conducted concurrently (described above in Short-Term Toxicity Studies, Oral), Trimethyl Pentanyl Diisobutyrate (0.0, 0.1% and 1.0%) was administered to albino Holtzman rats (n = 10/sex/group) for up to 99 days.[7] In the subchronic portion of the experiment, three groups were administered diets containing Trimethyl Pentanyl Diisobutyrate (0, 0.1% and 1.0%) for 99 days.

There were no test substance-related mortalities, and all rats exhibited normal appearance and behavior throughout the study. Feed consumption and utilization were not affected. The reduction (< 10%) in growth in the groups administered Trimethyl Pentanyl Diisobutyrate at 1.0% was not statistically significant. Liver weights, relative to body weights, were slightly increased in animals consuming the 1.0% diet immediately before the end of the experiment, but much of the increase was attributed to the rats' slightly lower body weights. No biologically-significant differences were observed among groups in hematology or clinical chemistry determinations. No morphologic evidence of toxicity was observed in any of the rats at necropsy or on microscopic examination of tissues from multiple organ systems. Analysis of the livers showed that when Trimethyl Pentanyl Diisobutyrate (0.1% and 1%) was fed to both sexes for 99 days, *p*-nitroanisole demethylase activity increased for both sexes at the high dose, while bilirubin glucuronyl transferase activity was elevated only in high-dose females. The authors considered 1.0% Trimethyl Pentanyl Diisobutyrate administered in the diet to be the NOAEL in both male and female rats under all conditions in this study.[7]

In a feeding study, albino Holtzman rats (n = 10/sex) were given Trimethyl Pentanyl Diisobutyrate (0.1% and 1.0% in feed) for 102 days.[7,34] The average estimated dosage rates over 100 days for the low-dose group was 75.5 and 83.5 mg/kg/day for males and females, respectively, and 772 and 858.5 mg/kg/day for the high-dose group, respectively. The rats were killed and necropsied on day 103. There were no test-substance related mortalities; one female rat was euthanized on Day 55 because of weight loss and signs of a respiratory infection. Rats in all groups demonstrated normal growth, and there were no differences in feed consumption or utilization. The rats also exhibited normal appearance and behavior throughout the study. No differences were observed among groups in hematology results. Slightly increased liver weights were observed in the 1.0% group of males relative to the control group, but differences were considered likely to be adaptive by the authors and not representative of a toxic effect. Kidney weights were decreased relative to controls in both the 0.1% and 1.0% groups of females, but the effect was attributed to unusually high kidney weights in the control group. No morphologic evidence of toxicity was found in any of the animals during gross necropsy or upon microscopic examination of a number of tissues from multiple organ systems. The authors considered 1.0% in the diet to be a NOAEL in both male and female rats.

In a feeding study, Beagle dogs (n = 4/sex) were administered Trimethyl Pentanyl Diisobutyrate (0, 0.1%, 0.35%, or 1.0% in feed) for 90 days.[7,34] All dogs survived, neurological reflexes were unimpaired, and no abnormal clinical signs or behavioral abnormalities were observed at any time. Weight gain and feed consumption were unaffected by treatment, and there were no abnormalities noted in a series of hematology, clinical chemistry, or urinalysis parameters measured during and at the end of the study. Slight alterations noted in some organ weights were within normal limits and were not considered toxicologically important. Gross and microscopic pathology findings were unremarkable. The NOAEL for both male and female dogs was reported to be 1.0%.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral Exposure

Trimethyl Pentanyl Diisobutyrate

In a reproductive/developmental toxicity study, conducted in accordance with Organization for Economic Co-operation Guidelines (OECD GL) 421 (Reproduction/Developmental Toxicity Screening Test), Trimethyl Pentanyl Diisobutyrate (0, 1.5, 4.5, or 15.0 mg/g feed) was administered to Sprague-Dawley (Crl:CD(SD)IGS BR) rats (n = 12/sex) *ad libitum* in the diet.[7,34] The female rats were treated over 4 phases of the study for a total of 40 to 51 days: premating (14 days), mating (1 to 8 days), gestation (21 to 23 days), and early lactation (4 to 5 days). All male rats were treated from the beginning of the premating period to the final treatment of the female rats for a total of 51 days. Females that delivered a litter, and their offspring, were killed on days 4 or 5 postpartum. Females that had evidence of mating but did not deliver were killed on gestation day (GD) 23. The final calculated dosage rate was approximately 0, 91, 276 and 905 mg/kg/day for male rats and 0, 120, 359 and 1135 mg/kg/day for female rats, respectively.

For the females in the high-dose group, there was a decrease in total number of implants, number of live pups on postnatal

day 4, and litter weights on postnatal days 0 and 4. There were no adverse effects on reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, percent pup survival, pre- and post-implantation loss, live and dead pups on postnatal day 0, percentage of male and female pups, mean pup body weight and pup body weight change, or reproductive organ weights in the adults. Reductions in body weight and feed consumption values in the high-dose group adults were transient and were not considered toxicologically significant. For the males, there were minimal reductions in sperm counts observed in the testes and/or epididymis of treated male rats, but there were no treatment-related gross or microscopic lesions in any groups and no adverse effect on reproductive performance. The NOAEL for developmental or reproductive toxicity was reported to be 4.5 mg/g feed in the diet, which was equivalent to 276 mg/kg/day for males and 359 mg/kg/day for females.[7,34]

In a combined repeated dose and reproductive/developmental toxicity study, Trimethyl Pentanyl Diisobutyrate (0, 30, 150 and 750 mg/kg/day in corn oil) was administered to Sprague-Dawley rats (n = 12/sex) by oral gavage for 44 (males) or 40 to 53 (females) days beginning prior to mating.[7,18,34] [See the Subchronic Toxicity Studies section for results related to repeated dose toxicity.] The control group received corn oil. All rats survived and there were no treatment-related clinical signs. One mating pair in the mid- and high-dose groups failed to copulate. Slight increases in feed consumption were observed in females during the gestation period only, but there was no clear relationship to the test substance. There were no gross or microscopic effects observed on any reproductive organ in either sex. All pregnant rats delivered normally and there were no adverse effects on any reproductive parameters observed. A decrease in estrous cycle length in the high-dose female group, compared to controls, was attributed to a larger than normal number of rats in the high-dose group with shorter cycle lengths; there were no differences when data for this study were compared to historical control data (mean estrous cycle 4.0 to 4.4 days for the previous 3 years). The NOAEL for reproductive toxicity of Trimethyl Pentanyl Diisobutyrate under the conditions of this study was reported to be 750 mg/kg/day for male and female rats. There were no treatment-related effects observed in the external examination of pups born, mortalities were similar across the groups, and pup body weights increased until sacrifice on day 4 of lactation. Necropsy of stillborn pups, dead pups, and pups surviving until day 4 of lactation did not demonstrate any treatment-related effects. The NOAEL for embryo/fetal toxicity was reported to be 750 mg/kg/day.

In a study conducted in accordance with OECD TG 414 (Prenatal Developmental Toxicity Study), pregnant Sprague-Dawley Crl:CD(SD) rats (n = 25) were given Trimethyl Pentanyl Diisobutyrate (0, 0.15%, 0.45%, or 1.50%) in feed on GD 6 through 20.[7] The dosage rates were calculated to be 0, 118, 343 and 1077 mg/kg/day, respectively. There were no mortalities among the dams. One female in each test group was not gravid. Net body weight gain in the high-dose group was lower than the control group. There were no macroscopic test substance-related observations reported. There were no adverse effects on the number of corpora lutea, implantation sites, viable fetuses or early/late resorptions observed. There were no dead fetuses in any group. The mean male, female, and combined fetal weights in the high-dose group were lower than those of the control group. However, these weights were within the laboratory's historical control data range for these study types. Because of lower body weight gains and/or body weight loss, the NOAEL for maternal toxicity was reported to be 343 mg/kg/day.

There were no test substance-related external and visceral malformations or developmental variations observed. When the total malformations and developmental variations were evaluated on a proportional basis, no differences from the control group were noted. Test substance-related skeletal malformations (bent scapula) were noted in one fetus from the mid-dose group and in 4 fetuses (3 litters) from the low-dose group. There was a higher mean litter proportion of the skeletal developmental variation in sternebra(e) nos. 5 and/or 6 (unossified) was observed in the high-dose group. The litter proportion of bent rib(s) was considered by the authors to represent skeletal variations rather than malformations. Based on lower mean fetal body weights at 1.50% (1077 mg/kg/day), an exposure level of 0.45% (343 mg/kg/day) was reported to be the NOAEL for embryo/fetal development for Trimethyl Pentanyl Diisobutyrate in the diet of rats.[7]

Glycol Distearate

In a study conducted in accordance with OECD TG 414 (Prenatal Developmental Toxicity Study) and EU Method B.31 (Prenatal Developmental Toxicity Study), Glycol Distearate (0, 100, 300, or 900 mg/kg/day; as a C16-18 mixture) was administered by gavage to pregnant Sprague-Dawley CD rats (n = 24) on GD 6 through 15.[5] The control group received 0.5% sodium carboxymethylcellulose and 0.25% Cremophor® in distilled water. The dams were killed and necropsied on GD 20. The pups were examined for litter size and weights, viability, sex ratio, and grossly visible abnormalities. The pups were also examined for external, visceral, and skeletal abnormalities. There were no mortalities during the study period. No Glycol Distearate-related symptoms were observed in the treatment groups when compared to the control group. Body weights, body weight gains, and corrected body weights were within expected ranges. There were no differences observed among the mean reproduction data of the test groups compared to the control group. Necropsies revealed no macroscopic changes in the dams of the treatment groups. No test substance-related effects were observed in the treatment groups. Pre-implantation loss, post-implantation loss, mean number of resorptions, embryonic deaths, and total fetuses were not affected by treatment. No treatment-related fetal abnormalities were found at necropsy. The NOAEL for maternal toxicity was reported to be > 900 mg/kg/day. The teratogenicity NOAEL was reported to be > 900 mg/kg/day.

GENOTOXICITY STUDIES

In Vitro

Neopentyl Glycol Diisononanoate

The Ames test was…used to evaluate the mutagenicity of [Neopentyl Glycol Diisononanoate] (in acetone; doses up to 5000 µg/plate) in the Salmonella typhimurium *strains…[TA1535, TA1537, TA98, TA100, and TA102].*[4] *Results were negative with and without metabolic activation.*

In vitro genotoxicity studies of monoalkylglycol dialkyl acid esters are summarized in Table 10.

Trimethyl Pentanyl Diisobutyrate was not mutagenic in mammalian cell mutation assays (up to 2000 µg/mL), Ames tests using *Salmonella typhimurium* and *Escherichia coli* (up to 5000 µg/plate), and a mammalian chromosome aberration test (up to 1000 µg/mL).[5,7,18,34] Diethylpentanediol Dineopentanoate was not mutagenic in an Ames test up to 5000 µg/plate.[16,36] Glycol Distearate was not mutagenic in Ames tests up to 5000 µg/plate.[5,37] Neopentyl Glycol Dicaprate was not mutagenic at up to 5000 µg/plate in an Ames test.[17] Neopentyl Glycol Diethylhexanoate was not mutagenic in a mammalian cell mutation assay (up to 600 µg/mL), an Ames test (up to 5000 µg/plate), and mammalian chromosome aberration tests (up to 100 µg/mL).[9] Propanediol Dicaprylate/Caprate was not mutagenic in an Ames test at 0.005 mL/plate.[38]

CARCINOGENICITY STUDIES

Carcinogenicity data were not found in the published literature and no unpublished data were provided.

OTHER RELEVANT STUDIES

Endocrine Activity

Trimethyl Pentanyl Diisobutyrate (0.001, 0.01, 0.1 or 1 mM) was tested for endocrine receptor agonist and antagonist activity in multiple cell lines.[39] The cells were exposed for 24 to 48 h (depending of the cell line). The cells tested were: a transfected estrogen receptor (ER) cell line (MCF7-ER) used to assess the potential for interactions with a human estrogen receptor (hER2); and cell lines, tailored for luciferase illumination with gene expression, containing the human peroxisome proliferator-activated receptor (hPPARy), human thyroid ß receptor (hTR ß), human estrogen receptor (hER1), and mouse aryl hydrocarbon receptor (mAhR). The results were positive for hER1 agonist activity with > 50% response (response exceeded 50% of the maximal standard induction or response was clearly dose related). Positive results were also observed for hER2 agonist activity in the transfected MCF7-ER cells, with a >10% response. The results were negative for mAhR, hPPARy, and hTR ß agonist activity in the activated luciferase cell lines. All cell lines were negative for endocrine receptor antagonism.

IRRITATION AND SENSITIZATION STUDIES

Irritation

Glycol Distearate

Two formulations [containing Glycol Distearate] were tested for 28 days [in rabbits].[3] *The concentration of Glycol Distearate ranged from 0.05% to 0.5%. According to the report, the skin irritation that was caused by the surfactant ranged from slight to severe.*

A separate but similar 28-day study reported on two formulations containing Glycol Distearate at a concentration in the range of 0.05-0.4%. Investigators associated both formulations with the development of primary irritation. The report noted no "gross necropsy or microscopic alterations" in the tissue related to the test.

A shampoo containing 1-3% Glycol Distearate was applied at concentrations of 0.05% and 0.3% to 10 animals [rabbits] (five male and five female) at each concentration. Slight transient skin irritation was observed in one rabbit at the 0.05% level and in most animals at the 0.3% level.

Draize type procedures were used to test…Glycol Distearate for primary irritation of albino rabbit skin; the ingredients were found to be nonirritating to slightly irritating…. In addition, when … Glycol Distearate [was] tested for corrosivity according to the procedures of the U.S. Department of Transportation, [it was] found to be noncorrosive to rabbit skin.

A shampoo formulation containing Glycol Distearate was tested in three separate experiments on groups containing six rabbits each (three males and three females). A fourth experiment involved similar procedures, but had five male and five female rabbits per group. The material was applied daily, five days per week to intact or abraded skin equivalent to 10% of the skin area of the back; this remained on the animal for seven hours each day before washing. [The shampoo was practically non-irritating.]

Two formulations were tested for 91 days. The concentration of Glycol Distearate applied to the animals [rabbits] ranged from 0.05% to 0.5%. The skin irritation that resulted was reported to be similar to that produced by other forms of shampoo.

Neopentyl Glycol Diisononanoate

Predictive human [n = 52] skin irritation tests results for undiluted … [Neopentyl Glycol Diisononanoate] were negative….[4]

Animal

Irritation assays are summarized in Table 11.

Trimethyl Pentanyl Diisobutyrate was not irritating to guinea pigs at 100% and was not, or was mildly, irritating to rabbits at 100%.[7,34] Diethylpentanediol Dineopentanoate (neat) was a non-irritant to rabbit skin.[16,36] Glycol Distearate was not irritating to rabbits and guinea pigs at up to 100%.[5,37] Neopentyl Glycol Diethylhexanoate (concentration not specified, tested neat) was not irritating to the skin of rabbits.[9] There were no signs of erythema or edema observed when Neopentyl Glycol Diheptanoate was administered to rabbits at 100%.[8]

Human

NEOPENTYL GLYCOL DICAPRATE

In a human patch test (n = 21 females, 2 males), Neopentyl Glycol Dicaprate (neat) was administered using Finn chambers for 30 to 60 min and 24-h.[17] There were no signs of irritation in any subject at any time period.

DIETHYLPENTANEDIOL DINEOPENTANOATE

In a human patch test (n = 45), Diethylpentanediol Dineopentanoate (neat; 1 mg) was dermally administered in Finn chambers, under occlusion, for 24 h.[16,36] The test sites were examined at 1 and 24 h after removal. No reactions were observed in any of the subjects. The test substance was a non-irritant.

Sensitization

Glycol Distearate

Sensitization studies were conducted in guinea pigs on Glycol Stearate and Glycol Distearate.[3] Each ingredient was injected intradermally into the shaven back of each of two male, white guinea pigs. Following an initial 0.05 mL injection, 0.1 mL injections were given three times a week for a total of ten injections. Two weeks later a challenge injection was given, and readings were taken 24 hours later. Both ingredients were found to be nonsensitizing [at 0.1%].

A repeated insult patch test with 50% w/v Glycol Distearate in mineral oil was performed on 125 subjects ranging in age from 19 to 76 years.[3] Patches containing 0.25 g of [*the*] *sample were applied for 24 h to the dorsal aspect of the upper arm of each individual. Patches were applied to the same site each Monday, Wednesday, and Friday of the three-week induction period. Each site was scored for irritation a total of nine times. Challenge patches were applied to both arms of each subject 14 days after the final insult patch; the sites were graded for sensitization reactions after 48 and 96 h. No visible skin changes characteristic of irritation or sensitization were observed in any subject; all scores were zero.*

Neopentyl Glycol Diisononanoate

A maximization test on [Neopentyl Glycol Diisononanoate] was performed ….[4] Undiluted test material was applied during the second induction and challenge phase. Initially, the skin was treated with SLS [sodium laurel sulfate] because topical induction with undiluted [Neopentyl Glycol Diisononanoate] did not induce skin irritation in a preliminary experiment. Neopentyl [Glycol Diisononanoate] was classified as a nonsensitizer.

Animal

Animal sensitization studies are summarized in Table 12.

In two skin sensitization studies, Trimethyl Pentanyl Diisobutyrate at 1% was not sensitizing in guinea pigs.[7,34] In a guinea pig maximization test, Diethylpentanediol Dineopentanoate was not sensitizing to albino guinea pigs when injected with Diethylpentanediol Dineopentanoate at 25% (in paraffin oil with Freund's complete adjuvant), then applied topically at 100%; the challenge was a topical application at 100%.[16,36] Glycol Distearate (100%) was not sensitizing in a Buehler test in Pirbright guinea pigs.[5] In a sensitization assay conducted in accordance with OECD TG 406, Glycol Distearate (concentration not specified, assumed 100%) was not sensitizing to guinea pigs.[37] In a test conducted in a manner similar to that described in OECD TG 406, Neopentyl Glycol Diheptanoate was not sensitizing to Dunkin-Hartley guinea pigs.[6,8] The induction phase was conducted using a concentration of 100% Neopentyl Glycol Diheptanoate and the challenge at 30% in corn oil and 100%.

Human

Summaries of human repeated insult patch tests (HRIPTs) are summarized in Table 13.

Trimethyl Pentanyl Diisobutyrate and Neopentyl Glycol Diethylhexanoate were not sensitizers in multiple HRIPTs at up to 100%.[7,9,34,40,41] Propanediol Dicaprylate/Caprate and Propanediol Dipelargonate were not sensitizers in HRIPTs.[42,43]

OCULAR IRRITATION STUDIES

Neopentyl Glycol Diisononanoate

A study evaluating the ocular irritation potential of [Neopentyl Glycol Diisononanoate] in rabbits was conducted… [Neopentyl Glycol Diisononanoate] (0.1 mL) … was classified as a minimal ocular irritant.[4]

In Vitro

Neopentyl Glycol Dicaprate (25% in corn oil) was predicted to have practically no irritation potential in a hen's egg test-chorio-allantoic membrane (HET-CAM) assay.[17] Propanediol Dicaprylate/Caprate (100%) was tested for potential ocular irritation using the EpiOcular™ in vitro assay.[44] Exposures were for 20 min and 1 and 4 h. The estimated Draize ocular irritation score was 0 and the test substance was classified as non-irritating.

Animal

Ocular irritation studies using rabbits are summarized in Table 14.

Trimethyl Pentanyl Diisobutyrate, Glycol Distearate, Neopentyl Glycol Diethylhexanoate, and Neopentyl Glycol Diheptanoate were not ocular irritants at 100% in rabbits.[5,7-9,34] Diethylpentanediol Dineopentanoate (undiluted) was a minimal ocular irritant in rabbits.[16,36]

CLINICAL STUDIES

Retrospective and Multicenter Studies

Glycol Distearate

Occupational Exposure: *Two manufacturers reported that they have been manufacturing Glycol Stearates and Glycol Distearates for between 20 and 30 years.[3] According to both, no employee reported that his or her health might have been adversely affected by exposure to these compounds. This conclusion was based upon: (a) 30 employees who for 10 years had potentially been exposed to Glycol Stearate for 1 % of their work time; (b) 70 employees who for 20 years had potentially been exposed to Glycol Distearate for 20% of their work time; and (c) 50 employees who for 30 years had potentially been exposed to Glycol Stearate for 5% of their work time. One manufacturer noted that its labor turnover was very low, so that some individuals had been exposed to the ingredients for many of the years during which they had been produced there.*

SUMMARY

This is a safety assessment of 28 monoalkylglycol dialkyl acid esters as used in cosmetics. The Panel has reviewed related ingredients, moieties, and component parts of these ingredients that have been previously reviewed by CIR. The ingredients in this report are structurally-related alkyl esters of monoalkyl diols that vary by type of diol and length of the carboxylic acid residues.

The most common cosmetic function for this group of ingredients is as a skin conditioning agent. Other reported functions of these ingredients include film former, hair conditioning agent, opacifying agent, plasticizer, slip modifier, solvent, surface modifier, and viscosity increasing agent – nonaqueous.

According to VCRP survey data received in 2017, Glycol Distearate was reported to be used in 1663 formulations, mostly in hair products (1041 formulations); this is an increase from 28 uses in 2001. Trimethyl Pentanyl Diisobutyrate and Neopentyl Glycol Diheptanoate are used in 399 (all nail products) and 415 (mostly in skin care products) formulations, respectively. The rest of the ingredients with reported uses were used in 102 or fewer formulations. As for the other ingredients that were previously reviewed by CIR, Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate and Neopentyl Glycol Diisononanoate had no uses reported to the VCRP in 2001 or 2017.

The results of the concentration of use survey conducted by the Council in 2016 indicate Neopentyl Glycol Diethylhexanoate had the highest reported maximum concentration of use; it is used at up to 57% in the categories of face and neck products and body and hand products. Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use in leave-on formulations; it is used up to 40% in lipsticks. In 2001, Glycol Distearate was reported to be used at up to 9% in rinse-off products and up to 6% in leave-on products; in 2016, the maximum concentrations of use were reported to have increased to 10% in hair products and 13.1% in eye liners, respectively.

In rats, orally administered, radio-labeled Trimethyl Pentanyl Diisobutyrate was rapidly absorbed and excreted, with renal excretion accounting for the majority of the recovered radioactivity. In urine, Trimethyl Pentanyl Diisobutyrate, 3-[^{14}C]-TMPD, and conjugates of TMPD and 2,2,4-trimethyl-3-hydroxyvaleric acid were detected. No radioactivity was detected in CO_2.

The dermal LD_{50} of Trimethyl Pentanyl Diisobutyrate was reported to be > 20 mL/kg in guinea pigs and > 2000 mg/kg in rabbits. Clinical signs were: diarrhea, few feces, and soiling of the anogenital area. Glycol Distearate was not toxic to rabbits at 100%.

The oral LD_{50} for Trimethyl Pentanyl Diisobutyrate was reported to be > 2000 mg/kg in rats. Clinical signs included moderate weakness and some vasodilatation. No clinical abnormalities were observed in mice administered up to 6400 mg/kg by gavage. The oral LD_{50} of Diethylpentanediol Dineopentanoate was reported to be ≥ 2500 mg/kg in rats. The oral LD_{50} for Glycol Distearate in rats was reported to be > 5000 mg/kg. At 13,000 mg/kg and above, diarrhea, wet oily coats, and nasal hemorrhage were observed within 4 days after dosing, which resolved Day 10. The oral LD_{50} for mice was reported to be > 5000 mg/kg. In another study in rats, there were no mortalities at up to 16,000 mg/kg; at 13,000 mg/kg and above, diarrhea, wet oily coats, and nasal hemorrhage were observed within 4 days after dosing, which resolved Day 10. The oral LD_{50} of Glycol Distearate was reported to be > 5000 mg/kg in mice. The oral LD_{50} of Neopentyl Glycol Diethylhexanoate was reported to be > 2000 mg/kg in rats and > 1880 mg/kg in mice. No mortalities or clinical signs of toxicity were observed when rats were orally administered a

single dose of Neopentyl Glycol Diheptanoate (2000 mg/kg).

In rats, the LC_{lo} of Trimethyl Pentanyl Diisobutyrate was reported to be > 0.12 mg/L in one 4-h inhalation toxicity test and 5.30 mg/L in another. The acute inhalation LC_{50} of Neopentyl Glycol Diheptanoate was reported to be > 5.22 mg/L in rats; clinical signs included hunched posture, increased respiratory rate, and piloerection.

Rats orally exposed to Trimethyl Pentanyl Diisobutyrate for 2 weeks showed increases in the liver weights of both sexes in the 500, 750, and 1000 mg/kg/day groups and in the kidney and adrenal gland weights of both sexes in the 750 and 1000 mg/kg/day groups. The NOAEL was reported to be 1.0% in both male and female rats administered Trimethyl Pentanyl Diisobutyrate in feed for up to 99 days. The oral NOAEL for Trimethyl Pentanyl Diisobutyrate was reported to be 30 mg/kg/day for males (44 days) and 150 mg/kg/day for females (40 to 53 days). All rats survived and there were no treatment-related clinical signs.

In male rats, the LOEL was reported to be 750 mg/kg/day and the NOAEL was reported to be 150 mg/kg/day for Trimethyl Pentanyl Diisobutyrate administered in feed for 90 days; the NOAEL in female rats was reported to be 750 mg/kg/day. The NOAEL in both male and female rats was reported to be 1.0% in a feeding study of Trimethyl Pentanyl Diisobutyrate administered for 102 days. There were no test-substance related mortalities and the rats also exhibited normal appearance and behavior throughout the study. The NOAEL for both male and female beagles was reported to be 1.0% in a feeding study of Trimethyl Pentanyl Diisobutyrate administered for 90 days. All dogs survived, neurological reflexes were unimpaired, and no abnormal clinical signs or behavioral abnormalities were observed at any time.

The NOAEL of Trimethyl Pentanyl Diisobutyrate for developmental or reproductive toxicity was reported to be 4.5 mg/g feed (equivalent to 276 mg/kg/day for males and 359 mg/kg/day for females) in the diet of rats administered from 14 days prior to mating through early lactation. For the females in the high-dose group, there was a decrease in total number of implants, number of live pups on postnatal day 4, and litter weight on postnatal days 0 and 4. There were no adverse effects on reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, percent pup survival, pre- and post-implantation loss, live and dead pups on postnatal day 0; percentage of male and female pups, mean pup body weight and pup body weight change, or reproductive organ weights in the adults. For the males, there were minimal reductions in sperm counts observed in the testes and/or epididymides of treated male rats, but there were no treatment-related gross or microscopic lesions in any groups and no adverse effect on reproductive performance.

The NOEL for reproductive toxicity of Trimethyl Pentanyl Diisobutyrate in a combined repeated dose and reproductive/developmental toxicity study was reported to be 750 mg/kg/day for male and female rats. The NOEL for Trimethyl Pentanyl Diisobutyrate administered throughout pregnancy for embryo/fetal toxicity was reported to be 750 mg/kg/day in rats. All pregnant rats delivered normally and there were no adverse effects on any reproductive parameters observed. In another study, due to lower body weight gains and/or body weight loss, the NOAEL for maternal toxicity was reported to be 4.5 mg/g/day Trimethyl Pentanyl Diisobutyrate in feed (343 mg/kg/day). Based on lower mean fetal body weights at 1.50% (15 mg/g/day; 1077 mg/kg/day), an exposure level of 0.45% (4.5 mg/g/day; 343 mg/kg/day) was reported to be the NOAEL for embryo/fetal development for Trimethyl Pentanyl Diisobutyrate in the diet of rats.

The NOAEL for the maternal toxicity of Glycol Distearate (as a C16-18 mixture) was reported to be ≥ 900 mg/kg and the teratogenicity NOAEL was reported to be ≥ 900 mg/kg when administered on GD 6 to 15. There were no mortalities during the study period. No Glycol Distearate-related symptoms were observed in the treatment groups when compared to the control group.

Trimethyl Pentanyl Diisobutyrate was not mutagenic in mammalian cell mutation assays (up to 2000 µg/mL), Ames tests (up to 5000 µg/plate), and a mammalian chromosome aberration tests (up to 1000 µg/mL). Diethylpentanediol Dineopentanoate was not mutagenic in an Ames test up to 5000 µg/plate. Glycol Distearate was not mutagenic in Ames tests up to 5000 µg/plate. Neopentyl Glycol Diethylhexanoate was not mutagenic in a mammalian cell mutation assay (up to 600 µg/mL), an Ames test (up to 5000 µg/plate), and mammalian chromosome aberration tests (up to 100 µg/mL). Neopentyl Glycol Dicaprate was not mutagenic at up to 5000 µg/plate in an Ames test. Propanediol Dicaprylate/Caprate was not mutagenic in an Ames test at 0.005 mL/plate.

In tests for endocrine receptor agonist and antagonist activity of Trimethyl Pentanyl Diisobutyrate in multiple cell lines, results were positive for hER1 agonist activity, with a > 50% response, and positive results were observed for hER2 agonist activity in the transfected MCF7-ER cells, with a > 10% response. The results were negative for mAhR, hPPARy, and hTR ß agonist activity in luciferase reporter cell lines. All cell lines were negative for endocrine receptor antagonism.

Trimethyl Pentanyl Diisobutyrate was not irritating to guinea pigs at 100% and was not or was mildly irritating to rabbits at 100%. Diethylpentanediol Dineopentanoate (neat) was a non-irritant to rabbit skin. Glycol Distearate was not irritating to rabbits and guinea pigs at 100%. Neopentyl Glycol Diethylhexanoate (tested neat) was not irritating to the skin of rabbits. There were no signs of erythema or edema observed when Neopentyl Glycol Diheptanoate was administered to rabbits at 100%.

In a human patch test, Neopentyl Glycol Dicaprate (neat) was not irritating when administered for up to 24 h. In a human patch test, Diethylpentanediol Dineopentanoate (neat) was a dermal non-irritant.

In two skin sensitization studies in guinea pigs, Trimethyl Pentanyl Diisobutyrate was not considered to be a skin sensitizer at 1%. In a guinea pig maximization test, Diethylpentanediol Dineopentanoate was not sensitizing to albino guinea pigs when injected with Diethylpentanediol Dineopentanoate at 25% (in paraffin oil with Freund's complete adjuvant), then applied topically at 100%; the challenge was a topical application at 100%. There were no signs of sensitization in a Buehler test of Glycol Distearate at 100% in guinea pigs. Neopentyl Glycol Diheptanoate at 100% was not sensitizing in guinea pigs when

challenged at 30% and 100%. In a guinea pig maximization test, Diethylpentanediol Dineopentanoate was a non-sensitizer at 25%.

In three HRIPTs, Trimethyl Pentanyl Diisobutyrate was not sensitizing at 1.0%. In two HRIPTs, Neopentyl Glycol Diethylhexanoate was not sensitizing at 100%. Propanediol Dicaprylate/Caprate and Propanediol Dipelargonate were not sensitizers in HRIPTs at up to 100%.

Neopentyl Glycol Dicaprate (25% in corn oil) was predicted to have practically no irritation potential in a HET-CAM assay. Propanediol Dicaprylate/Caprate was not an ocular irritant in an in vitro assay. Trimethyl Pentanyl Diisobutyrate, Glycol Distearate, Neopentyl Glycol Diethylhexanoate, and Neopentyl Glycol Diheptanoate were not ocular irritants at 100% in rabbits. Diethylpentanediol Dineopentanoate was a minimal ocular irritant in rabbits.

DISCUSSION

The Panel examined the available data for these 28 monoalkylglycol dialkyl acid ester cosmetic ingredients. Data from previous reports on three of these ingredients (e.g., Glycol Distearate, Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate, and Neopentyl Glycol Diisononanoate) and from reports on related ingredients, moieties, component parts, and potential hydrolysis product surrogates of these ingredients, were also examined.

When assessing safety, the Panel noted that Glycol Distearate had a substantial amount of data over multiple end points and was considered an appropriate representative molecule among these ingredients. The Panel was comfortable using this ingredient for read-across to inform on the safety of the other ingredients, given the molecular weights and log P values. Additionally, the acute dermal toxicity of the smaller ingredients (i.e., Neopentyl Glycol Diisononanoate and Trimethyl Pentanyl Diisobutyrate) demonstrated no concerns, and acute oral toxicity at relatively high doses presented little concern. Estimated and experimental log P values, ranging from 4.91 to 46.27, supported the statements that these ingredients are not likely to penetrate the skin to any significant amount. Safety was supported by the conclusions in previous safety assessments by CIR on related ingredients and several of the component parts of many of these ingredients. The Panel was not concerned about the lack of carcinogenicity data due to these data profiles (including negative Ames assays) and the lack of structural alerts for any of these ingredients. The Panel also noted that the reduction in sperm in the reproduction study on Trimethyl Pentanyl Diisobutyrate was not a significant toxicological result with regards to cosmetic use.

For the ingredient Diethylpentanediol Dineopentanoate, the Panel used the available toxicity data on this ingredient (e.g., acute oral, genotoxicity, irritation, and sensitization) in combination with toxicity data on one of its potential hydrolysis products, neopentanoic acid. Since toxicity data on the other potential hydrolysis product, 2,4-diethyl-1,5-pentanediol, were not available, the Panel used the data on Isopentyldiol and 1,5-Pentanediol, from the CIR report on alkane diols, as surrogates. The Panel was satisfied that this combination of data were sufficient to come to a conclusion of safety on Diethylpentanediol Dineopentanoate at its current reported maximum concentration of use (1% in rinse-off formulations).

The available impurity data show that the concentrations of potentially problematic source materials for the manufacture of these monoalkylglycol dialkyl acid esters are low or below detection. The component parts of these ingredients are highly reactive in the context of the synthetic process and are unlikely to survive hydrolysis in the finishing steps of manufacturing.

The Panel acknowledged that some of the monoalkylglycol dialkyl acid esters may be formed from plant-derived constituents (e.g., Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate and Glycol Dipalmate/Rapeseedate/Soyate. The Panel thus expressed concern regarding pesticide residues and heavy metal that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in an ingredient before blending them into cosmetic formulations. The Panel also acknowledged that some of the monoalkylglycol dialkyl acid esters may be formed from animal-derived constituents (e.g., Glycol Ditallowate). The Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of at least one ingredient in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the FDA that tallow derivatives are not risk materials for transmission of infectious agents.

There are two ingredients that contain a 2-ethylhexanoic acid residue (i.e., Glycol Diethylhexanoate and Neopentyl Glycol Diethylhexanoate). If absorbed and metabolized, the resulting metabolite, 2-ethylhexanoic acid, can be a liver and reproductive toxicant. The Panel considered the maximum concentrations at which these ingredients are expected to be used in cosmetics. For example, Neopentyl Glycol Diethylhexanoate is reported to be used up to 57% in products with dermal contact and Neopentyl Glycol Diheptanoate is reported to be used in hairsprays that might be inhaled at up to 19.5%. The Panel suggested that the process of metabolic conversion results in a time course that allows clearance of 2-ethylhexanoic acid at rates such that levels cannot attain toxicological significance. Also, the data present no reason to be concerned about toxicity from these ingredients or their metabolites at the levels used in cosmetics.

The Panel noted the possible presence of 1,4-dioxane and ethylene oxide impurities in ethylene glycol diester ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities from the ingredients containing ethylene glycol or ethylene glycol esters before blending them into cosmetic formulations.

The Panel recognizes that there are data gaps regarding use and concentration of some of these ingredients. However, the overall information available on the types of products in which these ingredients are used, and at what concentrations are in final

formulations, indicates a pattern of use which the Panel considered in assessing safety.

The Panel discussed the issue of incidental inhalation exposure from cologne, toilet waters, perfumes, other fragrance preparations, pump and aerosol hair sprays, spray body and hand products, and deodorants. These ingredients are reportedly used at concentrations up to 19.5% in cosmetic products that may be sprayed (Neopentyl Glycol Diheptanoate in a pump hair spray) and up to 16.8% in loose powder products (Neopentyl Glycol Dicaprate in face powders) that may become airborne. Neopentyl Glycol Dicaprate was reported to be used in spray deodorants at up to 4%. The limited data available from acute inhalation studies suggest little potential for respiratory effects at relevant doses. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics. The Panel noted that droplets/particles from cosmetic products would not be respirable to any appreciable amount. In addition, the Panel considered other data available to characterize the potential for monoalkylglycol dialkyl acid esters to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The Panel concluded that the following monoalkylglycol dialkyl acid ester ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Butylene Glycol Dicaprylate/Dicaprate
Butylene Glycol Diisononanoate*
Diethylpentanediol Dineopentanoate
Dioctadecanyl Didecyltetradecanoate*
Dioctadecanyl Ditetradecyloctadecanoate*
Glycol Dibehenate*
Glycol Diethylhexanoate
Glycol Dilaurate
Glycol Dioleate*
Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate*
Glycol Dipalmate/Rapeseedate/Soyate*
Glycol Dipivalate*
Glycol Distearate
Glycol Ditallowate*
Hexanediol Distearate*
Neopentyl Glycol Dicaprate
Neopentyl Glycol Dicaprylate/Dicaprate
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate*
Neopentyl Glycol Diethylhexanoate
Neopentyl Glycol Diheptanoate
Neopentyl Glycol Diisononanoate
Neopentyl Glycol Diisostearate
Neopentyl Glycol Dilaurate*
Propanediol Dicaprylate
Propanediol Dicaprylate/Caprate
Propanediol Diisostearate*
Propanediol Dipelargonate*
Trimethyl Pentanyl Diisobutyrate

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

TABLES

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

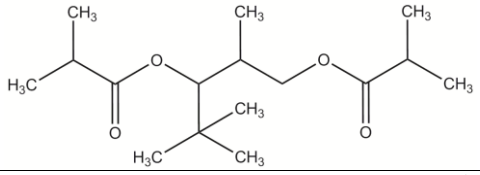
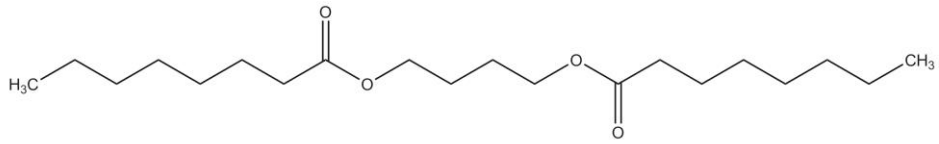
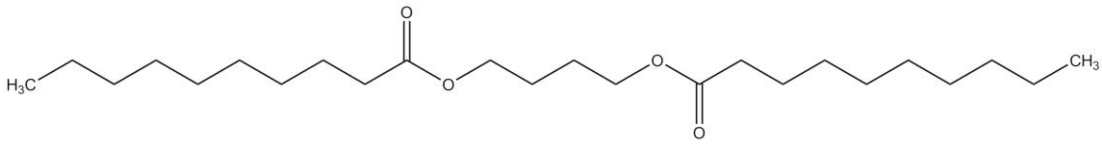
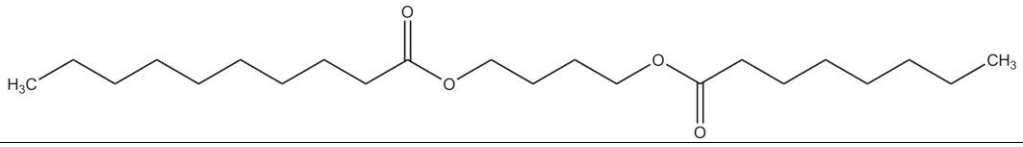
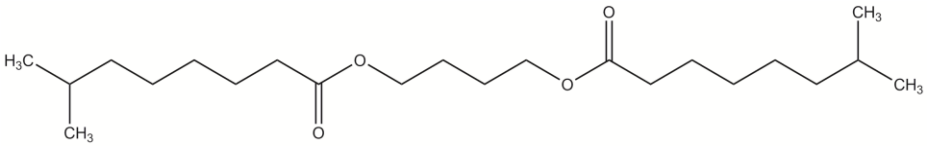
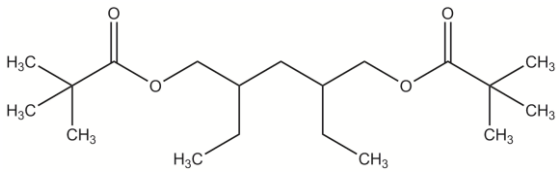
Ingredient CAS No.	Definition & Structure	Function(s)
Trimethyl Pentanyl Diisobutyrate 6846-50-0	Trimethyl Pentanyl Diisobutyrate is the organic compound that conforms to the formula: 	Plasticizer
Butylene Glycol Dicaprylate/Dicaprate	Butylene Glycol Dicaprylate/Dicaprate is a mixture of the butylene glycol diesters of caprylic and capric acids.   	Skin-conditioning agent - occlusive
Butylene Glycol Diisononanoate	Butylene Glycol Diisononanoate is the diester of butylene glycol and branched chain nonanoic acids. It conforms generally to the formula:  [one example of an "iso]	Skin-conditioning agent – emollient; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Diethylpentanediol Dineopentanoate 762268-78-0	Diethylpentanediol Dineopentanoate is the organic compound that conforms to the formula: 	Hair conditioning agent; skin-conditioning agent - miscellaneous

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

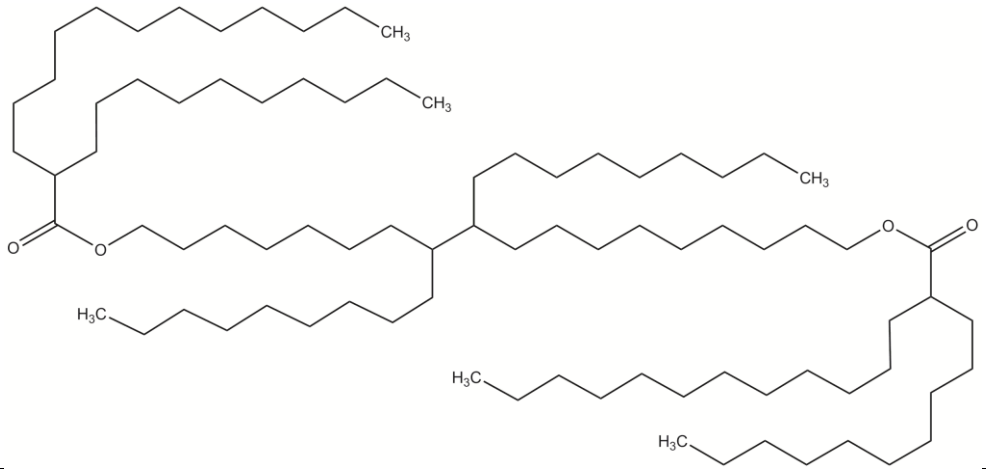
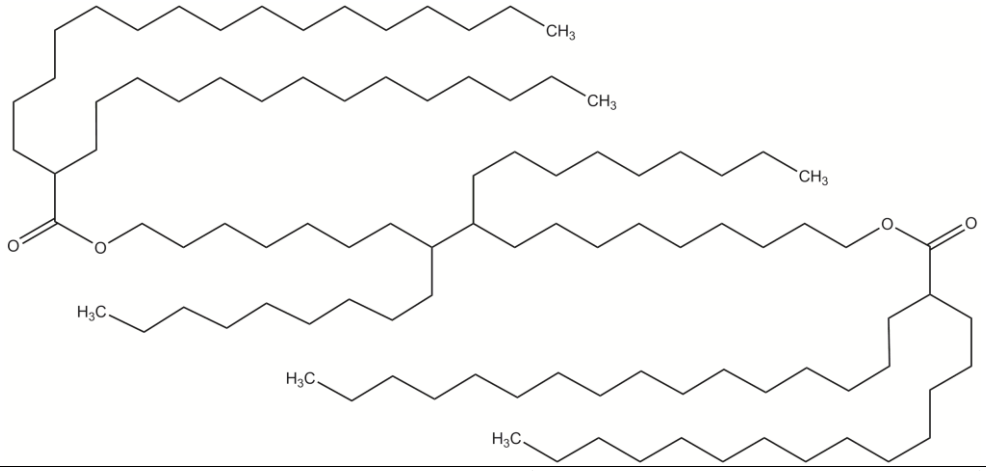
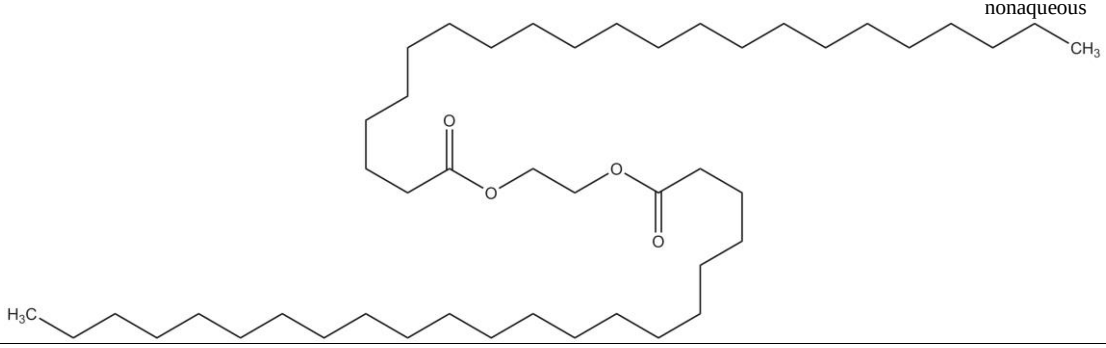
Ingredient CAS No.	Definition & Structure	Function(s)
Dioctadecanyl Didecyltetradecanoate	Dioctadecanyl Didecyltetradecanoate is the organic compound that conforms to the formula: 	Skin-conditioning agent – emollient; skin-conditioning agent - miscellaneous
Dioctadecanyl Ditetradecyloctadecanoate	Dioctadecanyl Ditetradecyloctadecanoate is the organic compound that conforms to the formula: 	Skin-conditioning agent – emollient; skin-conditioning agent - miscellaneous
Glycol Dibehenate 79416-55-0	Glycol Dibehenate is the diester of ethylene glycol and behenic acid. It conforms generally to the formula: 	Opacifying agent; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

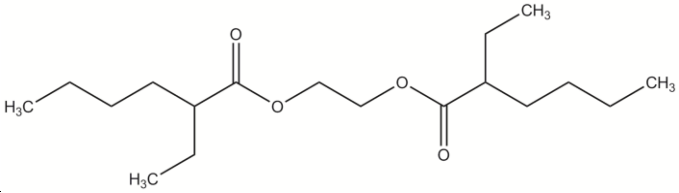
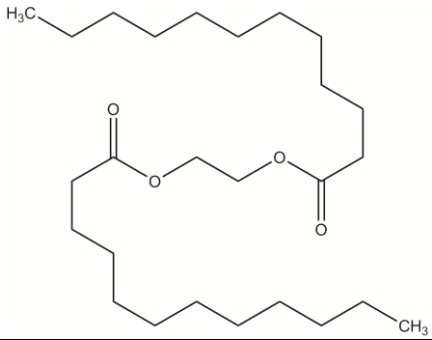
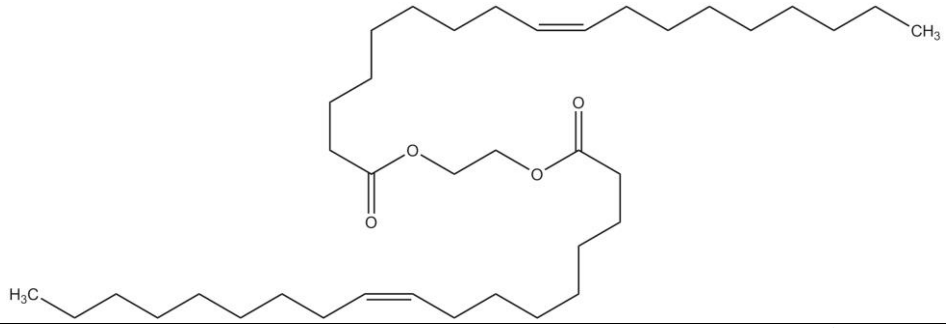
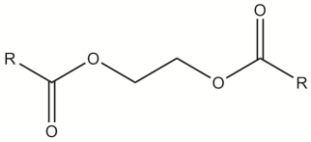
Ingredient CAS No.	Definition & Structure	Function(s)
Glycol Diethylhexanoate	Glycol Diethylhexanoate is the diester of ethylene glycol and 2-ethylhexanoic acid. It conforms to the formula: 	Skin-conditioning agent – occlusive; viscosity increasing agent – nonaqueous
Glycol Dilaurate 624-04-4	Glycol Dilaurate is the diester of ethylene glycol and lauric acid. It conforms to the formula: 	Skin-conditioning agent viscosity increasing agent – nonaqueous – occlusive
Glycol Dioleate	Glycol Dioleate is the diester of ethylene glycol and oleic acid. It conforms to the formula: 	Opacifying agent; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate	Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate is the diester of ethylene glycol with a mixture of fatty acids derived from palm oil, palm kernel oil, olive oil and macadamia nut oil.  [wherein RC(O)- represents fatty acid residues derived from palm oil, palm kernel oil, olive oil and macadamia nut oil.]	Skin-conditioning agent - emollient

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

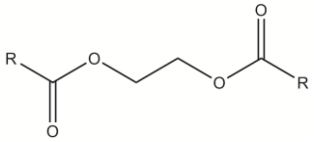
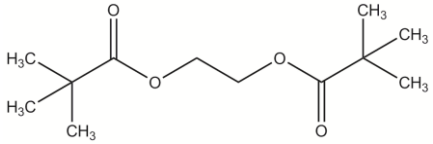
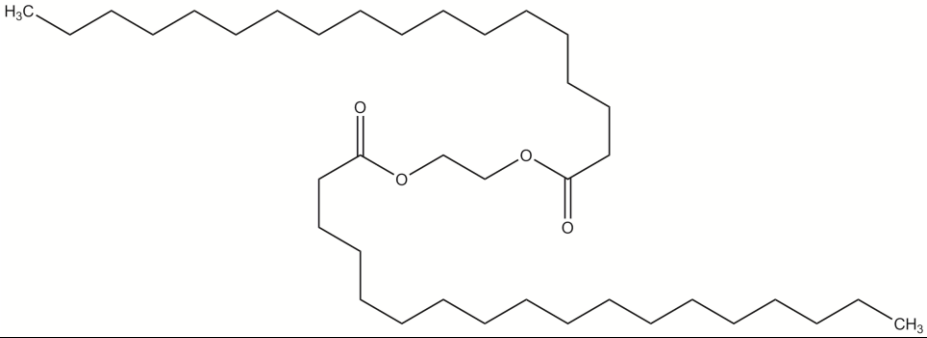
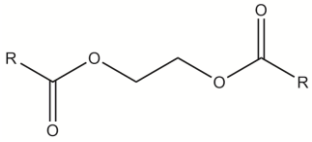
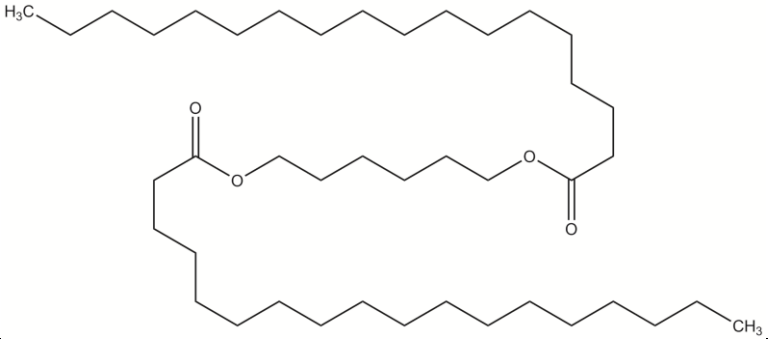
Ingredient CAS No.	Definition & Structure	Function(s)
Glycol Dipalmate/Rapeseedate/Soyate	Glycol Dipalmate/Rapeseedate/Soyate is the diester of ethylene glycol with a mixture of palm acid, rapeseed acid and soy acid.  [wherein RC(O)- represents fatty acid residues derived from palm acid, rapeseed acid and soy acid.]	Skin-conditioning agent - emollient
Glycol Dipivalate	Glycol Dipivalate is the organic compound that conforms to the formula: 	Skin-conditioning agent – emollient
Glycol Distearate 627-83-8 91031-31-1	Glycol Distearate is the diester of ethylene glycol and stearic acid. It conforms generally to the formula: 	Opacifying agent; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Glycol Ditallowate	Glycol Ditallowate is the diester of ethylene glycol and Tallow Acid. It conforms generally to the formula:  where RCO- represents the fatty acids derived from tallow.	Opacifying agent; skin-conditioning agent – occlusive
Hexanediol Distearate 26730-92-7	Hexanediol Distearate is the diester of hexanediol and stearic acid. It conforms generally to the formula: 	Skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

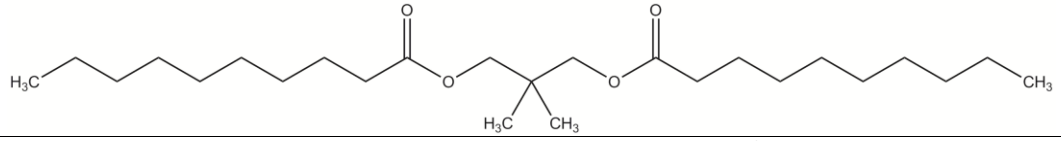
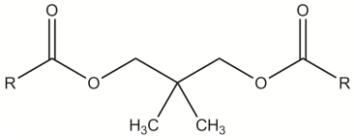
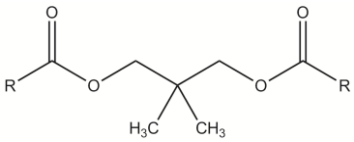
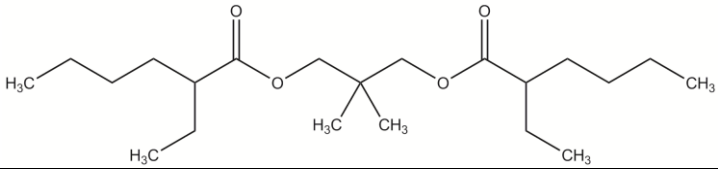
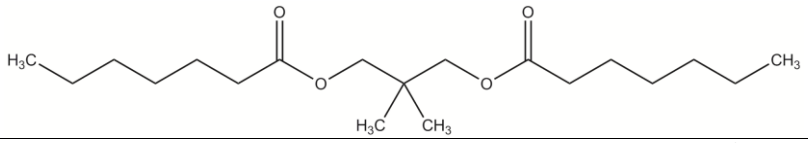
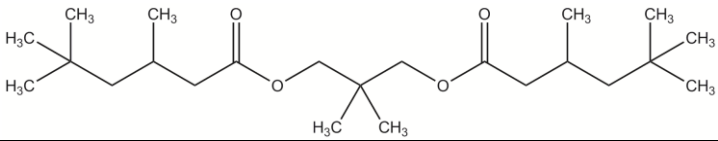
Ingredient CAS No.	Definition & Structure	Function(s)
Neopentyl Glycol Dicaprate 27841-06-1	Neopentyl Glycol Dicaprate is the diester of neopentyl glycol and decanoic acid that conforms to the formula: 	Skin-conditioning agent – emollient; viscosity increasing agent - nonaqueous
Neopentyl Glycol Dicaprylate/Dicaprate 70693-32-2	Neopentyl Glycol Dicaprylate/Dicaprate is the diester of neopentyl glycol and a blend of caprylic and capric acids.  [wherein RC(O)- represents fatty acid residues derived from caprylic and capric acids.]	Skin-conditioning agent – emollient; viscosity increasing agent - nonaqueous
Neopentyl Glycol Dicaprylate/ Dipelargonate/Dicaprate	Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate is the diester of neopentyl glycol and a blend of caprylic, pelargonic and capric acids.  [wherein RC(O)- represents fatty acid residues derived from caprylic, pelargoinc, and capric acids.]	Skin-conditioning agent – emollient; viscosity increasing agent - nonaqueous
Neopentyl Glycol Diethylhexanoate 28510-23-8	Neopentyl Glycol Diethylhexanoate is the diester of neopentyl glycol and 2-ethylhexanoic acid. It conforms to the formula: 	Skin-conditioning agent – emollient; viscosity increasing agent - nonaqueous
Neopentyl Glycol Diheptanoate 68855-18-5	Neopentyl Glycol Diheptanoate is the diester of neopentyl glycol and heptanoic acid. It conforms to the formula: 	Skin-conditioning agent – emollient; viscosity increasing agent – nonaqueous
Neopentyl Glycol Diisononanoate 27841-07-2	Neopentyl Glycol Diisononanoate is the organic compound that conforms to the formula: 	Skin-conditioning agent – emollient

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

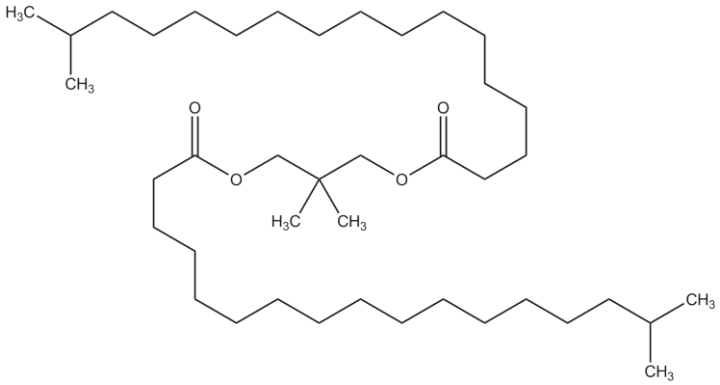
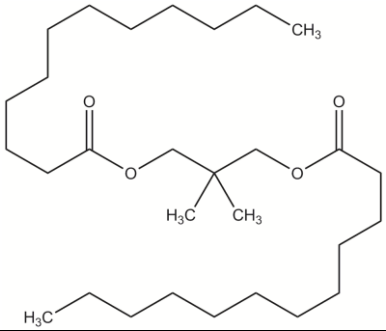
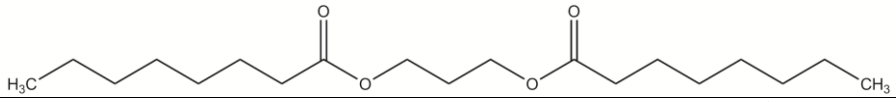
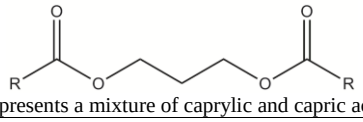
Ingredient CAS No.	Definition & Structure	Function(s)
Neopentyl Glycol Diisostearate 109884-54-0	Neopentyl Glycol Diisostearate is the diester of neopentyl glycol and isostearic acid. It conforms to the formula:  [one example of an "iso"]	Skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Neopentyl Glycol Dilaurate 10525-39-0	Neopentyl Glycol Dilaurate is the diester of neopentyl glycol and lauric acid. It conforms to the formula: 	Skin-conditioning agent – emollient; viscosity increasing agent – nonaqueous
Propanediol Dicaprylate 1020852-63-4 56519-71-2	Propanediol Dicaprylate is the organic compound that conforms to the formula: 	Skin-conditioning agent – emollient; solvent
Propanediol Dicaprylate/Caprate 1072005-10-7	Propanediol Dicaprylate/Caprate is the organic compound that conforms generally to the formula:  where RC(O)- represents a mixture of caprylic and capric acid residues.	Skin-conditioning agent – emollient

Table 1. Definitions, idealized structures, and functions of the monoalkylglycol dialkyl acid esters in this safety assessment.[1,CIR Staff]

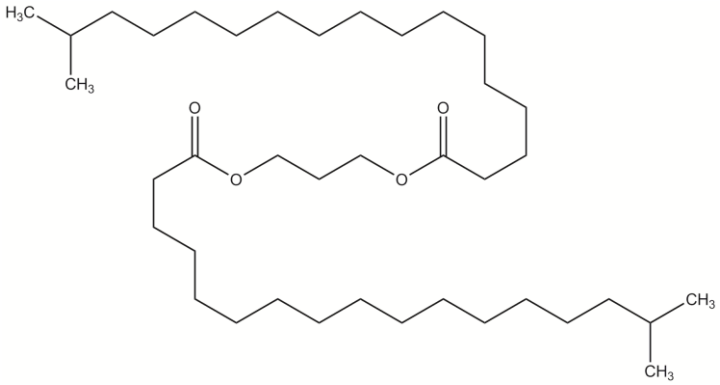
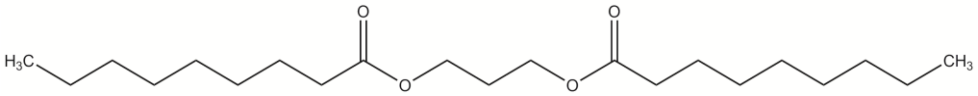
Ingredient CAS No.	Definition & Structure	Function(s)
Propanediol Diisostearate	Propanediol Diisostearate is the organic compound that conforms generally to the formula:  [one example of an "iso"]	Skin-conditioning agent – emollient
Propanediol Dipelargonate 28267-33-6	Propanediol Dipelargonate is the organic compound that conforms to the formula: 	Skin-conditioning agent – emollient

Table 2. Previous safety assessments by CIR of monoalkylglycol dialkyl acid esters and related ingredients, moieties, and component parts.

Ingredient, Related Ingredients, or Component	Conclusion (year)[a]	Reference
Glycol Distearate; Glycol Stearate, Glycol Stearate SE	Safe as used (1982)	2,3
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate, Neopentyl Glycol Diisononanoate, Pelargonic Acid (nonanoic acid) and nonanoate esters	Safe as used (2011)	4
Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, Dipropylene Glycol	Safe as used (2006)	45,46
Alkane diols (1,5-Pentanediol and Isopentyldiol)	Safe in cosmetics in the present practices of use and concentration; the data are insufficient to come to a conclusion of safety for 1,4-Butanediol (2017, tentative report)	47
Propylene glycol esters	Safe as cosmetic ingredients in the practices of use and concentration described in this safety assessment (2014)	48
Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid	Safe in the present practices of use and concentration (2006)	45,49
Plant-derived fatty acid oils (which primarily comprise glyceryl triesters)	Safe as used (2011)	50
Alkyl esters (e.g., Isooctyl Caprylate/Caprate, Cetearyl Isononanoate, and Cetearyl Behenate)	Safe in cosmetic formulations in the present practices of use and concentration when formulated to be non-irritating (2013)	51
Tallow, Tallow Glyceride, Tallow Glycerides, Hydrogenated Tallow Glyceride, and Hydrogenated Tallow Glycerides	Safe in present practices of use (1990, 2006)	52,53
Alkyl ethylhexanoates	Safe in cosmetic formulations in the present practices of use and concentrations when formulated to be nonirritating (2015). 2-Ethylhexanoic acid, a possible metabolite, had been shown to be a liver and developmental toxicant in animal studies at high doses; in developmental toxicity studies, it was postulated that the maternal liver toxicity began a cascade of effects that included metallothionein (MT) induction, zinc accumulation in the liver due to MT binding, and a resulting zinc deficiency in	54

Table 2. Previous safety assessments by CIR of monoalkylglycol dialkyl acid esters and related ingredients, moieties, and component parts.

Ingredient, Related Ingredients, or Component	Conclusion (year)[a]	Reference
	the developing embryo; the zinc deficiency causes the developmental toxicity; a reproductive/developmental toxicity study was also performed with up to 1% dietary di-2-ethylhexyl terephthalate (DEHT; a 2-ethylhexanoic acid precursor); no reproductive or developmental effects were observed, suggesting that the process of metabolic conversion of DEHT to 2-ethylhexanol and subsequent hydrolysis to 2-ethylhexanoic acid results in a time course of 2-ethylhexanoic acid appearance such that allows clearance before sufficient levels can arise to produce acute liver toxicity.	

[a] Please see the original reports for details (https://www.cir-safety.org/ingredients).

Table 3. Chemical and physical properties of monoalkylglycol dialkyl acid esters in this safety assessment.

Property	Value	Reference
Trimethyl Pentanyl Diisobutyrate		
Physical Form	Liquid	7
Color	Colorless/clear	7
Odor	Slight	7
Molecular Weight g/mol	286.41	18
Density	0.94	7
	0.92	7
Viscosity kg/(s*m)	0.005	7
Vapor pressure mmHg @ 20°C	0.0009	32
	0.0113	7
	0.00066	18
	0.089	35
Melting Point °C	-70	32
	-10	18
Boiling Point °C	281.5	18
	280	18,32
Water Solubility g/L @ 27.5°C & pH 3.6-4/6	0.0127	7
@ 23.65°C & pH 4.09-4.83	13.3	7
@ 23.65°C & pH 7.79-8.26	13.2	7
@ 20.5°C	0.001-0.002	32
@ 25°C	0.015	18
log P	4.91 est.	14
Butylene Glycol Dicaprylate/Dicaprate		
Molecular Weight g/mol	342.52 – 398.63	15
log P	7.28 – 9.24 est.	15
Butylene Glycol Diisononanoate		
Physical Form	Liquid	55
Molecular Weight g/mol	370.57	55
Water Solubility	Insoluble	55
log P	8.12 est.	14
Diethylpentanediol Dineopentanoate		
Physical Form	Liquid	16
Color	Colorless to very pale yellow	16
Odor	Faint characteristic	16
Molecular Weight g/mol	328.49	56
Boiling Point °C	> 200	16
Water Solubility	Insoluble	16
log P	6.42 est.	14

Table 3. Chemical and physical properties of monoalkylglycol dialkyl acid esters in this safety assessment.

Property	Value	Reference
Dioctadecanyl Didecyltetradecanoate		
Physical Form	Liquid	57
Molecular Weight g/mol	1240.21	57
Water Solubility	Insoluble	57
log P	38.42 est.	14
Dioctadecanyl Ditetradecyloctadecanoate		
Physical Form	Liquid	58
Molecular Weight g/mol	1464.64	58
Water Solubility	Insoluble	58
log P	46.27 est.	14
Glycol Dibehenate		
Molecular Weight g/mol	707.20	59
log P	20.05 est.	14
Glycol Diethylhexanoate		
Physical Form	Liquid	9
Color	Pale yellow	9
Molecular Weight g/mol	314.47	15
Density/Specific Gravity @ 20°C	0.94 est.	9
Vapor Density mmHg	0 est.	9
Melting Point °C	< -20	9
Boiling Point °C	75	9
log P	7.66 est. 9.62 est.	9 9
Glycol Dilaurate		
Molecular Weight g/mol	426.67	60
log P	10.23 est.	14
Glycol Dioleate		
Molecular Weight g/mol	590.97	61
log P	15.69 est.	14
Glycol Dipivalate		
Molecular Weight g/mol	230.30	15
log P	3.13 est.	14
Glycol Distearate		
Physical Form	Solid Waxy solid	5 3
Color	White White to cream	5 3
Molecular Weight g/mol	595.0	62
Density/Specific Gravity @ 78°C g/cm^3	0.858	5
Viscosity kg/(s*m)@ 80°C	8.04	
Melting Point °C	75 75.3 79 74.7 67-68 75 - 75.5	5 5 5,62 5 5 5
Boiling Point °C @ 20 mmHg @ 15 mmHg	241 209	5 5
Water Solubility g/L @ 25°C	0	5
log P	16.12 est.	5
Hexanediol Distearate		
Molecular Weight g/mol	651.11	63
log P	18.08 est.	14

Table 3. Chemical and physical properties of monoalkylglycol dialkyl acid esters in this safety assessment.

Property	Value	Reference
Neopentyl Glycol Dicaprate		
Molecular Weight g/mol	412.65	64
Density @ 20°C	0.93 est.	6
log P	9.62 est.	6
Neopentyl Glycol Dicaprylate/Dicaprate		
Physical Form	Liquid Oily liquid	6 65
Color	Clear or yellowish	65
Molecular Weight g/mol	356.55 – 412.66	15
Density @ 25°C	0.890-0.920	65
Melting Point °C	< 20	6
Water Solubility g/L @ 20°C & pH 5.4-6.8	92.9	6
log P	7.66 – 9.62 est.	14
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate		
Molecular Weight g/mol	356.60 - 412.66	15
log P	7.66 – 9.62 est.	14
Neopentyl Glycol Diethylhexanoate		
Physical Form	Liquid	8,11,12
Color	Pale yellow Clear	8 11
Odor	Slight, characteristic	11
Molecular Weight g/mol	356.54	12
Specific Gravity @ 25°C	0.920	11
Melting Point °C	< -20	8
Water Solubility	Insoluble	11
Other Solubility Hydrophobic solvents (esters, mineral oil, mineral spirits, and aromatic hydrocarbons)	Soluble	11
log P	7.51 est.	14
Neopentyl Glycol Diheptanoate		
Physical Form	Liquid	6,8
Color	Light straw	6,8
Molecular Weight g/mol	328.5	8
Density/Specific Gravity @ 20°C @ 20°C	0.927 0.92	8 8
Viscosity kg/(s*m) @ 25°C @ 40°C @ 100°C	1.29 0.58 0.193	8 8 8
Vapor pressure mmHg @ 20°C	0 est.	8
Melting Point °C	-33	8
Water Solubility g/L @ 20°C & pH 6.2 - 6.7	< 0.05	8
log P	6.68 est.	8
Neopentyl Glycol Diisononanoate		
Molecular Weight g/mol	384.59	4
Melting Point °C	132.4 est.	4
Boiling Point °C	565.02 est.	4
log P	7.03 est.	4
Neopentyl Glycol Diisostearate		
Molecular Weight g/mol	637.07	66
log P	17.34 est.	14
Neopentyl Glycol Dilaurate		
Molecular Weight g/mol	468.75	67
Density	0.911	67
Boiling Point °C	532.6	67
log P	11.59 est.	14

Table 3. Chemical and physical properties of monoalkylglycol dialkyl acid esters in this safety assessment.

Property	Value	Reference
Propanediol Dicaprylate		
Physical Form	Liquid	13
Color	White	13
Odor	Neutral	13
Molecular Weight g/mol	328.49	15
Specific Gravity @ 25°C	0.91-0.93	13
Melting Point °C	< -5	13
Water Solubility	Insoluble	13
log P	6.79 est.	14
Propanediol Dicaprylate/Caprate		
Molecular Weight g/mol	328.49 – 384.60	15
Specific Gravity @ 25°C	0.91 - 0.93	68
log P	6.79 – 8.75 est.	14
Propanediol Diisostearate		
Molecular Weight g/mol	609.03	15
log P	16.46 est.	14
Propanediol Dipelargonate		
Physical Form	Liquid	69
Color	Clear	69
Molecular Weight g/mol	356.54	70
Water Solubility	Insoluble	69
Other Solubility		
Ethanol	Miscible	69
Propylene Glycol	Insoluble	69
Isopropyl Myristate	Miscible	69
Castor Oil	Miscible	69
Mineral Oil	Miscible	69
Isododecane	Miscible	69
log P	7.77 est.	14

est.=estimated

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
Acute Dermal				
Neopentanoic acid				
New Zealand White Rabbit[a] (4/sex)	50, 200, 794, or 3160 mg/kg	Similar to OECD Guideline 402 (Acute Dermal Toxicity). Test substance was in contact for 24 h under occlusion. The rabbits were then observed for 14 days.	LD_{50} = 3160 mg/kg Two rabbits died within 48 h of exposure in the 3160 mg/kg group. Death was preceded by marked depression, severe dyspnea, prostration, excessive urination, and coma. Congestion of lungs, adrenals, kidneys, blanched areas on liver and spleen, inflammation of the bladder mucosa and gastrointestinal tract.	10
Rat (4/sex)	2 or 4 mL, neat	Test substance was in contact for 24 h under occlusion. The rabbits were then observed for 9 days.	LD_{50} = between 2-4 mL None of the rats died in the low-dose group. All of the males and 2 of 4 females died in the high-dose group by day 2.	10

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
1,5 Pentanediol				
Male New Zealand (albino) Rabbit (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	[71]
		Acute Oral		
Neopentanoic acid				
Male Sprague-Dawley rats (n=5)	34.6, 120, 417, 1450, 5000, or 10000 mg/kg in corn oil by gavage	Similar to OECD Guideline 420 (Acute Oral Toxicity - Fixed Dose Method). Rats were observed for 14 days after dosing.	LD_{50} = 2000 mg/kg None of the rats died in the 3 low-dose groups. 2 died on day 2 in the1450 mg/kg group, all 5 died by day 2 in the 5000 mg/kg group, and all 5 died within 24 h in the 10,000 mg/kg group. Clinical signs: 1450 mg/kg-slight to marked depression, dyspnea and ataxia at 24 h, death within 48 h post-dose. Survivors showed depression, severe dyspnea, depressed reflexes, sprawling, incoordination, and abnormal gait. 5000 and 10000 mg/kg-depression, dyspnea, ataxia, and sprawling of limbs within one hour post-dose. Marked depression, severe dyspnea and prostration preceded death in all animals within 1 to 48 h. Gross pathology: 5000 and 10000 mg/kg - congestion of lungs, liver, kidneys, and adrenals; pyloric portion of the stomach grossly hemorrhagic.	[10]
Wistar rats (4/sex)	0.5, 1.0 or 2.0 mL/kg	Fixed dose procedure. Rats were observed for 9 days after dosing. No further details were provided.	LD_{50} = between 1 and 2 mL/kg No rats died in the 0.5 mL/kg group; 1 female died on day 4 in the 1.0 mL/kg group; all rats died on day 1 of the 2.0 mL/kg group.	[10]
1,5 Pentanediol				
Carworth-Wistar rat (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} of 5.89 g/kg ± 1.96 standard deviations was reported, LD_{50} range reported was 5.38 to 6.44 g/kg	[71]
Sprague-Dawley rat (12 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	[72]
Guinea Pig (not specified)	Not Specified	Not Specified	LD_{50} = 4.6 g/kg; somnolence, excitement, and muscle weakness noted details provided)	[73]
Mouse (not specified)	Not Specified	Not Specified	LD_{50} = 6.3 g/kg; somnolence, excitement, and muscle weakness noted (details provided)	[73]
Rabbit (not	Not Specified	Not Specified	LD_{50} = 6.3 g/kg; somnolence, excitement,	[73]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
specified)			and muscle weakness noted (no further details provided)	
Isopentyldiol				
CD-1 mouse (5/sex)	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	[74]
Acute Inhalation				
Neopentanoic acid				
Wistar rats (3/sex)	5.30 mg/L for 4 h	Nose only application. Rats were examined for clinical signs hourly during exposure and daily for 14 days.	LC_{50} > 5.3 mg/L During exposure, decreased respiratory rate was observed in all rats. On removal from the chamber all rats exhibited decreased respiratory rate and ataxia. 1 h post-exposure, a slight recovery was evident in all animals as ataxia was no longer apparent. Signs of hunched posture and piloerection were observed in rats for short periods on removal from the chamber. Wet fur was commonly recorded both during and for a short period after exposure. Rats recovered quickly to appear normal on day 2 or 3 post-exposure. These observations are considered to be associated with the restraint procedure and, in isolation, are not indicative of toxicity.	[10]
Male Swiss mice, Wistar rats, Hartley guinea pigs (10)	4.0 mg/L for 6 h	Mice, rats and guinea pigs exposed to vaporized test substance in whole body inhalation chambers for 6 hours at the nominal concentration of 4 mg/L. All groups were monitored for 14 days for clinical signs of toxicity.	Mice-LC_{100} = 4.0 mg/L Rats-LC_{50} = < 4 mg/L Guinea pig-LC_{50} = < 4 mg/L All mice died within 24 h of exposure. 2 rats (on day 2 and 5 post exposure) and 1 guinea pig (between 8 and 24 h post exposure) died.	[10]
1,5 Pentanediol				
Albino rat (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	[71]
Sprague-Dawley rat (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 was reported; no mortality; gross pathology revealed no findings	[72]
Short-term Dermal Toxicity				
Neopentanoic acid				
Rabbit (4)	30 or 300 mg/kg for 24 h under occlusion	10 exposure, 5 days/week over 2 weeks.	Generally, rabbits in the low-dose group showed an overall body weight gain; in the high-dose group, an overall slight weight loss was noted. Gross pathological findings at necropsy consisted of parasitic cysts in the liver and fibrous, pitted kidneys, congestion of the lungs, and congestion of the pancreas. Dermal: low-dose group showed slight or moderate erythema, atonia, and desquamation. Exposed skin of 1 rabbit showed slight edema following the third	[10]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
			and fourth application and a circumscribed area of corrosion during the last 4 days of the study. High-dose group rabbits generally showed moderate erythema following all applications, slight to marked edema following the first 5 applications, and moderate or marked atonia and desquamation following the last 7 applications. In 3 of the rabbits discolored areas which subsequently became necrotic were noted following the third application. The necrosis persisted throughout the study.	
Short-term Oral Toxicity				
Neopentanoic acid				
Fischer 344 rats (7/sex)	10, 30, 100, or 300 mg/kg/d; 5 mL/kg in water/PEG 200 (50/50 v/v)	OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents)	NOAEL = 30 mg/kg/day Immediately after dosing the 100 or 300 mg/kg/day groups, rats were observed to sneeze and produce a dark nasal discharge, probably resulting from a mild irritant effect of the volatile acid test substance on nasal mucosa. A slightly lower bodyweight in the 300 mg/kg/day dose group females was considered to be of uncertain relation to treatment. There was no effect on male bodyweight, food intake, hematological parameters, or histopathological observations at any dose level. Changes in alkaline phosphatase, cholesterol, creatinine and bilirubin in females suggested a slight change in liver function at the 100 and 300 mg/kg/day doses, however, there was no associated histopathological changes. Minor differences in hepatic macroscopic appearance, liver weight and kidney weight were not accompanied by any histopathological change. These differences were considered to be related to adaptive or functional changes and not a toxic effect. There was no evidence of a cumulative toxic effect at any dose level. However, transient irritancy or adaptive changes were seen at 30, 100 and 300 mg/kg/day. Minor differences in liver and kidney weight were seen at 10 mg/kg/day; these were of uncertain relationship with treatment.	[10]
Genotoxicity				
Neopentanoic acid				
S. typhimurium TA 1535, TA 1537, TA 98, TA 100 and *E. coli* WP2	50.0, 150, 500, 1500 and 5000 µg per plate in water with and without metabolic activation	OECD Guideline 471 (Bacterial Reverse Mutation Assay) Positive controls: 9-aminoacridine, 2-nitrofluorene, sodium azide, methylmethanesulfonate, and 2-aminoanthracene	Negative with and without metabolic activation	[10]
L5178Y/TK+/- Mouse Lymphoma	3.99, 7.98, 16.0, 31.9, 63.8, 128, 255, 511 and 1021 µg/mL	OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test). Positive controls: 7,12-dimethylbenzanthracene methylmethanesulfonate	Negative with and without metabolic activation	[10]
Chinese Hamster Ovary (CHO) Cells	100, 250, 500, 750, 1020 µg/mL	OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test)	Negative	[10]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
1,5 Pentanediol				
Salmonella typhimurium (TA98, TA100, TA1535, TA1537)	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	[72]
Salmonella typhimurium (TA98, TA100, TA1535, TA1537)	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	[72]
Isopentyldiol				
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	[74]
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	[74]
Dermal Irritation				
Neopentanoic acid				
New Zealand White rabbit (6)	100%; 0.5 mL	OECD Guideline 404 (Acute Dermal Irritation/Corrosion)	Mean erythema score: 3.61 out of 4; mean edema score: 1.83 out of 4. Topical application elicited severe erythema in one rabbit, moderate to severe erythema in two rabbits, well-defined erythema in one rabbit and very slight erythema in two rabbits at 45 min after application. Erythema then increased. At 24 h, four rabbits had severe erythema, one rabbit with well-defined erythema and one with slight erythema. Erythema increased again at 48 and 72 h. Erythema increased slightly again at day 7 where all rabbits were noted with severe erythema. Changes in erythema were accompanied by changes in edema.	**[10]**
New Zealand White rabbit (8)	100%; 0.5 mL	Applied to intact and abraded skin for 24 h under occlusion.	Highly irritating	**[10]**
1,5 Pentanediol				
Albino rabbit (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)	[71]
Vienna White Rabbit (1 male, 5 females)	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	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	[72]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
		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	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)	
Human (30)	5% in a topical formulation	Patch test was performed; test substance was applied (single application) to inner forearms and occlusively covered with a patch; 24 h post-application the patch was removed and skin was immediately assessed and assessed again 48 and 72 h after patch removal; standard light conditions used	Non-irritating, no indications of hypersensitivity or photo-sensitivity	[75]
Isopentyldiol				
New Zealand White rabbit (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	[74]
Male New Zealand White rabbit (9)	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	[74]
Human (13 males and 17 females)	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	Isopentyldiol 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	[74]
		Sensitization		
Neopentanoic acid				
Guinea pig (10/sex; controls, 5/sex)	Induction Intradermal induction: 0.05% w/v; Topical induction: 25% w/v; Topical challenge: 10% w/v in corn oil	OECD Guideline 406 (Skin Sensitization)/guinea pig maximization test	Not sensitizing	[10]
1,5 Pentanediol				
Human (20 males)	5% in a scalp wash formulation	Scalp wash was used ≥ 2 times/day for 4 weeks (no other products were used on hair during this time); scalp skin was assessed periodically throughout study; after 4 weeks, test substance was applied (single application) to inner forearms and occlusively	Non-irritating, non-sensitizing	[75]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
		covered with a patch; 24 h post-application, the patch was removed and skin was immediately assessed and assessed again 48 and 72 h after patch removal		
Human (30)	25% in a topical formulation	Single application of test substance to inner forearms and occlusively covered with a patch; 24 h post-application, the patch was removed and skin was immediately assessed and assessed again 48 and 72 h after patch removal; this patch test was repeated 1 week later and at week 6	Non-irritating, non-sensitizing	[75]
Isopentyldiol				
Dunkin-Hartley Guinea Pig (20, 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	[74]
Photosensitization/Phototoxicity				
1,5 Pentanediol				
Human (30)	5% in a topical formulation	Test substance was applied (single application) to inner forearms; test sites on skin were then exposed to UV-A light (30 J/cm^2) and UV-B light (0.05 J/cm^2); test skin sites were covered with occlusive patch for 24 h and then patch was removed; skin was assessed immediately after patch removal and again at 48, 72, and 96 h post-application	Non-phototoxic and non-photosensitizer; study authors stated that 1,5-pentanediol does not absorb in long-wave ultra-violet range	[75,76]
Isopentyldiol				
Dunkin-Hartley Guinea Pig (10 test animals, 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	[74]
Dunkin-Hartley Guinea Pig (10 test animals, 10	Undiluted (used on test animals during induction and	Induction: to the shaved and chemically depilated back of each test animal, 0.025 ml of test substance was	Isopentyldiol was non-photosensitizing; 1 animal was killed before challenge because of probable pneumonia; no skin reactions	[74]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
controls)	challenge); distilled water (controls); 0.1% tetrachlorosalicylani-lide in petrolatum (positive controls)	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	post-application of treatment during induction or challenge phases; positive controls performed as expected	
Ocular Irritation				
Neopentanoic acid				
New Zealand White rabbit (4)	100%; 0.2 mL	OECD Guideline 405 (Acute Eye Irritation/Corrosion)	Mean overall irritation score: 3.8 out of 16 over 7 days. There was a severe pain response. Highly irritating.	[10]
New Zealand White rabbit (6)	100%; 3 mg	OECD Guideline 405	Minimal signs of eye irritation were present after exposure. Immediately following application, the rabbits exhibited blinking and preening. Responses consisted of moderate conjunctivitis in all rabbits at 1 h, which gradually diminished in severity and was clear by day 4 post exposure. Slight iritis in two rabbits persisted for 2 h. Transient dullness in one rabbit and opacity of cornea in another rabbit with some sloughing or corneal epithelium at 24 and 48 h. All signs of irritation resolved after day 4 and confirmed by negative fluorescein examination on day 7 post exposure.	[10]
1,5 Pentanediol				
Rabbit (6)	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	[71]
Rabbit (not specified)	Not specified	Not specified	Mildly irritating	[77]
Vienna White rabbit (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	[72]

Table 4. Available toxicity studies for the hydrolysis product of Diethylpentanediol Dineopentanoate, neopentanoic acid, and on 1,5 pentanediol and isopentyldiol.

Animal (n)	Dose/ Concentration(s)	Methods	Results	Reference
Isopentyldiol				
New Zealand White rabbit (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	[74]

[a] One place in the study says "rat," another says "rabbit." The rest of the name "New Zealand White" in the summary is usually associated with rabbits.

Table 5. Frequency of use according to duration and exposure of monoalkylglycol dialkyl acid esters.[23,24]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Butylene Glycol Dicaprylate/Dicaprate		Diethylpentanediol Dineopentanoate		Glycol Diethylhexanoate		Glycol Dilaurate	
Total/range	**93**	**1.3-10**	**NR**	**1**	**NR**	**5**	**NR**	**1.3**
Duration of use[a]								
Leave-on	93	1.3-10	NR	NR	NR	5	NR	1.3
Rinse-off	NR	NR	NR	1	NR	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	1	1.3-9	NR	NR	NR	NR	NR	NR
Incidental ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	51; 5[b]; 13[c]	10	NR	NR	NR	NR	NR	NR
Incidental inhalation-powders	2[d]; 13[c]	10; 8[d]	NR	NR	NR	NR	NR	1.3[d]
Dermal contact	92	NR	NR	1	NR	5	NR	1.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	NR	NR	NR	NR
Baby	2	NR	NR	NR	NR	NR	NR	NR

Table 5. Frequency of use according to duration and exposure of monoalkylglycol dialkyl acid esters.[23,24]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Neopentyl Glycol Dicaprate		Neopentyl Glycol Dicaprylate/Dicaprate		Neopentyl Glycol Diethylhexanoate		Neopentyl Glycol Diheptanoate	
Total/range	**69**	**0.1-50**	**102**	**0.017-22.7**	**77**	**0.9-57**	**415**	**1-33**
Duration of use								
Leave-on	64	0.1-40	91	0.045-22.7	71	0.9-57	409	1-33
Rinse-off	5	0.24-50	10	0.017-15	6	1.5-11	6	1.9-9
Diluted for (bath) use	NR	11	1	NR	NR	NR	NR	NR
Exposure type								
Eye area	5	3.5-50	2	0.094-18.9	14	1-36.5	20	2.8-18
Incidental ingestion	17	5-40	27	1.9-22.7	12	3.1-11.3	4	7
Incidental Inhalation-sprays	3[b]; 7[c]	6; 3.5-6[b]	19[b]; 17[c]	0.045-0.9[b]	8[b]; 6[c]	3.6-9.3; 0.9-7.5[d]	6; 295[b]; 54[c]	5-19.5; 3-19.5[b]
Incidental inhalation-powders	7[c]	2.5-16.8; 1-28.5[d]	1[d]; 17[c]	1; 2.2[d]	1; 6[c]	1.1-2; 3-57[d]	54[c]	2.4; 1-20.7[d]
Dermal contact	52	0.1-50	65	0.017-19	57	0.9-57	405	1-33
Deodorant (underarm)	NR	0.1[e]; 4[f]	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	1-6	10	0.045-0.9	8	1.5-9.3	6	1.9-19.5
Hair-coloring	NR	3.5	NR	NR	NR	1.8	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	17	5-40	28	0.017-22.7	13	3.1-11.3	6	7-9
Baby	NR	NR	1	NR	NR	NR	NR	1.2-2.2

	Neopentyl Glycol Diisostearate		Propanediol Dicaprylate		Propanediol Dicaprylate/Caprate		Trimethyl Pentanyl Diisobutyrate	
Total/range	**3**	**0.2-1.1**	**7**	**1**	**1**	**13.5**	**399**	**0.1-9.8**
Duration of use								
Leave-on	3	0.9-1.1	6	1	1	13.5	399	0.1-9.8
Rinse-off	NR	0.2	1	NR	NR	NR	NR	2
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type[a]								
Eye area	NR	NR	2	NR	NR	NR	NR	NR
Incidental ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	1[b]	NR	2[b]; 2[c]	NR	1[b]	NR	NR	NR
Incidental inhalation-powders	NR	0.9[d]	2[c]	1[d]	NR	13.5[d]	NR	NR
Dermal contact	2	0.9-1.1	7	1	1	13.5	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	0.2	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	399	0.1-9.8
Mucous Membrane	1	NR	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

NR = Not Reported; Totals = Rinse-off + leave-on+diluted for (bath) use product uses.

[a] 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.

[b] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[c] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[d] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[e] Not spray.

[f] Spray

Table 6. Current and historical frequency and concentration of use of monoalkylglycol dialkyl acid esters according to duration and exposure.[4,23,24]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2017	**2001**	**2016**	**2001**	**2017**	**2009**	**2016**	**2009**
	Glycol Distearate				**Neopentyl Glycol Diisononanoate**			
Totals*	**1663**	**28**	**0.5-13.1**	**0.2-9**	**NR**	**NR**	**1.3-5**	**1**
Duration of Use								
Leave-On	59	1	0.2-13.1	*1-6*	NR	NR	1.3	NR
Rinse-Off	1531	26	0.05-10	*0.2-9*	NR	NR	2-5	1
Diluted for (Bath) Use	73	1	0.2-5	*0.4-3*	NR	NR	NR	NR
Exposure Type								
Eye Area	1	NR	0.2-13.1	3	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 17[a]; 14[b]	NR	1-2.5[a]	2-6[b]	NR	NR	NR	NR
Incidental Inhalation-Powder	14[b]	NR	2.5; 2-5.4[c]	2-6[b]	NR	NR	NR	NR
Dermal Contact	621	19	0.05-13.1	0.2-6	NR	NR	1.3-5	1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	539	9	0.39-10	2-9	NR	NR	NR	NR
Hair-Coloring	502	NR	0.5-8	0.2-0.5	NR	NR	NR	NR
Nail	NR	NR	2	NR	NR	NR	NR	NR
Mucous Membrane	432	16	0.2-5	0.4-3	NR	NR	NR	NR
Baby Products	15	NR	0.4-0.6	1	NR	NR	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.

NR – no reported use

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 7. Monoalkylglycol dialkyl acid esters with no reported use.[4,23,24]

Butylene Glycol Diisononanoate	Dioctadecanyl Didecyltetradecanoate
Dioctadecanyl Ditetradecyloctadecanoate	Glycol Dibehenate
Glycol Dioleate	Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate
Glycol Dipalmate/Rapeseedate/Soyate	Glycol Dipivalate
Glycol Ditallowate	Hexanediol Distearate
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate	Neopentyl Glycol Dilaurate
Propanediol Diisostearate	Propanediol Dipelargonate

Table 8. Code of Federal Regulations that apply to monoalkylglycol dialkyl acid esters in this safety assessment.

Ingredient(s)	Regulation
Trimethyl Pentanyl Diisobutyrate	21CFR175.105 – may be used as a stabilizer in adhesives used in food packaging. 21CFR177.1200 - For use only in cellophane coatings and limited to use at a level not to exceed 10% by weight of the coating solids except when used as provided in § 178.3740 of this Chapter. 21CFR178.3740 - For use only in cellulosic plastics in an amount not to exceed 15% by weight of the finished food-contact article, provided that the finished plastic article contacts food only of the types identified in § 176.170(c) of this chapter, table 1, under Categories I, II, VI-B, VII-B, and VIII. I. Nonacid, aqueous products; may contain salt or sugar or both (pH above 5.0). II. Acid, aqueous products; may contain salt or sugar or both, and including oil-in-water emulsions of low- or high-fat content. VI. Beverages: B. Nonalcoholic. VII. Bakery products other than those included under Types VIII or IX of this table: B. Moist bakery products with surface containing no free fat or oil. VIII. Dry solids with the surface containing no free fat or oil (no end test required).
Glycol Distearate	21CFR73.1 - …[M]ay be safely used as diluents in color additive mixtures for food use exempt from certification, subject to the condition that each straight color in the mixture has been exempted from certification or, if not so exempted, is from a batch that has previously been certified and has not changed in composition since certification. If a specification for a particular diluent is not set forth in this part 73, the material shall be of a purity consistent with its intended use. (a) *General use.* (1) Substances that are generally recognized as safe under the conditions set forth in section 201(s) of the act. (2) Substances meeting the definitions and specifications set forth under subchapter B of this chapter, and which are used only as prescribed by such regulations. (2) *Diluents in color additive mixtures for coloring shell eggs.* Items listed in paragraph (a) of this section and the following, subject to the condition that there is no penetration of the color additive mixture or any of its components through the eggshell into the egg [as diethylene glycol distearate and ethylene glycol distearate].
Glycol Distearate, Glycol Ditallowate	21CFR176.210 - Defoaming agents may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions: (a) The defoaming agents are prepared from one or more of the substances named in paragraph (d) of this section, subject to any prescribed limitations. (b) The defoaming agents are used to prevent or control the formation of foam during the manufacture of paper and paperboard prior to and during the sheet-forming process. (c) The quantity of defoaming agent or agents added during the manufacturing process shall not exceed the amount necessary to accomplish the intended technical effect. (d) Substances permitted to be used in the formulation of defoaming agents include substances subject to prior sanctions or approval for such use and employed subject to the conditions of such sanctions or approvals, substances generally recognized as safe for use in food, substances generally recognized as safe for use in paper and paperboard, and substances listed in this paragraph, subject to the limitations, if any, prescribed. (1) Fatty triglycerides, and the fatty acids, alcohols, and dimers derived therefrom: Beef tallow. Diethylene glycol (esters).

Table 9. Acute toxicity studies of monoalkylglycol dialkyl acid esters.

Ingredient	Animal (n)	Methods; Results	Reference
		Dermal	
Trimethyl Pentanyl Diisobutyrate	Hartley guinea pigs (n = 3)	100%; 5, 10, or 20 mL/kg (4.63, 9.26, or 18.53 g/kg). Following depilation of abdomens, a single dose of undiluted test material was applied under occlusion for 24 h. Guinea pigs were observed on days 2, 7, and 14 after removal. There were no clinical signs. Two guinea pigs lost weight. LD_{50} > 20 mL/kg.	7,18,34
Trimethyl Pentanyl Diisobutyrate	Guinea pigs (not specified)	5 mg/kg. Slightly irritating.	18
Trimethyl Pentanyl Diisobutyrate	New Zealand White rabbits (n = 5/sex)	100% (2000 mg/kg). OECD TG 402 (Acute Dermal Toxicity). Test substance was administered to clipped skin, approximately 10% of the body surface, under semi-occlusion for 24 h. Residual test substance was removed with paper towels soaked in tap water. There were no mortalities. Clinical signs were: instances of diarrhea, few feces, and soiling of the anogenital area, which were resolved by day 14. Bodyweight gains were normal. At necropsy results were normal in 3 males and 3 females. Abnormalities included small spleen in 1 male, slight or scattered red areas in the thymus of 1 male, and slight or scattered red areas in the pancreas of 1 male and 2 females. LD_{50} > 2000 mg/kg.	7,34
Glycol Distearate	New Zealand White rabbits (n = 3/sex)	100% (0.5 g) was applied to shaved and abraded skin (2.5 cm^2) under occlusion for 25 h. All rabbits appeared active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behavior.	5
Glycol Distearate	New Zealand White rabbits (n = 3)	100%. Amount and duration not specified. Observed at 1, 24, 48 and 72 h and 7 days. No signs of systemic effects.	5

Table 9. Acute toxicity studies of monoalkylglycol dialkyl acid esters.

Ingredient	Animal (n)	Methods; Results	Reference
		Oral	
Trimethyl Pentanyl Diisobutyrate	Rats (n = 2)	800, 1600, or 3200 mg/kg by gavage and observed for 2 weeks. There were no mortalities. Effects were observed at 3200 mg/kg. Weight gains were normal. Clinical signs: moderate weakness and some vasodilatation following dosing.	7,18,34
Trimethyl Pentanyl Diisobutyrate	Female Wistar rats (n = 5)	2000 mg/kg by gavage and observed for 2 weeks. There were no mortalities. Weight gains were normal. Wet anogenital areas were observed on Days 0 and 1. Necropsies were unremarkable. LD_{50} > 2000 mg/kg.	7,34
Trimethyl Pentanyl Diisobutyrate	Mice (n = 2)	400, 800, 1600, 3200 or 6400 mg/kg by gavage and observed for 2 weeks. 1 mouse died within 1 day (not known which group but not in 6400 mg/kg group). Weight gains were normal. No clinical abnormalities were observed.	7,18,34
Diethylpentanediol Dineopentanoate	Female Sprague-Dawley CD rats (n = 6)	OECD TG 423 (Acute Oral Toxicity). The rats were treated by oral gavage with an undiluted dose of 2000 mg/kg and observed for 14 days. There were no mortalities. Ataxia and/or hunched posture were observed after treatment; all rats recovered 1 day after dosing. Weight gains were as expected and no abnormalities were observed at necropsy. LD_{50} was estimated to be > 2500 mg/kg	16,36
Glycol Distearate	Sprague-Dawley rats (n = 5/sex)	5000 mg/kg (2.5% in CMC) by oral gavage in two 2.2 - 2.3 mL doses within 24 h. Observed for 14 days. No mortalities or clinical signs of toxicity. LD_{50} > 5000 mg/kg.	5
Glycol Distearate	Rats (not specified)	OECD TG 401 (Acute Oral Toxicity) LD_{50} > 2000 mg/kg	37
Glycol Distearate	Female Swiss mice (n = 5)	Single dose at 5000 mg/kg by gavage. LD_{50} > 5000 mg/kg. No mortalities or clinical signs of toxicity were observed up to the end of the 14-day observation period.	5
Neopentyl Glycol Dicaprate	Female Sprague Dawley CD rats (n = 6)	OECD TG 423 (Acute Oral Toxicity). Single dose at 2000 mg/kg neat after fasting. LD_{50} > 2000 mg/kg. No mortalities or clinical signs of toxicity were observed.	17
Neopentyl Glycol Diethylhexanoate	Male and female rats (not specified)	Single dose at 2000 mg/kg in corn oil by gavage. OECD TG 401 (Acute Oral Toxicity) LD_{50} > 2000 mg/kg No mortalities or clinical signs of toxicity were observed.	9
Neopentyl Glycol Diethylhexanoate	Female Swiss mice (n = 5)	Single dose at 2 mL/kg (no details on administration) No mortalities or clinical signs of toxicity were observed up to the end of the 14-day observation period. LD_{50} > 2000 mL/kg (> 1880 mg/kg)	9
Neopentyl Glycol Diheptanoate	Male and female Alderley Park (Alpk: APfSD) albino rats (not specified)	Single dose at 2000 mg/kg in corn oil by gavage; OECD TG 401 (Acute Oral Toxicity). No mortalities or clinical signs of toxicity were observed up to the end of the 14-day observation period.	8
		Inhalation	
Trimethyl Pentanyl Diisobutyrate	Rats (n = 3)	Whole body apparatus at 0.12 mg/L (10 ppm) for 6 h and observed for 14 days. There were no mortalities or clinical signs. Weight gains were normal. LC_{lo} > 0.12 mg/L.	7,34
Trimethyl Pentanyl Diisobutyrate	Rats (n = 3)	Whole body apparatus at 5300 mg/L (453 ppm) for 6 h and observed for 14 days. There were no mortalities. Discolored (pink) extremities were observed. Weight gains were normal. LC_{lo} > 5300 mg/L.	7,18,34
Neopentyl Glycol Diheptanoate	RccHanTM;Wist rats (n = 3/sex)	Nose only apparatus for 4 h and observed for 14 days. Mean achieved test atmosphere concentration = 2.14 mg/mL (13.5 mg/L nominal). MMAD/GSD: 1.42 µm/2.56 µm. No mortalities. Clinical signs included: hunched posture and piloerection for short period after removal from exposure chamber. Increased respiratory rate was observed in all rats. On removal from chamber and 1 h post-exposure, all rats exhibited increased respiratory rates and ataxia. One day after exposure, all rats still showed increased respiratory rate and hunched posture with occasional instances of piloerection. All rats appeared normal at days 5 to 8 post-exposure. At necropsy, no macroscopic abnormalities were observed. LC_{50} > 5.22 mg/L (analytical).	6,8

CMC = carboxymethyl cellulose; GDS = Geometric standard deviation; MMAD = Mass median aerodynamic diameter; OECD TG = Organisation for Economic Co-operation and Development Test Guidelines

Table 10. In vitro genotoxicity studies of monoalkylglycol dialkyl acid esters.

Test Article	Concentration/Vehicle	Procedure	Test System	Results	Reference
Trimethyl Pentanyl Diisobutyrate	Without metabolic activation: 0,10, 15, 20, 25, 30, and 40 µg/mL With metabolic activation: 0, 250, 500, 750, 1000, 1500, 2000 µg/mL DMSO	OECD TG 476 (In Vitro Mammalian Cell Mutation Assay)	CHO cells	Negative with and without metabolic activation. Controls had expected response.	[7]
Trimethyl Pentanyl Diisobutyrate	Not specified	OECD TG 476 (In Vitro Mammalian Cell Mutation Assay)	CHO cells	Negative with and without metabolic activation.	[34]
Trimethyl Pentanyl Diisobutyrate	100, 250, 500, 1000, 2500, 5000 µg/plate DMSO	EU Method B.13/14 (Mutagenicity - Reverse Mutation Test Using Bacteria) [Ames test]	*S. typhimurium* (TA98, TA100, TA1535, and TA1537); *E. coli* (WP2 uvr A pKM 101)	Negative with and without metabolic activation. Controls had expected response.	[7]
Trimethyl Pentanyl Diisobutyrate	Not specified	OECD TG 471 (Bacterial Reverse Mutation Test)	*S. typhimurium* and *E. coli* (strains not specified)	Negative with and without metabolic activation.	[34]
Trimethyl Pentanyl Diisobutyrate	0, 312.5, 625, 1250, 2500 or 5000 µg/plate	Japanese Guideline for Screening Mutagenicity	*S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538); *E. coli* (uvrA)	Negative with and without metabolic activation.	[18]
Trimethyl Pentanyl Diisobutyrate	Without metabolic activation: 6.25, 12.5, 17.5, 25.0, 37.5, 50.0 µg/mL With metabolic activation: 125, 175, 250, 350, 500, 1000 µg/mL DMSO	OECD TG 473 (In vitro Mammalian Chromosome Aberration Test), OPPTS 870.5375 and EU B.10 (Mutagenicity - In Vitro Mammalian Chromosome Aberration Test)	CHO cells	Negative with and without metabolic activation. Controls had expected response.	[5]
Trimethyl Pentanyl Diisobutyrate	Not specified	OECD TG 473 (In vitro Mammalian Chromosome Aberration Test)	CHO cells	Negative with and without metabolic activation.	[34]
Trimethyl Pentanyl Diisobutyrate	Not specified	Japanese Guideline for Screening Mutagenicity	CHO cells	Negative with and without metabolic activation. Cytotoxic at 0.018 and 0.04 mg/mL with and without metabolic activation, respectively.	[18]
Diethylpentanediol Dineopentanoate	312.5, 625, 1250, 2500, and 5000 µg/plate with and without metabolic activation	Ames test	*S. typhimurium* (TA98, TA100, TA1535, and TA1537); *E. coli* (WP2 uvr A pKM 101)	Negative	[16,36]
Glycol Distearate	Experiment 1: 8, 40, 200, 1000 and 5000 µg/plate with and without metabolic activation Experiment 2: 61.73, 185.19, 555.56, 1666.67 and 5000 µg/plate with and without metabolic activation	Ames test; 3 days of exposure	*S. typhimurium* (TA98, TA100, TA1535, and TA1537)	Negative with and without metabolic activation. Controls had expected response.	[5]
Glycol Distearate	Experiment 1: 0.1, 0.3, 1.0, 3.0, 10.0, 33.0, 100.0 and 333.0 µg/mL with and without metabolic activation Experiment 2: 3.0, 10.0, 33.0, 100.0, 125.0, 140.0 and 175.0 µg/mL without metabolic activation 0, 0.1, 0.3, 1.0, 3.0, 10.0, 33.0, 100.0 and 333.0 µg/mL with metabolic activation	Ames test; Experiment 1: 3 h of exposure Experiment 2: 24 h of exposure without metabolic activation; 3 h of exposure with metabolic activation	*S. typhimurium* (TA98, TA100, TA1535, and TA1537)	Negative with and without metabolic activation. Controls had expected response.	[5]
Glycol Distearate	Not specified	OECD TG 471 (Bacterial	Not specified	Negative	[37]

Table 10. In vitro genotoxicity studies of monoalkylglycol dialkyl acid esters.

Test Article	Concentration/Vehicle	Procedure	Test System	Results	Reference
		Reverse Mutation Test)			
Glycol Distearate	Not specified	OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test)	Not specified	Negative	[37]
Neopentyl Glycol Dicaprate	5 concentrations: 50-5000 µg/plate in acetone	OECD TG 471 (Bacterial Reverse Mutation Test)	*S. typhimurium* (TA98, TA100, TA1535, and TA1537)	Negative. An oily precipitate was observed at ≥ 1500 µg/plate.	[17]
Neopentyl Glycol Diethylhexanoate	Experiment 1: 0.03, 0.1, 0.3, 1, 3, 10, 33, 100 µg/mL with and without metabolic activation Experiment 2: 0.03, 0.1, 0.3, 1, 3, 10, 33, 100 µg/ml (with metabolic activation; 0.3, 1, 3, 10, 33, 66, 85, 100, 125, 150 µg/mL: 1, 5, 10, 17.5, 25, 75, 100, 125, 50, 175, 200, 225, 250, 275 and 300 µg/mL; and 0.3, 1, 3, 10, 33, 100, 200, 300, 400, 500 and 600 µg/mL without metabolic activation.	OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test), EU Method B.17 (Mutagenicity-In Vitro Mammalian Cell Gene Mutation Test)	Mouse lymphoma L5178Y cells	Fluctuations in cytotoxicity without metabolic activation. Negative with and without metabolic activation. Controls had expected response.	[9]
Neopentyl Glycol Diethylhexanoate	Pretest: 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate without metabolic activation Main test: 50, 150, 500, 1500 and 5000 µg/plate with and without metabolic activation in acetone	EPA OPPTS 870.5265 (The *Salmonella typhimurium* Bacterial Reverse Mutation Test)	*S. typhimurium* (TA98, TA100, TA102, TA1535, and TA1537)	Precipitation at and above 1500 µg/plate. Negative with and without metabolic activation. Controls had expected response.	[9]
Neopentyl Glycol Diethylhexanoate	Range finding study: 3 h: 3, 10, 33, 100 and 333 µg/mL with and without metabolic activation 24 and 48 h: 3, 10, 33, 100, 333, 1000 and 3333 µg/mL without metabolic activation Experiment 1: 3 h: 3, 10, 33, 100 and 333 µg/mL with and without metabolic activation Experiment 2: 3 h: 50, 100 and 350 µg/mL with metabolic activation 24 and 48 h: 5, 10, 50, 150 and 200 µg/mL without metabolic activation 48 h: 10, 30, 50, 60, 70, 80, 90 and 100 µg/mL without metabolic activation In ethanol	OECD TG 473 (In vitro Mammalian Chromosome Aberration Test), EU Method B.10 (Mutagenicity - In Vitro Mammalian Chromosome Aberration Test)	Cultured peripheral human lymphocytes	Cytotoxic at 100 µg/mL without metabolic activation at 48 h. Negative with and without metabolic activation. Controls had expected response.	[9]
Neopentyl Glycol Diethylhexanoate	25, 75 and 150 µg/mL with and without metabolic activation	Chromosome aberration	Human lymphocytes from single male donor	Negative with and without metabolic activation. Controls had expected response.	[9]
Propanediol Dicaprylate/Caprate	0.005 mL/plate	Ames test without metabolic activation; 3 h of exposure with metabolic activation	*S. typhimurium* (TA 97a, TA98, TA100, TA102, and TA1535)	Negative with and without metabolic activation. Controls had expected response	[38]

CHO = Chinese hamster Ovary cells; DMSO = Dimethyl sulfoxide; OECD TG = Organisation for Economic Co-operation and Development Guidelines

Table 11. Animal dermal irritation studies of monoalkylglycol dialkyl acid esters.

Ingredient (concentration/dose)	Test Population	Procedure	Results	Reference
Trimethyl Pentanyl Diisobutyrate (100%; 5, 10, or 20 mL/kg; 4.63, 9.26, or 18.53 g/kg)	Hartley guinea pigs (n = 3)	Administered to depilated abdomens under occlusion for 24 h. Observed on days 2, 7, and 14 after removal.	At the 24- to 48-h examinations, slight to moderate edema and/or erythema with some hemorrhage was observed. Only desquamation was observed at the 1- and 2-week examinations.	[7]
Trimethyl Pentanyl Diisobutyrate (100%; 2000 mg/kg)	New Zealand White rabbits (n = 5/sex)	Administered to the clipped skin, approximately 10% of body surface under semi-occlusion for 24 h. Residual test substance was removed with paper towels soaked in tap water.	At removal, there was no erythema or edema observed in two males and one female. Very slight erythema (Grade 1) was present in one male and three females, and well defined erythema (Grade 2) was observed in one female. Very slight edema (Grade 1) was present in two males and one female and slight edema (Grade 2) was observed one male and two female. Seven days after removal of test substance, all males and three females were normal; two females had severe erythema (Grade 4) with flaking skin. One female had slight edema (Grade 2) and one had very slight edema (Grade 1).	[7]
Trimethyl Pentanyl Diisobutyrate (100%; 0.5 mL)	New Zealand White rabbits (n = 1 male, 2 females)	Administered to shaved skin under semi-occlusion for 4 h in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion)	There were no signs of irritation observed during study. Conclusion: not considered an irritant or corrosive.	[7,34]
Diethylpentanediol Dineopentanoate (neat)	New Zealand white rabbits (n = 3)	Administered to intact skin under semi-occlusion for 24 h in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion)	At 24, 48, and 72 h, the mean erythema/eschar scores were 0.67, 1.00, and 1.33, respectively; the edema scores were 0.00, 0.33, and 0.33, respectively. Signs of irritation were resolved at 7 days after exposure. No other clinical signs were observed. Classified as a non-irritant to rabbit skin.	[16,36]
Glycol Distearate (100%; 0.5 g)	New Zealand White rabbits (n = 3/sex)	Applied to shaved and abraded skin (2.5 cm^2) under occlusion for 25 h. Test site was observed at removal and 72 h after removal.	There were no signs of erythema or edema during study period. Draize scores for erythema and edema were 0 out of 4.	[5]
Glycol Distearate (100%)	New Zealand White rabbits (n = 3)	Applied to skin under occlusion; amount and duration not specified. Test site was observed at 1, 24, 48 and 72 h and 7 days after administration.	No effects on skin were observed during study period in any rabbit. Draize scores for erythema and edema were 0 out of 4.	[5]
Glycol Distearate (not specified)	Rabbits (not specified)	OECD TG 404 (Acute Dermal Irritation/ Corrosion)	Not irritating.	[37]
Glycol Distearate (25%, 50%, 75%, and 100% in water)	Pirbright guinea pigs (n = 3)	Applied under occlusion for 6 h. 100% was applied in a few drops of distilled water.	No signs of irritation.	[5]
Neopentyl Glycol Diethylhexanoate (not specified, tested neat)	New Zealand White rabbits (n = 3)	No further details were provided	Erythema and edema scores were 0 at 24, 48, and 72 h after administration	[9]
Neopentyl Glycol Diethylhexanoate (not specified, tested neat)	New Zealand White rabbits (n = 3)	4 h of exposure	Erythema scores were 0 at 24, 48, and 72 h after administration. Edema scores were 0.33, 0, and 0, respectively. No signs of irritation were observed in two rabbits. Slight erythema and transient slight edema were observed in third rabbit, which was completely resolved 2 days after removal of test substance.	[9]
Neopentyl Glycol Diheptanoate (100%; 0.5 mL)	New Zealand White rabbits (n = 3)	Administered to shaved skin under semi-occlusion for 4 h in accordance with OECD TG 404 (Acute Dermal Irritation/Corrosion). Application site examined at 1, 24, 48 and 72 h.	No signs of erythema or edema were observed during the test period.	[8]

OECD GL = Organisation for Economic Co-operation and Development Guidelines

Table 12. Animal sensitization studies of monoalkylglycol dialkyl acid esters

Ingredient	Concentration	Animal (n)	Assay	Results	Reference
Trimethyl Pentanyl Diisobutyrate	1% in acetone	guinea pigs (4, 5 solvent control, 4 positive control)	Induction and challenge were by open epicutaneous exposure. Positive control was phenylhydrazine. Examinations at 24 and 48 h after the challenge dose.	No positive sensitization reactions in the test or negative control groups. Positive control group had the expected response. Not considered a skin sensitizer in this study.	[7]
Trimethyl Pentanyl Diisobutyrate	1% in organic solvent	Guinea pigs (3),	Dermal sensitization study. No further details were provided.	No signs of sensitization	[34]
Diethylpentanediol Dineopentanoate	Injected 25% (0.1 mL in paraffin oil and Freund's adjuvant) then treated topically with 100%. Challenge was topical application at 100% (0.5 mL)	Male albino Hartley guinea pigs (10; controls = 5)	In accordance with OECD TG 406 (skin sensitization)	No reactions were observed in any of treated guinea pig. Test substance was a non-sensitizer.	[16,36]
Glycol Distearate	100% in a few drops of water for both induction and challenge	Pirbright guinea pigs (20; 10 controls)	Test sites were examined 24 and 48 h after challenge	No signs of sensitization.	[5]
Glycol Distearate	Not specified, assumed 100%	Guinea pigs (not specified)	In accordance with OECD TG 406	Not sensitizing	[37]
Neopentyl Glycol Diheptanoate	Induction phase was conducted at 100%, challenge at 30% in corn oil and 100%.	Male Dunkin-Hartley guinea pigs (20; 10 controls)	In accordance with OECD TG 406	One guinea pig had mild redness at 24 h after the high-dose challenge; there were no signs of any type of reaction at the test sites at 48 h. Not sensitizing	[6,8]

OECD TG = Organization for Economic Co-operation Guidelines

Table 13. HRIPTs of monoalkylglycol dialkyl acid esters.

Ingredient	Details	n	Results	Reference
Trimethyl Pentanyl Diisobutyrate	1.0% in acetone. Occlusive patches were applied to backs of subjects for 24 h each 3 times per week for a total of 9 applications. Challenge patch was applied after 10-17 days to a naïve site.	102	At 48 h after challenge, 2 subjects exhibited "slight, confluent or patchy erythema", which persisted to 96 h. One subject experienced a spreading reaction beyond patch area with all test articles (assumed multiple tests were being conducted at once), which developed into a papular rash of the entire torso; subject described a history of such reactions, and was discontinued from study and followed to resolution. Another subject exhibited slight reactions at challenge, which was generally consistent with irritation.	7
Trimethyl Pentanyl Diisobutyrate	1.0% in acetone. Semi-occlusive patches were applied 3 times per week for 3 weeks. After a 2-week rest, the challenge patch was applied to a naïve site.	200	Isolated instances of slight to mild redness were observed during induction. There were3 instances of slight redness during challenge phase. Test substance was non-sensitizing.	34
Trimethyl Pentanyl Diisobutyrate	1.0% in acetone. Semi-occlusive patches were applied 3 times per week for 3 weeks. Patches were in place for 24 h. Challenge was applied after a two-week rest.	203	Two subjects exhibited slight erythema to test substance on at least 5 occasions out of the 9 exposures. None of the subjects had a reaction at challenge. Test material was reported to be non-sensitizing.	41
Neopentyl Glycol Diethylhexanoate	100%; 0.2 mL, 0.2 mg. Test substance was applied to upper back of subjects 3 times per week for 3 weeks. Patches were left in place for 24 h. A challenge patch was applied to naïve site after a 10- to 14-day rest. Reactions were scored 24-48 h after application of test material.	50	No adverse reactions of any kind were observed during the course of this study; the test substance was not an irritant or a sensitizer.	40
Neopentyl Glycol Diethylhexanoate	100%; 0.2 mL-Webril adhesive patches were applied 3 times per week for 9 applications and left in place for 24 h. Challenge was applied after approximately 14 days.	96	During the induction phase one subject exhibited faint, minimal erythema. No reactions were observed during the rest and challenge phases of the experiment. No sensitizing reactions were reported.	9
Propanediol Dicaprylate/Caprate	100%; 0.2 mL, 0.2 mg. Test substance was applied to upper back of subjects 3 times per week for 3 weeks. Patches were left in place for 24 h. A challenge patch was applied to naïve site after a 10- to 14-day rest. Reactions were scored 24-48 h after application of test material.	50	No adverse reactions of any kind were observed during the course of this study.	42
Propanediol Dipelargonate	100%; 0.2 mL, 0.2 mg. Test substance was applied to upper back of subjects 3 times per week for 3 weeks. Patches were left in place for 24 h. A challenge patch was applied to naïve site after a 10- to 14-day rest. Reactions were scored 24-48 h after application of test material.	50	No adverse reactions of any kind were observed during the course of this study.	43

HRIPT = Human repeated insult patch test

Table 14. Ocular irritation studies on New Zealand White rabbits.

Ingredient	Concentration (%)	n	Method	Results	Reference
Trimethyl Pentanyl Diisobutyrate	100	6	0.1 mL. Instilled into one eye, the other served as the control. 3 were washed immediately, 3 were not. Observed at 1, 24, 48, and 72 h.	There was slight redness for 1 unwashed eye and 3 washed eyes at the 1 h. There was no staining in unwashed or washed eyes when tested with fluorescein dye at 24 h. There were no abnormal systemic signs noted during the observation period.	[7,34]
Diethylpentanediol Dineopentanoate	Neat; 0.1 mL	3	OECD TG 405 (Acute Eye Irritation/Corrosion). Eyes were not rinsed.	All eyes were normal at 24 h after treatment. Maximum score of 4.0 (Class 3 on a 1 to 8 scale) according to a modified Kay and Calandra scale. Minimal irritant	[16,36]
Glycol Distearate	100	3/sex	0.1 g. Instilled into one eye, other eye served as control. Eyes were examined at 24, 48 and 72 h after instillation	After 24 h, 4 rabbits had mild redness and 2 of 6 had moderate redness. At 48 h, 4 rabbits had mild redness visible, which was fully reversible in 2 rabbits and persistent up to 72 h in 2 rabbits. After 24 h, 1 rabbit had mild chemosis, which was fully reversible within 48 h. Average irritation scores (out of 4) for redness, swelling, iris corrosion, and cornea corrosion were 0.78, 0.06, 0.0, and 0.0, respectively. Not an ocular irritant.	[5]
Glycol Distearate	Not specified, tested neat	3	Instilled into one eye, other eye served as control. Eyes were examined at 24, 48 and 72 h after instillation.	No effects on cornea and iris were observed during the study period in any rabbit. At 1 h after instillation, moderate conjunctivae reactions were observed; these conjunctivae reactions were reduce at 24 and 48 h, and all effects were fully resolved in all rabbits at 72 h. Average irritation scores for conjunctivae, iris corrosion, and cornea corrosion were 0.7, 0.0, and 0.0, respectively. Not an ocular irritant.	[5]
Neopentyl Glycol Diethylhexanoate	Not specified, tested neat	3	Eyes were examined at 4, 24, 48, 72 h and 7 days after instillation.	Conjunctival reactions were observed in all 3 animals after 4 h, which resolved within 24 h in 1 rabbit and within 48 h in other 2 rabbits. Not irritating.	[9]
Neopentyl Glycol Diethylhexanoate	Not specified, tested neat	3[a]	Instilled into one eye, other served as the control. The eyes were examined at 1h and 1, 2, and 3 days after instillation.	Slight erythema was observed in all rabbits 1 h after instillation, which was resolved in 2 rabbits at 1 day and the third at day 2. Erythema was observed in 1 rabbit and discharge was observed in all 3 rabbits only at 1 h after instillation. Not irritating.	[9]
Neopentyl Glycol Diheptanoate	100; 0.1 mL	2 males	OECD TG 405 (Acute Eye Irritation/Corrosion); EU Method B.5 (Acute Toxicity: Eye Irritation / Corrosion). Eyes were examined at 1, 24, 48 and 72 h after instillation.	No effects on cornea or iris observed. Moderate (grade 2) conjunctival irritation was observed in both rabbits 1 h after treatment. At 24 h, only minimal conjunctival irritation (grade 1) was present, which was resolved at 48 h. Not irritating.	[8]

OECD TG = Organisation for Economic Co-operation and Development Test Guidelines
[a] Strain of rabbit not specified.

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