Safety Assessment of Monoalkylglycol Dialkyl Acid Esters as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	November 11, 2016
Panel Meeting Date:	December 5-6, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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Cosmetic Ingredient Review

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: November 11, 2016

Subject: Safety Assessment of Monoalkylglycol Dialkyl Acid Esters as Used in Cosmetics

Attached is the Draft Report of Monoalkylglycol Dialkyl Acid Esters as used in cosmetics. [*magdae122016Rep*] These ingredients in this report are structurally related to each other as alkyl esters of monoalkyl diols that vary by type of diol and lengths of the fatty acid residues. Three of these ingredients (Glycol Distearate, Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate, and Neopentyl Glycol Diisononanoate) have been previously review and were found to be safe as used. They are included here because of their similar chemical structure. The previous reports are included in this packet. [*magdae122016Prev_1,2,3*]

In October 2016, the Scientific Literature Review (SLR) was posted with a request for any additional information, including dermal penetration, chronic dermal toxicity, inhalation toxicity, carcinogenicity, and dermal irritation and sensitization data. HRIPTs, an *in vitro* ocular irritation assay, and a mutagenicity assay were submitted. [*magdae122016Data_1*] Product information sheets on Glycol Distearate were also submitted. [*magdae122016Data_2*] The Council submitted concentration of use data. [*magdae122016Data_3,4*]

1,4-Butanediol Bisdecanoate and 1,2-Hexanediyl Dicaprate are reported to function as skin bleaching agents. Skin bleaching agent is not a cosmetic function; use as a skin bleaching agent is classified as a drug use and does not fall under the purview of CIR. No other functions were reported for these two ingredients. Neither of these ingredients have any reported uses in the VCRP data in the Council's survey.

Council comments have been addressed. [*magdae122016PCPC*]

If no further data are needed, the Panel should develop the basis for the Discussion and issue a Tentative Report. If more data are required, the Panel should list the data that are needed for a conclusion of safety, and issue an Insufficient Data Announcement.

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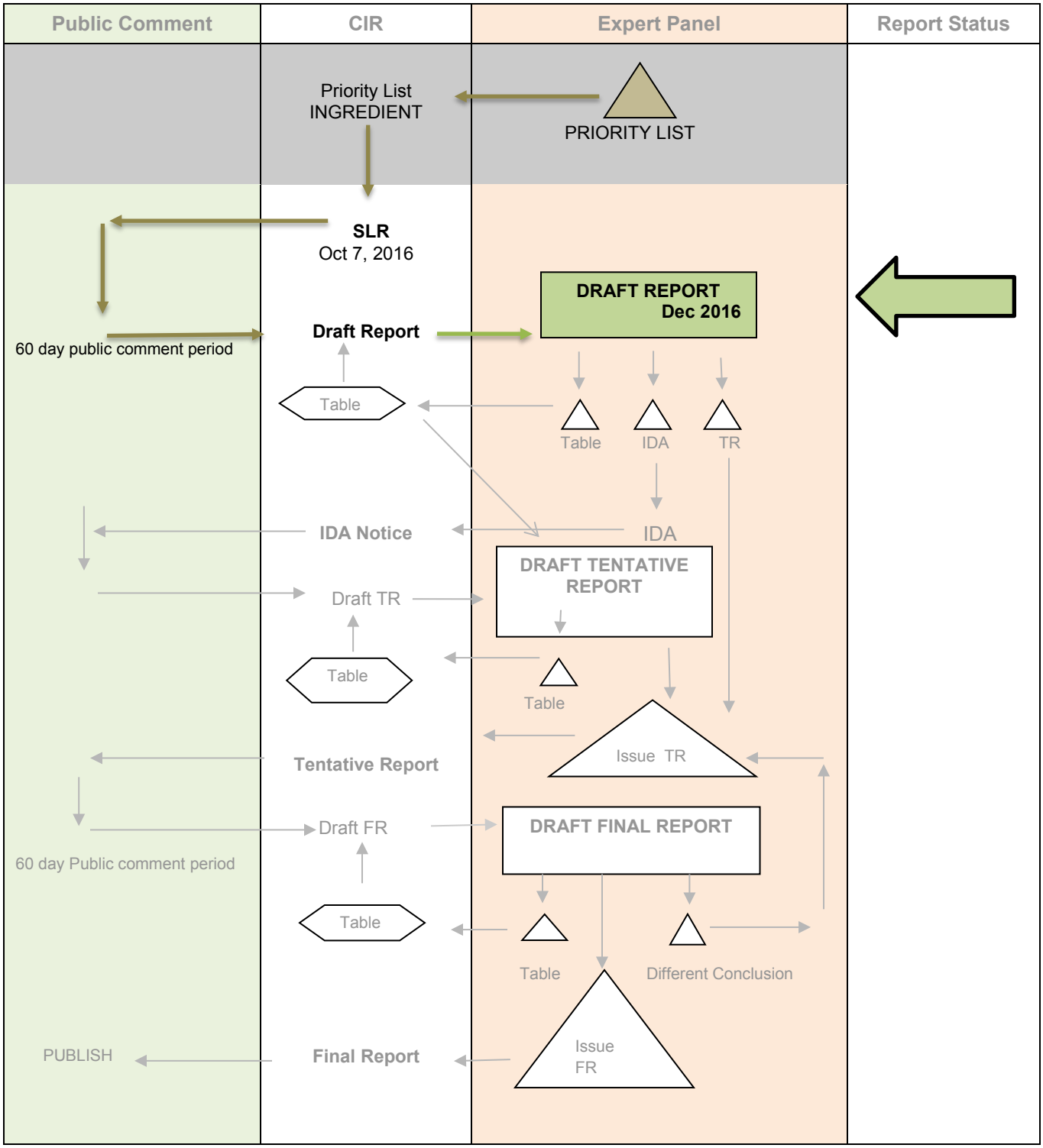
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Monoalkylglycol Dialkyl Acid Esters

MEETING Dec 2016



History - Monoalkylglycol Dialkyl Acid Esters

1982, 2001 – Glycol Distearate is safe as used.

2011 - Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate and Neopentyl Glycol Diisononanoate are safe as used.

2015 – Monoalkylglycol Dialkyl Acid Esters added to the priority list.

October 6, 2016 – SLR posted for public comment.

December, 2016 – The Panel is to examine the Draft Report.

Monoalkylglycol Dialkyl Acid Esters Data Profile for ***December*, 2016**. Writer – Lill Becker																					
		ADME		Acute toxicity			Repeated dose toxicity			Irritation					Sensitization						
	Use	Log K_{ow}	Dermal Penetration	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Animal	Ocular In Vitro	Dermal Animal	Dermal Human	Dermal In Vitro	Animal	Human	In Vitro	Repro/Devel	Genotoxicity	Carcinogenicity	Phototoxicity
Trimethyl Pentanyl Diisobutyrate	N			N	N	N	N			N		N			N	N		N	N		
1,4-Butanediol Bisdecanoate																					
Butylene Glycol Dicaprylate/Dicaprate	N																				
Butylene Glycol Diisononanoate																					
Butylethylpropanediol Dimer Dilinoleate																					
Diethylpentanediol Dineopentanoate	N																				
Dioctadecanyl Didecyltetradecanoate																					
Dioctadecanyl Ditetradecyl-octadecanoate																					
Glycol Dibehenate																					
Glycol Diethylhexanoate	N																				
Glycol Dilaurate	N																				
Glycol Dioleate																					
Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate																					
Glycol Dipalmate/Rapeseedate/Soyate																					
Glycol Dipivalate																					
Glycol Distearate	O N			O N	N			O		N		O N			O N	O		N	N		
Glycol Ditallowate																					
Hexanediol Distearate																					
1,2-Hexanediyl Dicaprate																					
Neopentyl Glycol Dicaprate	N																				
Neopentyl Glycol Dicaprylate/Dicaprate	N																				
Neopentyl Glycol Dicaprylate/ Dipelargonate/Dicaprate																					
Neopentyl Glycol Diethylhexanoate	N			N						N		N				N			N		
Neopentyl Glycol Diheptanoate	N			N		N				N		N			N						
Neopentyl Glycol Diisononanoate	O N			O	O					O		O			O	O			O		
Neopentyl Glycol Diisostearate	N																				
Neopentyl Glycol Dilaurate																					
Propanediol Dicaprylate	N																				
Propanediol Dicaprylate/Caprate	N										N					N			N		
Propanediol Diisostearate																					
Propanediol Dipelargonate																N					

O – Data from previous reports.

N – New data in this report.

Monoalkylglycol Dialkyl Acid Esters

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Trimethyl Pentanyl Diisobutyrate	6846-50-0	Y	N	6/0	36/0	Y	Y	Y	?	Y	N	Y	N	Y/0	N	N	N	N
1,4-Butanediol Bisdecanoate	26719-50-6	Y	N	682/0	14/0	N	N	N	N	N	N	N	N	N	N	N	N	N
Butylene Glycol Dicaprylate/Dicaprate		Y	N	0	0	N	N	N	N	N	N	N			N		N	Y
Butylene Glycol Diisononanoate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Butylethylpropanediol Dimer Dilinoleate		Y	N	2/0	0	N	N	N	N	N	N	N			N		N	N
Diethylpentanediol Dineopentanoate	762268-78-0	Y	13/0	13/0	0	N	N	N	N	N	N	N	N	N	N	N	N	Y
Dioctadecanyl Didecyltetradecanoate		Y	N	0	0	N	N	N	N	N	N	N			N		N	Y
Dioctadecanyl Ditetradecyloctadecanoate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Glycol Dibehenate	79416-55-0	Y	N	0	2/0	N	N	N	N	N	N	N	N	N	N	N	N	Y
Glycol Diethylhexanoate		Y	N	0	0	N	Y		N	N	N	N			N		N	N
Glycol Dilaurate	624-04-4	Y	N	5/0	175/0	N	N	N	N	N	N	N	N	N	N	N	N	Y
Glycol Dioleate		Y		13/0	12/0	N	N	N	N	N	N	N			N		N	N
Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Glycol Dipalmate/ Rapeseedate/Soyate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Glycol Dipivalate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Glycol Distearate	627-83-8 91031-31-1	Y	N	16/0	3/0	Y	Y	Y	N	N	Y	N	N	N	N	N	N	N
Glycol Ditallowate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Hexanediol Distearate	26730-92-7	Y	N	0	2/0	N	N	N	N	N	N	N	N	N	N	N	N	Y
1,2-Hexanediyl Dicaprate		Y	N	4/0	0	N	N	N	N	N	N	N			N		N	N
Neopentyl Glycol Dicaprate	27841-06-1	Y	N	0	2/0	N	Y	N	N	N	N	N	N	N	N	N	N	N
Neopentyl Glycol Dicaprylate/Dicaprate	70693-32-2	Y	N	0	0	N		Y	N	N	N	N	N	N	N	N	N	Y

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Neopentyl Glycol Dicaprylate/ Dipelargonate/ Dicaprate		Y	N	0	0	N	N	N	N	N	N	N			N		N	Y
Neopentyl Glycol Diethylhexanoate	28510-23-8	Y	N	0	27/0	N	N	Y	N	N	N	N	N	N	N	N	N	Y
Neopentyl Glycol Diheptanoate	68855-18-5	Y	N	0	5/0	N	Y	Y	N	N	N	N	N	N	N	N	N	N
Neopentyl Glycol Diisononanoate	27841-07-2	Y	N	0	1/0	N	N	N	N	N	N	N	N	N	N	N	N	N
Neopentyl Glycol Diisostearate	109884-54-0	Y	27/0	0	0	N	N	N	N	N	N	N	N	N	N	N	N	Y
Neopentyl Glycol Dilaurate	10525-39-0	Y	N	0	1/0	N	N	N	N	N	N	N	N	N	N	N	N	
Propanediol Dicaprylate	1020852-63-4 56519-71-2	Y	N	1/0	0	N	Y	Y	N	N	N	N	N	N	N	N	N	Y
Propanediol Dicaprylate/Caprate	1072005-10-7	Y	N	0	0	N	N	N	N	N	N	N	N	N	N	N	N	Y
Propanediol Diisostearate		Y	N	0	0	N	N	N	N	N	N	N			N		N	N
Propanediol Dipelargonate	28267-33-6	Y	N	0	4/0	N	N	N	N	N	N	N	N	N	N	N	N	N

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INTRODUCTION

This is a review of the available scientific literature and unpublished data relevant to assessing the safety of 31 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 that vary by type of diol and lengths of the fatty acid residues. The ingredients in this report are:

Trimethyl Pentanyl Diisobutyrate
1,4-Butanediol Bisdecanoate
Butylene Glycol Dicaprylate/Dicaprate
Butylene Glycol Diisononanoate
Butylethylpropanediol Dimer Dilinoleate
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
1,2-Hexanediyl Dicaprate
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

According to the *International Cosmetic Dictionary and Handbook* (*Dictionary*), the functions of these ingredients include: film former, hair conditioning agent, opacifying agent, plasticizer, skin-conditioning agents (emollient, miscellaneous, and occlusive), slip modifier, solvent, surface modifier, and viscosity increasing agent – nonaqueous.[1] 1,4-Butanediol Bisdecanoate and 1,2-Hexanediyl Dicaprate are reported to function as skin bleaching agents. Skin bleaching agent is not a cosmetic function; use as a skin bleaching agent is classified as a drug use and, as such, does not fall under the purview of Cosmetic Ingredient Review (CIR).

Glycol Distearate has been previously reviewed by the CIR Expert Panel (Panel) and was found to be safe as used; the conclusion was reaffirmed by the Panel 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.[4]

The Panel has reviewed related ingredients, moieties, and component parts of these ingredients (Table 2). Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid; Butylene Glycol; Tallow and related ingredients; propylene glycol esters; and plant-derived fatty acid oils are safe as used.[3-10] Alkyl esters are safe in cosmetic formulations in the present practices of use and concentration when formulated to be non-irritating.[11] Alkane diols are currently under review by the CIR Panel; an insufficient data announcement was issued in September 2016.[12]

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.[13-17] 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 details (http://www.cir-safety.org/ingredients).

CHEMISTRY

Definition and Structure

The ingredients in this report are structurally related to each other as alkyl esters of monoalkyl diols. Each ingredient is a diester of a diol (glycol). These ingredients vary by the type of diol and the lengths of the fatty acid residues (Figure 1).

For example, 1,4-Butanediol Bisdecanoate is a diol (1,4-butanediol) esterified at both ends with a fatty acid (decanoic acid) (Figure 2).

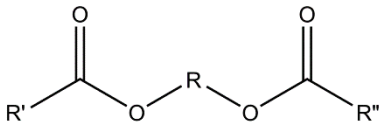


Figure 1. Monoalkylglycol Dialkyl Acid Esters in which "ORO" is the residue of a diol and "R'C(O)" and "R"C(O)" are the residues of a fatty acids.

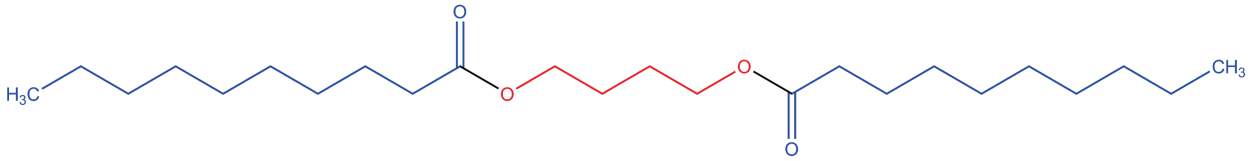


Figure 2. 1,4-Butanediol Bisdecanoate

Physical and Chemical Properties

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 (Table 3).[16,18-20] However, longer chain diesters, such as Glycol Distearate, can be white to cream-colored waxy solids.[3] The physical properties of these ingredients may vary within specified limits according to the proportions of mono- and diesters 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.

Trimethyl Pentanyl Diisobutyrate is stable at pH 4.0 and 7.0.[21] The half-life at pH 9 is 178 days.

UV Absorption

Data provided by a manufacture indicated that Neopentyl Glycol Diisononanoate did not absorb significantly in the 250 to 400 nm range.[4] The structural components of the monoalkylglycol dialkyl acid esters are not indicative of potential absorption. Accordingly, absorption would not be expected for these ingredients.

Method of Manufacture

In general, alkyl esters can be produced industrially via the esterification of carboxylic acids with the corresponding glycols (with or without a metal catalyst).[22] The sources of these carboxylic acids and glycols are often natural or are derived from natural sources (e.g., Glycol Dipalmate/Rapeseedate/Soyate and Glycol Ditallowate). Acids from natural 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. Because the former is known to be contaminated with traces of 1,4-dioxane, it is possible that such traces also appear in the synthesized material.[23] The cosmetic industry should use additional purification steps to remove 1,4-dioxane, from the ingredient before blending into cosmetic formulations.

A batch of Neopentyl Glycol Diheptanoate was reported to be >99% pure; the impurities were not named.[14]

One batch of Trimethyl Pentanyl Diisobutyrate was reported to be >99% pure, and another batch was reported to be 98.95% pure.[15] 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.[21]

A product data sheet for a product mixture containing Glycol Distearate (88%-95%), ethylene glycol monostearate (5%-15%), and ethylene glycol (<4%) reported that this product contained <1 ppb tolulene.[24,25] This product mixture does not contain >10 ppm of the following: cadmium, mercury, antimony, arsenic, chromium, cobalt, nickel, lead, or silver.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the 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 VCRP database. Use concentration data are submitted by Industry in response to surveys, conducted by the Council, of maximum reported use concentration by product category.

According to VCRP survey data received in 2016, Glycol Distearate was reported to be used in 1613 formulations, mostly in hair products (1029 formulations); this is an increase from 28 uses in 2001(Table 4 and Table 5).[2,4,26] Trimethyl Pentanyl Diisobutyrate and Neopentyl Glycol Diheptanoate are used in 315 (all nail products) and 337 (mostly in skin care products) formulations, respectively. The rest of the ingredients with reported uses were used in 94 or fewer formulations. As for the other ingredients that were previously reviewed by CIR, Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate had no uses reported to the VCRP in 2001 or 2016 and Neopentyl Glycol Diisononanoate is no longer reported to be used in a cleansing product (the only use reported).

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).[27] Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use; it is used up to 50% (in eye makeup removers).

In 2001, Glycol Distearate was reported to be used at up to 9% in rinse-off products (non-coloring hair products) and up to 6% in leave-on products (body and hand products); in 2016, the maximum concentrations of use were reported to have increased to 10% (non-coloring hair products) and 13.1% (products used around the eye), respectively.[2,4,27] 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 received from industry. For example, Glycol Diethylhexanoate had no reported uses in the VCRP, but a maximum use concentration in a foundation 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 the 2016 VCRP and industry survey are listed in Table 6.

Several of these ingredients (e.g., Butylene Glycol Dicaprylate/Dicaprate, Glycol Diethylhexanoate, Glycol Distearate and Neopentyl Glycol Dicaprate) are reported to be used in products applied near the eye (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., Butylene Glycol Dicaprylate/Dicaprate, Neopentyl Glycol Dicaprate, Neopentyl Glycol Dicaprylate/Dicaprate, Neopentyl Glycol Diethylhexanoate, Neopentyl Glycol Diheptanoate, and Neopentyl Glycol Diisostearate) at up to 40%. Neopentyl Glycol Dicaprate is used in bath oils, tablets and salts that may come in contact with mucus membranes at up to 11% (before it is diluted for the bath). Neopentyl Glycol Dicaprylate/Dicaprate and Neopentyl Glycol Diheptanoate are reported to be used in baby products (i.e. 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, Butylene Glycol Dicaprylate/Dicaprate, Glycol Distearate, and Neopentyl Glycol Diheptanoate were reported to be used in cologne and toilet waters, perfumes, and/or other fragrance preparations at up to 5%. Neopentyl Glycol Dicaprate was reported to be used in aerosol hair sprays at up to 6%; Neopentyl Glycol Diheptanoate was reported to be used in a pump hair spray at up to 19.5%, and Neopentyl Glycol Diethylhexanoate was reported to be used at up to 3.6% in aerosol hair sprays and 9.3% in pump hair sprays. Neopentyl Glycol Diethylhexanoate is reported to be used in spray body and hand products10%. Neopentyl Glycol Dicaprate was reported to be used in spray deodorants at up to 4%. Butylene Glycol Dicaprylate/Dicaprate, Neopentyl Glycol Dicaprate, Neopentyl Glycol Dicaprylate/Dicaprate, Neopentyl Glycol Diethylhexanoate, Neopentyl Glycol Diheptanoate were reported to be used in face powders at up to 16.8% and could possibly be inhaled. 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.[28-32] 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.[28,30] 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.[28] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Conservative estimates of inhalation exposures to respirable particles during the use of loos-powder cosmetic products are 400- to 1000-fold less than protective regulatory guidance limits for inert airborne respirable particles in the workplace.[33]

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.[34]

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, nail care products, vinyl flooring, sporting goods, traffic cones, vinyl gloves, inks, water-based paints, and toys.[35]

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 7.

The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) rates Trimethyl Pentanyl Diisobutyrate as Tier 1.[36] Chemicals identified based on the Tier I assessment do not to pose an unreasonable risk to workers, public health, and/or the environment.

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

ORAL EXPOSURE

Trimethyl Pentanyl Diisobutyrate

In an oral metabolic fate and disposition study of radio-labeled Trimethyl Pentanyl Diisobutyrate (as diisobutyrate ester of 2,2,4-trimethyl-1,3-pentanediol-3-^{14}C), 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.[37,38] An additional set of rats was also administered approximately 186.7 mg/kg radio-labeled 2,2,4-trimethyl-1,3-pentanediol (TMPD-3-^{14}C), a potential metabolite of Trimethyl Pentanyl Diisobutyrate. Trimethyl Pentanyl Diisobutyrate was rapidly absorbed and excreted, with renal excretion accounting for 47%-72% of the dose within 5-10 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 TMPD-3-^{14}C or its metabolites. Less than 1% of the administered radioactivity was retained in the tissues and carcass. In the rats administered TMPD-3-^{14}C, urinary excretion accounted for 94% of the dose with 93% being extracted within the first 48 h. Expired air contained no detectable $^{14}CO_2$ 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 TMPD-3-^{14}C, 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 the 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 2,2,4-trimethyl-1,3-pentanediol-3-^{14}C), the test substance was administered to Sprague-Dawley rats (n=5/group) by gavage.[37] 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%-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%-99% of the dose. The majority of the recovered Trimethyl Pentanyl Diisobutyrate was in the form of metabolites. The amount of residual test substance 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).[39] Analysis of the extract showed that 8% to 36% of the dose remained as Trimethyl Pentanyl Diisobutyrate, 18%-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).[39] At 48 h after dosing, the major urinary metabolite was the *O*-glucuronide of TMPD (72%-73% of the dose). Other compounds detected in the urine were the sulfate (6.4%-6.5%) and free forms of TMPD (1%-1.7%), and free 2,2,4-trimethyl-3-hydroxyvaleric acid (3%) and its glucuronide (4.3%-4.4%).

TOXICOLOGICAL STUDIES

Acute Dose Toxicity

Dermal

Neopentyl Glycol Diisononanoate; 2011

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 8.

The dermal LD_{50} of Trimethyl Pentanyl Diisobutyrate was reported to be >20 mL/kg in guinea pigs and >2000 mg/kg in rabbits.[15,21,37] Clinical signs were: instances of diarrhea, few feces, and soiling of the anogenital area. Glycol Distearate was not toxic to rabbits at 100%.[13]

Oral

Neopentyl Glycol Diisononanoate; 2011

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; 1982

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 8.

The oral LD_{50} of Trimethyl Pentanyl Diisobutyrate was reported to be >2000 mg/kg in rats.[15,21,37] Clinical signs included moderate weakness and some vasodilatation. No clinical abnormalities were observed in mice administered up to 6400 mg/kg by gavage.[15,21,37] The oral LD_{50} or Glycol Distearate for mice was reported to be >5000 mg/kg.[13] The oral LD_{50} of Neopentyl Glycol Diethylhexanoate was reported to be >2000 mg/kg in rats and >1880 mg/kg in mice.[17] No mortalities or clinical signs of toxicity were observed when rats were orally administered a single dose of Neopentyl Glycol Diheptanoate (2000 mg/kg).[16]

Inhalation

Acute inhalation toxicity studies are summarized in Table 8.

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.[21,37,38] 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.[16,40]

Short-Term Toxicity Studies

Dermal

Glycol Distearate; 1982

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 hematologic, 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 (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 study for a combined repeated dose/reproduction and development 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.[37,38] 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.[38]

- 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. 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 prior to the end of the experiment in animals consuming the 1.0% diet, 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*-NO_2-anisole 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*-NO_2-anisole 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.[38]

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.[21,37,38] 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 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 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; 1982

Two formulations [containing Glycol Distearate] were tested 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.[37,38] 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 correlated with microscopic examination). In male rats, the lowest-observed-effects-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, 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.[38] 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. [See Short-Term Toxicity Studies for data on the other two experiments]

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 minimal reduction (<10%) in growth in the groups administered Trimethyl Pentanyl Diisobutyrate at 1.0% was not statistically significant. Liver weights, relative to body weight, were slightly increased in animals consuming the 1.0% diet immediately prior to 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*-NO_2-anisole demethylase activity increased for both sexes at the high dose, while bilirubin glucuronyl transferase activity was elevated only for 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.[38]

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.[37,38] 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 due to weight loss and symptoms 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. Slightly increased liver weights were observed in the 1.0% group of males relative to the control group, but differences were likely considered adaptive by the authors and not representative of a toxic effect. Kidney weights were reduced 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 autopsy 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.[37,38] 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.[37,38] The female rats were treated over 4 phases of the study for a total of 40-51 days:

- premating (14 days)
- mating (1-8 days)
- gestation (21-23 days)
- early lactation (4-5 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 showed 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 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. 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 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 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.[37,38]

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 40-53 (females) days beginning prior to mating.[21,37,38] [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 no-observed-effect level (NOEL) 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 NOEL 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.[38] 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. Due to lower body weight gains and/or body weight loss, the NOAEL for maternal toxicity was reported to be 4.5 mg/g of feed (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% (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.[38]

Glycerol Distearate

Glycerol Distearate (0, 100, 300, or 900 mg/kg/day) was administered by gavage to pregnant Sprague-Dawley CD rats (n=24) on GD 6 through 15.[13] 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 Glycerol 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 between 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; 2011

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 9.

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

tests (up to 1000 µg/mL).[13,15,21,37] Glycol Distearate was not mutagenic in Ames tests up to 5000 µg/plate.[13] 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).[17] Propanediol Dicaprylate/Caprate was not mutagenic in an Ames test at 0.005 mL/plate.[41]

CARCINOGENICITY STUDIES

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

OTHER RELEVANT STUDIES

Endocrine Effects

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.[42] 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); CALUX® cell lines (Chemically Activated LUciferase 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 a >50% response (response exceeded 50 % of the maximal standard induction or whose 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 CALUX® cell lines. All cell lines were negative for endocrine receptor antagonism.

IRRITATION AND SENSITIZATION STUDIES

Irritation

Glycol Distearate; 1982

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; 2011

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

Animal

Irritation assays are summarized in Table 10.

Trimethyl Pentanyl Diisobutyrate was not irritating to guinea pigs at 100% and was not or was mildly irritating to rabbits at 100%.[37,38] Glycol Distearate was not irritating to rabbits and guinea pigs at 100%.[13] Neopentyl Glycol Diethylhexanoate (concentration not specified, tested neat) was not irritating to the skin of rabbits.[17] There were no signs of erythema or edema observed when Neopentyl Glycol Diheptanoate was administered to rabbits at 100%.[16]

Sensitization

Glycol Distearate; 1982

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 often 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 hours 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 hours. No visible skin changes characteristic of irritation or sensitization were observed in any subject; all scores were zero.

Neopentyl Glycol Diisononanoate; 2011

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 laureth 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

Trimethyl Pentanyl Diisobutyrate

In a skin sensitization study of Trimethyl Pentanyl Diisobutyrate (1% in acetone) in guinea pigs (n=4, 5 solvent control, 4 positive control), induction and challenge were by open epicutaneous exposure.[38] The positive control was phenylhydrazine. Skin examinations at 24 and 48 h after the challenge dose indicated no positive sensitization reactions in the test or negative control groups. The positive control group had the expected response. Trimethyl Pentanyl Diisobutyrate was not considered a skin sensitizer in this study.

In a skin sensitization study of Trimethyl Pentanyl Diisobutyrate (1% in organic solvent) in guinea pigs (n=3), there were no signs of sensitization.[37] No further details were provided.

Glycol Distearate

A Buehler test of Glycol Distearate (100% in a few drops of water for both induction and challenge) in Pirbright guinea pigs (n=20; 10 controls) was conducted.[13] The test sites were examined 24 and 48 h after challenge. There were no signs of sensitization.

Neopentyl Glycol Diheptanoate

In a test conducted in a manner similar to that described in OECD TG 406 (Skin Sensitization) of Neopentyl Glycol Diheptanoate, male Dunkin-Hartley guinea pigs (n=20; 10 controls) were used. The induction phase was conducted at 100% and the challenge at 30% in corn oil and 100%.[14,16] There was one guinea pig with 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. It was concluded that the test substance was not sensitizing.

Human

Summaries of human repeated insult patch tests (HRIPTs) are summarized in Table 11.

Trimethyl Pentanyl Diisobutyrate and Neopentyl Glycol Diethylhexanoate were not sensitizers in multiple HRIPTs at up to 100%.[17,37,38,43,44]

Propanediol Dicaprylate/Caprate and Propanediol Dipelargonate were not sensitizers in HRIPTs.[45,46]

OCULAR IRRITATION STUDIES

Neopentyl Glycol Diisononanoate; 2011

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

Propanediol Dicaprylate/Caprate (100%) was tested for potential ocular irritation using the EpiOcular™ in vitro assay.[47] Exposures were for 20 min and 1 and 4 h. The estimated Draize ocular irritation score was 0 for and the test substance was classified as non-irritating.

Animal

Ocular irritation studies using rabbits are summarized in Table 12.

Trimethyl Pentanyl Diisobutyrate, Glycol Distearate, Neopentyl Glycol Diethylhexanoate, and Neopentyl Glycol Diheptanoate were not ocular irritants at 100% in rabbits.[13,16,17,37,38]

CLINICAL STUDIES

Retrospective and Multicenter Studies

Glycol Distearate; 1982

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 review of the available scientific literature and unpublished data relevant to assessing the safety of 31 monoalkylglycol dialkyl acid esters as used in cosmetics. The ingredients in this report are structurally related alkyl esters of monoalkyl diols that vary by type of diol and lengths of the fatty acid residues.

The functions of these ingredients include: film former, hair conditioning agent, opacifying agent, plasticizer, skin-conditioning agents (emollient, miscellaneous, and occlusive), slip modifier, solvent, surface modifier, and viscosity increasing agent – nonaqueous. 1,4-Butanediol Bisdecanoate and 1,2-Hexanediyl Dicaprate are reported to function as skin bleaching agents. Skin bleaching agent is not a cosmetic function; use as a skin bleaching agent is classified as a drug use and, as such, does not fall under the purview of CIR.

According to VCRP survey data received in 2016, Glycol Distearate was reported to be used in 1613 formulations, mostly in hair products (1029 formulations); this is an increase from 28 uses in 2001. Trimethyl Penanyl Diisobutyrate and Neopentyl Glycol Diheptanoate are used in 315 (all nail products) and 337 (mostly in skin care products) formulations, respectively. The rest of the ingredients with reported uses were used in 94 or fewer formulations. As for products that were previously reviewed by CIR, Neopentyl Glycol Dicaprylate/ Dipelargonate/Dicaprate and Neopentyl Glycol Diisononanoate had no reported uses in the 2001 and the 2016 VCRP database. Neopentyl Glycol Diisononanoate is no longer reported to be used in a cleansing product.

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%. Neopentyl Glycol Dicaprate had the next highest reported maximum concentration of use; it is used up to 50%. 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% and 13.1%, respectively

In rats, orally administered Trimethyl Pentanyl Diisobutyrate was rapidly absorbed and excreted, with renal excretion accounting for the majority of the recovered radioactivity. In urine, Trimethyl Pentanyl Diisobutyrate, TMPD-3-^{14}C, and conjugates of TMPD and 2,2,4-trimethyl-3-hydroxyvaleric acid were detected. None of the test substance was detected in CO_2.

The 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} 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 of 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 Glycerol Distearate 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 Glycerol 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). 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). Glycol Distearate was not mutagenic in Ames tests up to 5000 µg/plate. 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 the CALUX® 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%. 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 two skin sensitization studies in guinea pigs, Trimethyl Pentanyl Diisobutyrate was not considered to be a skin sensitizer at 1%. 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 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%.

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.

DISCUSSION

To be developed.

CONCLUSION

To be developed.

TABLES

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

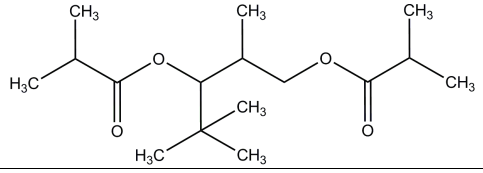
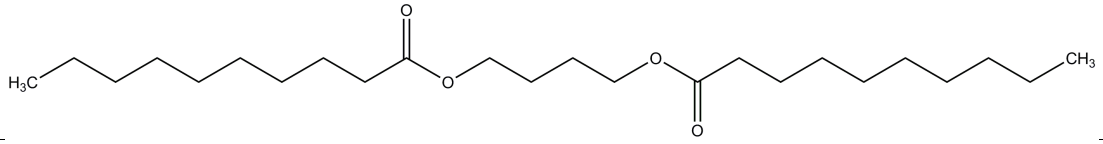
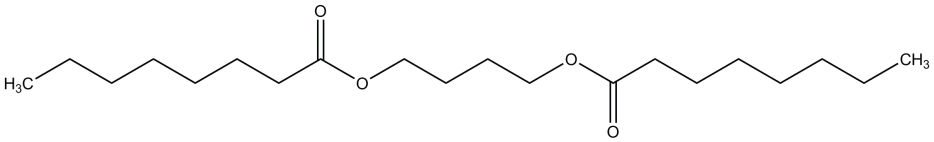
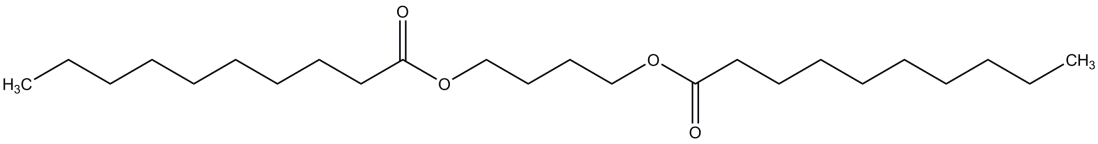
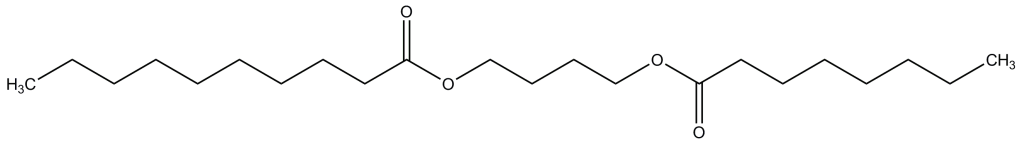
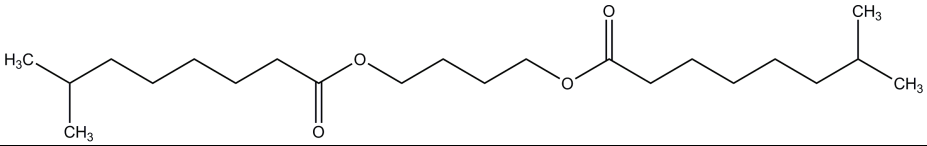
Ingredient CAS No.	Definition & Structure	Function(s)
Trimethyl Pentanyl Diisobutyrate 6846-50-0	Trimethyl Pentanyl Diisobutyrate is the organic compound that conforms to the formula: 	Plasticizer
1,4-Butanediol Bisdecanoate 26719-50-6	1,4-Butanediol Bisdecanoate is the organic compound that conforms to the formula: 	Skin bleaching agent*
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:  	Skin-conditioning agent – emollient; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Butylethylpropanediol Dimer Dilinoleate	Butylethylpropanediol Dimer Dilinoleate is the product of the esterification of Dilinoleic Acid with butylethylpropanediol.	Film former; skin-conditioning agent – miscellaneous; slip modifier; surface modifier

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

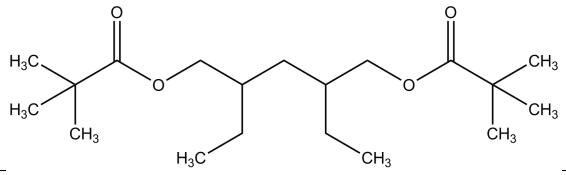
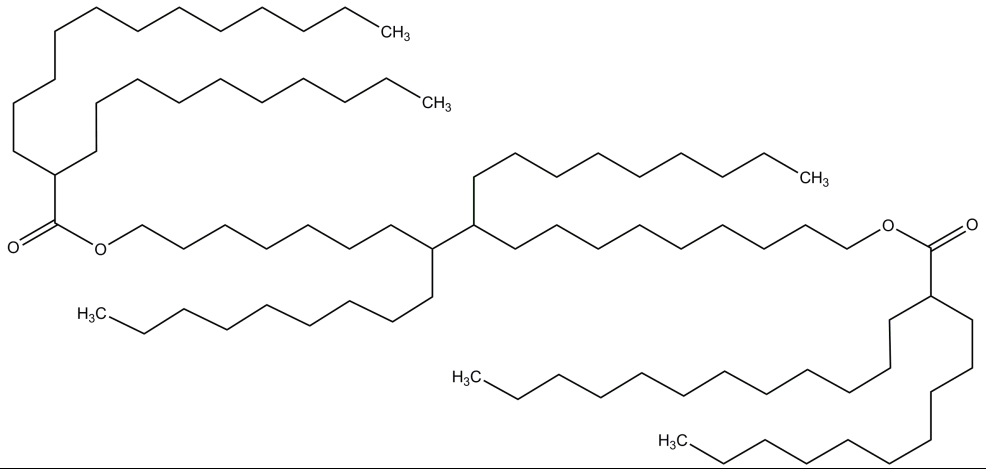
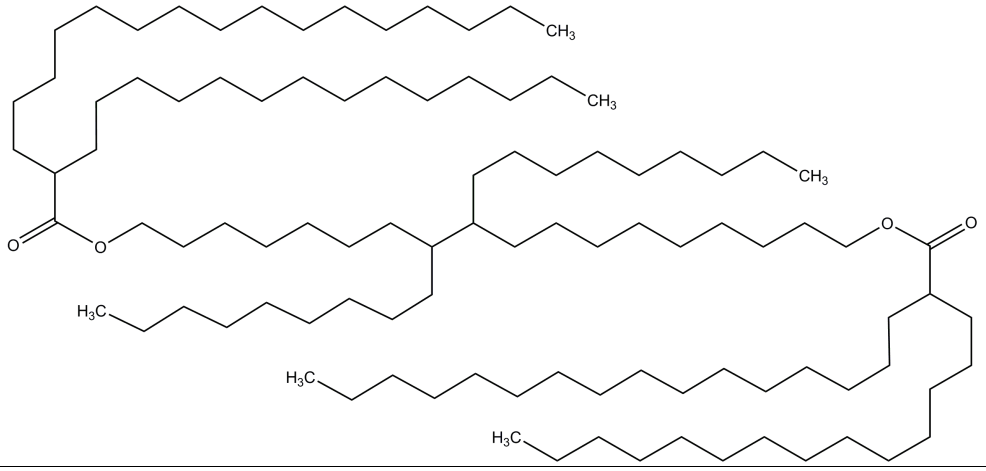
Ingredient CAS No.	Definition & Structure	Function(s)
Diethylpentanediol Dineopentanoate 762268-78-0	Diethylpentanediol Dineopentanoate is the organic compound that conforms to the formula: 	Hair conditioning agent; skin-conditioning agent - miscellaneous
Dioctadecanyl Didecyltetradecanoate	Dioctadecanyl 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

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

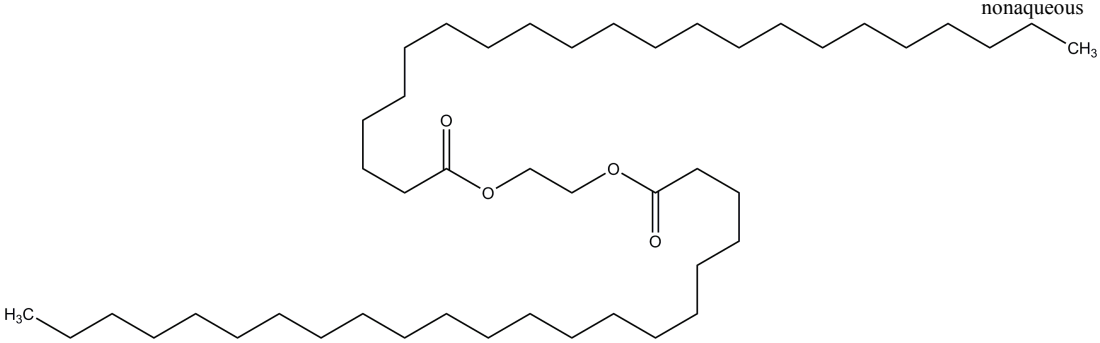
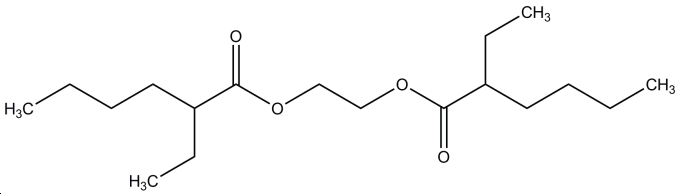
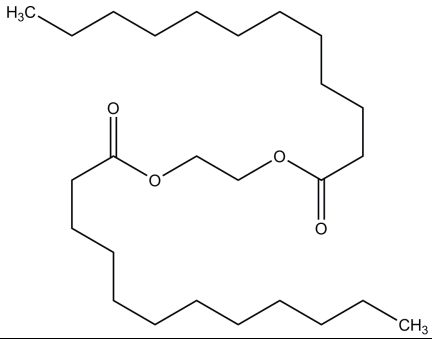
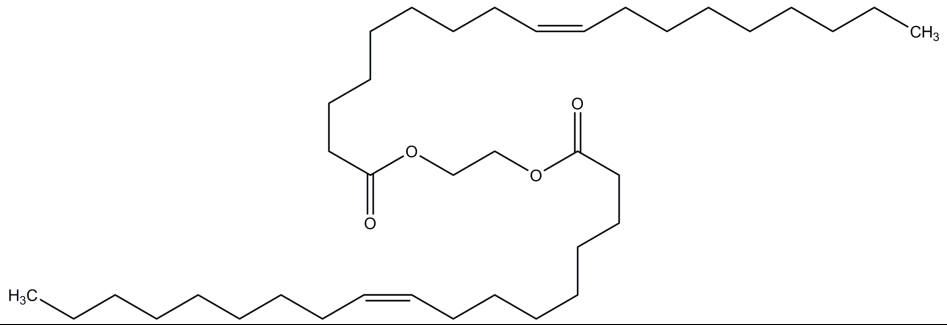
Ingredient CAS No.	Definition & Structure	Function(s)
Glycol Dibehenate 79416-55-0	Glycol Dibehenate is the diester of ethylene glycol and behenic acid. It conforms generally to the formula: 	Opacifying agent; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Glycol Diethylhexanoate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

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

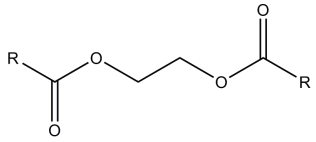
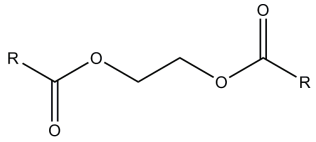
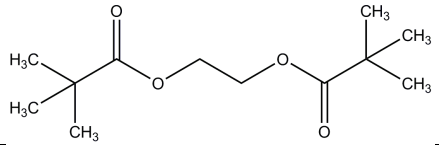
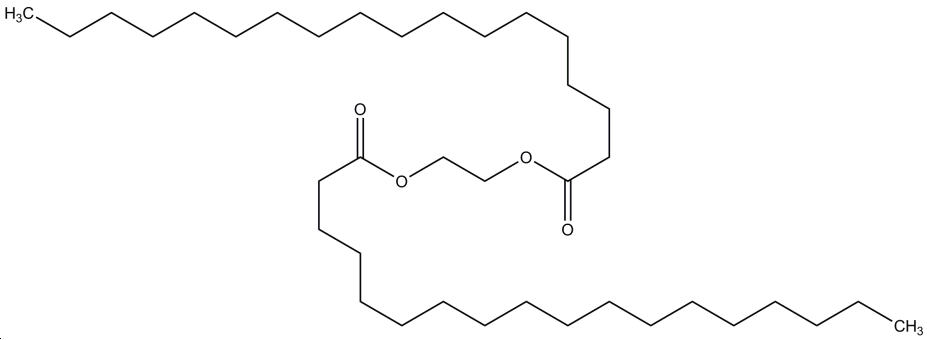
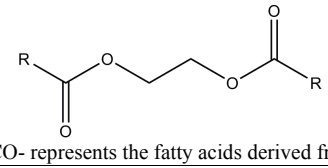
Ingredient CAS No.	Definition & Structure	Function(s)
Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate	Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate is the diester of ethylene glycol with a mixture of fatty acids derived from palm oil, palm kernel oil, olive oil and macadamia nut oil.  [wherein RC(O)- represents fatty acid residues derived from palm oil, palm kernel oil, olive oil and macadamia nut oil.]	Skin-conditioning agent - emollient
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

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

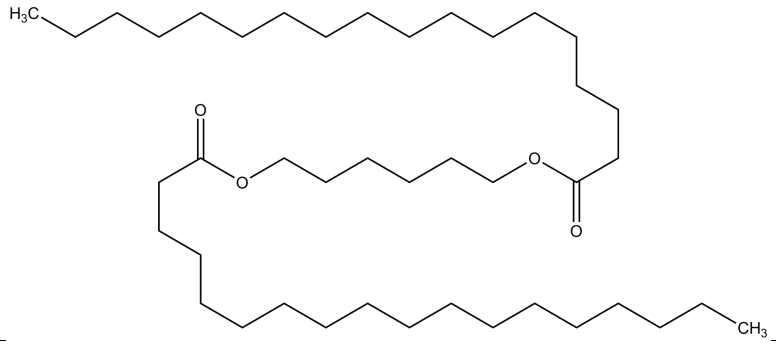
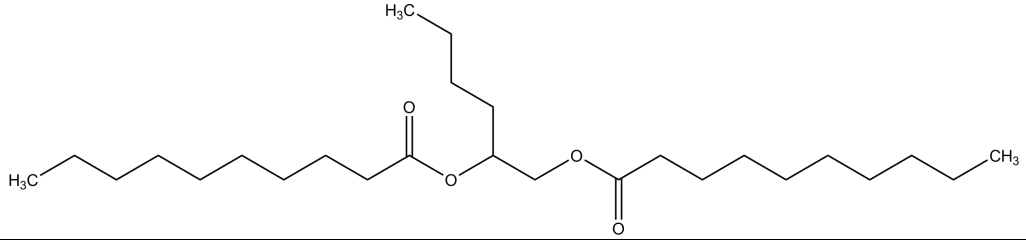
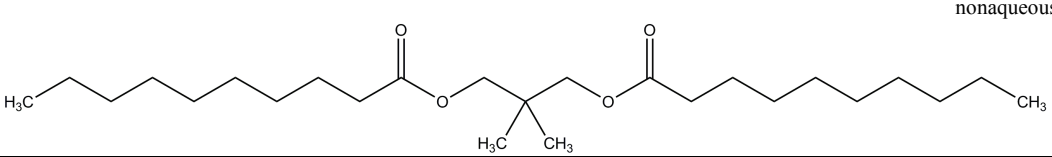
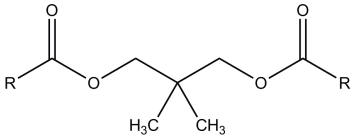
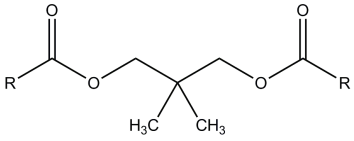
Ingredient CAS No.	Definition & Structure	Function(s)
Hexanediol Distearate 26730-92-7	Hexanediol Distearate is the diester of hexanediol and stearic acid. It conforms generally to the formula: 	Skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
1,2-Hexanediyl Dicaprate	1,2-Hexanediyl Dicaprate is the organic compound that conforms to the formula: 	Skin bleaching agent*
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

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

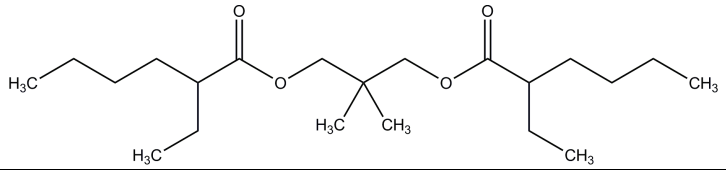
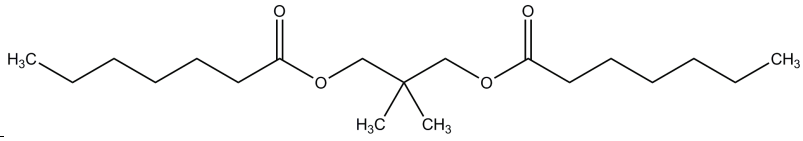
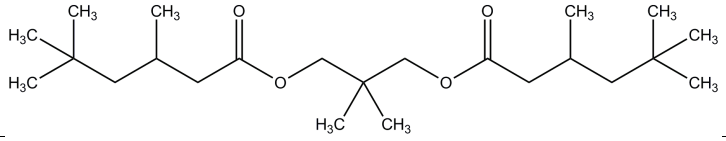
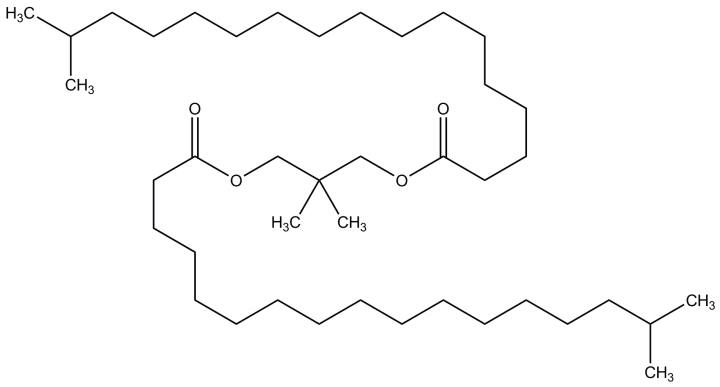
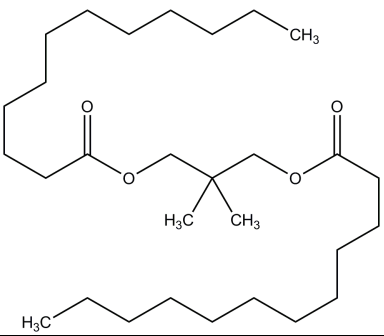
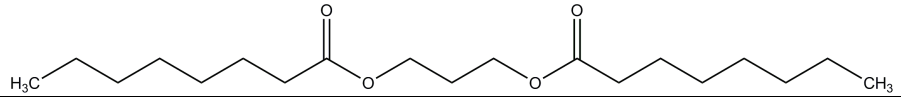
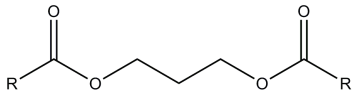
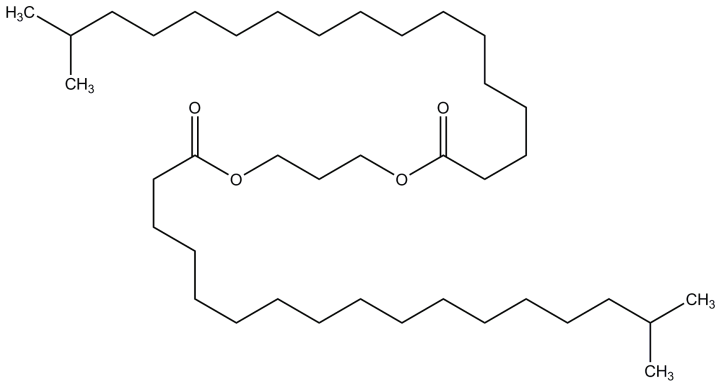
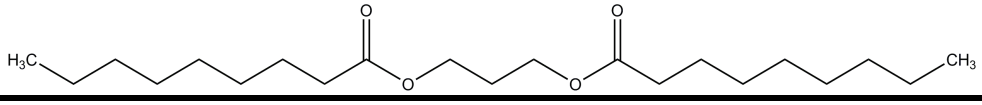
Ingredient CAS No.	Definition & Structure	Function(s)
Neopentyl Glycol Diethylhexanoate 28510-23-8	Neopentyl Glycol Diethylhexanoate is the diester of neopentyl glycol and 2-ethylhexanoic acid. It conforms to the formula: 	Skin-conditioning agent – emollient; viscosity increasing agent - nonaqueous
Neopentyl 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
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

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 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 RCO- represents a mixture of caprylic and capric acid residues.	Skin-conditioning agent – emollient
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

* Skin-bleaching agent is not a cosmetic function.

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; maximum concentrations of use)	Reference
Glycol Distearate; Glycol Stearate, Glycol Stearate SE	Safe as used (1982, 2001; 12% in leave-ons)	2,3
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate, Neopentyl Glycol Diisononanoate, Pelargonic Acid (nonanoic acid) and nonanoate esters	Safe as used (2011; 74% in leave-ons)	4
Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, Dipropylene Glycol	Safe as used (2006, 2006; 89% in leave-ons)	7,48
Alkane diols	Insufficient data announcement (2016; 39.9% in leave-ons)	12
Propylene glycol esters	Safe as cosmetic ingredients in the practices of use and concentration described in this safety assessment (2014; 60% in leave-ons and 15.8% in rinse-offs)	8
Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid	Safe in the present practices of use and concentration (2006; 9% in leave-ons and 4% in rinse-offs, 20% in hair products, 15% in bath products)	7,10
Plant-derived fatty acid oils (which primarily comprise glyceryl triesters)	Safe as used (2011; 100% in leave-ons)	9
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 (78% in leave-ons)	11
Tallow, Tallow Glyceride, Tallow Glycerides, Hydrogenated Tallow Glyceride, and Hydrogenated Tallow Glycerides	Safe in present practices of use (1990, 2006; 78% in leave-ons)	5,6

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

Property	Value	Reference
Trimethyl Pentanyl Diisobutyrate		
Physical Form	Liquid	15
Color	Colorless/clear	15
Odor	Slight	15
Molecular Weight g/mol	286.41	21
Density	0.94	15
	0.92	15
Viscosity kg/(s m)	0.005	15
Vapor pressure mmHg @ 20ºC	0.0009	35
	0.0113	15
	0.00066	21
	0.089	39
Melting Point ºC	-70	21,35
	69.9	21
	<-10	21
Boiling Point ºC	281.5	21
	280	21,35
Water Solubility g/L @ 27.5ºC & pH 3.6-4/6	0.0127	15
@ 23.65ºC & pH 4.09-4.83	13.3	15
@ 23.65ºC & pH 7.79-8.26	13.2	15
@ 20.5ºC	0.001-0.002	35
@ 25ºC	0.015	21
Disassociation constants		
pKa @ 25 ºC	-4.87 est.[a]	15
Glycol Dibehenate		
Molecular Weight g/mol	707.20	49
Glycol Diethylhexanoate		
Physical Form	Liquid	17
Color	Pale yellow	17
Density/Specific Gravity @ 20ºC	0.94 est.[b]	17
Vapor Density mmHg	0 est.[b]	17
Melting Point ºC	<20	17
Boiling Point ºC	75	17
log P_{ow}	>6	17
	7.51 est.[c]	17
Glycol Dilaurate		
Molecular Weight g/mol	426.67	50
Glycol Distearate		
Physical Form	Solid; leaves	13
	Waxy solid	3
Color	White	13
	White to cream	3
Molecular Weight g/mol	595.0	51
Density/Specific Gravity @ 78ºC	858.1	13
Viscosity kg/(s m)@ 80ºC	8.04	
Melting Point ºC	75	13
	75.3	13
	79	13,51
	74.7	13
	67-68	13
	75-75.5	13
Boiling Point ºC @ 20 mmHg	241	13
@ 15 mmHg	209	13
Water Solubility g/L @ 25ºC	<0	13
Disassociation constants		
Log Pow	16.12 est.[b]	13
Hexanediol Distearate		
Molecular Weight g/mol	651.11	52
Neopentyl Glycol Dicaprate		
Density @ 20ºC	0.93 Est.[b]	14
Disassociation constants (pKa, pKb) @ºC		
logPow	9.62 est.[c]	14

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

Property	Value	Reference
Neopentyl Glycol Dicaprylate/Dicaprate		
Physical Form	Liquid	14
	Oily liquid	53
Color	Clear or yellowish	53
Molecular Weight g/mol	420.63	54
Density @ 25ºC	0.890-0.920	53
Melting Point ºC	<20	14
Water Solubility g/L @ 20ºC & pH 5.4-6.8	92.9	14
Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate		
Molecular Weight g/mol	981.51	55
	1017.55 est.[d]	4
Neopentyl Glycol Diethylhexanoate		
Physical Form	Liquid	16,18,19
Color	Pale yellow	16
	Clear	18
Odor	Slight, characteristic	18
Molecular Weight g/mol	356.54	19
Specific Gravity @ 25ºC	0.920	18
Melting Point ºC	<-20	16
Water Solubility	Insoluble	18
Other Solubility		
Hydrophobic solvents (esters, mineral oil, mineral spirits, and aromatic hydrocarbons)	Soluble	18
Neopentyl Glycol Diheptanoate		
Physical Form	Liquid	14,16
Color	Light straw	14,16
Molecular Weight g/mol	328.5	16
Density/Specific Gravity @ 20ºC	0.927	16
@ 20ºC	0.92	16
Viscosity kg/(s m) @ 25ºC	1.29	16
@ 40ºC	0.58	16
@ 100ºC	0.193	16
Vapor pressure mmHg @ 20ºC	0 est.[b]	16
Melting Point ºC	-33	16
Water Solubility g/L @ 20ºC & pH 6.2-6.7	<0.05	16
log P_{ow}	6.68 est.[c]	16
Disassociation constants		
pKa	0 est.[b]	16
Neopentyl Glycol Diisosononanoate		
Molecular Weight g/mol	384.59	4
Melting Point ºC	132.4 est.[d]	4
Boiling Point ºC	565.02 est.[d]	4
Log P_{ow}	7.03 est.[d]	4
Neopentyl Glycol Diisostearate		
Molecular Weight g/mol	637.07	56
Propanediol Dicaprylate		
Physical Form	Liquid	20
Color	White	20
Odor	Neutral	20
Specific Gravity @ 25ºC	0.91-0.93	20
Melting Point ºC	<-5	20
Water Solubility	Insoluble	20
Propanediol Dicaprylate/Caprate		
Specific Gravity @ 25ºC	0.91-0.93	57

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

Property	Value	Reference
Propanediol Dipelargonate		
Physical Form	Liquid	[58]
Color	Clear	[58]
Water Solubility	Insoluble	
Other Solubility		
Ethanol	Miscible	[58]
Propylene Glycol	Insoluble	[58]
Isopropyl Myristate	Miscible	[58]
Castor Oil	Miscible	[58]
Mineral Oil	Miscible	[58]
Isododecane	Miscible	[58]

[a] Calculation based on SPARC online calculator v 4.6, University of Georgia (http://archemcalc.com/sparc/)
[b] Calculation based on KOWWIN v1.68, Estimation Programs Interface Suite™ for Microsoft® Windows v4.10. US EPA, United States Environmental Protection Agency, Washington, DC, USA.
[c] QSAR and Combinatorial Science, Vol. 23, as implemented by SPARC, March 2008
[d] ChemDraw. Cambridge, MA: Cambridge Soft Corporation; 2002.

Table 4. Frequency of use according to duration and exposure of monoalkylglycol dialkyl acid esters.[26,27]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Trimethyl Pentanyl Diisobutyrate		**Butylene Glycol Dicaprylate/Dicaprate**		**Diethylpentanediol Dineopentanoate**		**Glycol Diethylhexanoate**	
Total/range	**315**	**0.1-9.8**	**94**	**1.3-10**	**NR**	**1**	**NR**	**5**
Duration of use[a]								
Leave-on	315	0.1-9.8	94	1.3-10	NR	NR	NR	5
Rinse-off	NR	2	NR	NR	NR	1	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	1	1.3-9	NR	NR	NR	NR
Incidental ingestion	NR	NR	1	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	51; 5[b]; 13[c]	10	NR	NR	NR	NR
Incidental inhalation-powders	NR	NR	2[d]; 13[c]	10; 8[d]	NR	NR	NR	NR
Dermal contact	NR	NR	93	NR	NR	1	NR	5
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	315	0.1-9.8	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	NR	NR	NR	NR
Baby	NR	NR	2	NR	NR	NR	NR	NR

Table 4. Frequency of use according to duration and exposure of monoalkylglycol dialkyl acid esters.[26,27]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Glycol Dilaruate		Neopentyl Glycol Dicaprate		Neopentyl Glycol Dicaprylate/Dicaprate		Neopentyl Glycol Diethylhexanoate	
Total/range	**NR**	**1.3**	**57**	**0.1-50**	**82**	**0.017-22.7**	**65**	**0.9-57**
Duration of use								
Leave-on	NR	1.3	52	0.1-40	71	0.045-22.7	59	0.9-57
Rinse-off	NR	NR	5	0.24-50	10	0.017-15	6	1.5-11
Diluted for (bath) use	NR	NR	NR	11	1	NR	NR	NR
Exposure type								
Eye area	NR	NR	5	3.5-50	2	0.094-18.9	14	1-36.5
Incidental ingestion	NR	NR	18	5-40	13	1.9-22.7	11	3.1-11.3
Incidental Inhalation-sprays	NR	NR	3[b]; 7[c]	6; 3.5-6[b]	18[b]; 15[c]	0.045-0.9[b]	8[b]; 6[c]	3.6-9.3; 0.9-7.5[d]
Incidental inhalation-powders	NR	1.3[d]	7[c]	2.5-16.8; 1-28.5[d]	1[d]; 15[c]	1; 2.2[d]	1; 6[c]	1.1-2; 3-57[d]
Dermal contact	NR	1.3	39	0.1-50	60	0.017-19	46	0.9-57
Deodorant (underarm)	NR	NR	NR	0.1[e]; 4[f]	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	1-6	9	0.045-0.9	8	1.5-9.3
Hair-coloring	NR	NR	NR	3.5	NR	NR	NR	1.8
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	18	5-40	14	0.017-22.7	12	3.1-11.3
Baby	NR	NR	NR	NR	1	NR	NR	NR

	Neopentyl Glycol Diheptanoate		Neopentyl Glycol Diisostearate		Propanediol Dicaprylate		Propanediol Dicaprylate/Caprate	
Total/range	**337**	**1-33**	**3**	**0.2-1.1**	**7**	**1**	**2**	**13.5**
Duration of use								
Leave-on	331	1-33	3	0.9-1.1	6	1	2	13.5
Rinse-off	6	1.9-9	NR	0.2	1	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type[a]								
Eye area	21	2.8-18	NR	NR	2	NR	NR	NR
Incidental ingestion	5	7	1	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	6; 237[b]; 37[c]	5-19.5; 3-19.5[b]	1[b]	NR	2[b]; 2[c]	NR	2[b]	NR
Incidental inhalation-powders	37[c]	2.4; 1-20.7[d]	NR	0.9[d]	2[c]	1[d]	NR	13.5[d]
Dermal contact	326	1-33	2	0.9-1.1	7	1	2	13.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	6	1.9-19.5	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	0.2	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	7-9	1	NR	NR	NR	NR	NR
Baby	NR	1.2-2.2	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 5. Current and historical frequency and concentration of use of monoalkylglycol dialkyl acid esters according to duration and exposure.[2,4,26,27]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2016	**2001**	**2016**	**2001**	**2016**	**2009**	**2016**	**2009**
	Glycol Distearate				**Neopentyl Glycol Diisononanoate**			
Totals*	**1613**	**28**	**0.5-13.1**	**0.2-9**	**NR**	**NR**	**1.3-5**	**1**
Duration of Use								
Leave-On	60	1	0.2-13.1	*1-6*	NR	NR	1.3	NR
Rinse-Off	1484	26	0.05-10	*0.2-9*	NR	NR	2-5	1
Diluted for (Bath) Use	69	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; 11[a]; 13[b]	NR	1-2.5[a]	2-6[b]	NR	NR	NR	NR
Incidental Inhalation-Powder	13[b]	NR	2.5; 2-5.4[c]	2-6[b]	NR	NR	NR	NR
Dermal Contact	583	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	535	9	0.39-10	2-9	NR	NR	NR	NR
Hair-Coloring	494	NR	0.5-8	0.2-0.5	NR	NR	NR	NR
Nail	NR	NR	2	NR	NR	NR	NR	NR
Mucous Membrane	409	16	0.2-5	0.4-3	NR	NR	NR	NR
Baby Products	17	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 6. Monoalkylglycol dialkyl acid esters with no reported use in the 2016 VCRP or by the Council.[26,27]

1,4-Butanediol Bisdecanoate	Butylene Glycol Diisononanoate
Butylethylpropanediol Dimer Dilinoleate	Dioctadecanyl Didecyltetradecanoate
Dioctadecanyl Ditetradecyloctadecanoate	Glycol Dibehenate
Glycol Dioleate	Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate
Glycol Dipalmate/Rapeseedate/Soyate	Glycol Dipivalate
Glycol Ditallowate	Hexanediol Distearate
1,2-Hexanediyl Dicaprate	Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate*
Neopentyl Glycol Dilaurate	Propanediol Diisostearate
Propanediol Dipelargonate	

* No reported uses in the VCRP in 2009 and 2016.

Table 7. 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 8. 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. LD_{50}>20 mL/kg.	38
Trimethyl Pentanyl Diisobutyrate	Guinea pigs (not specified)	5 mg/kg. Slightly irritating.	21
Trimethyl Pentanyl Diisobutyrate	Guinea pigs (n=3)	5 to 20 mL/kg for 24 h under occlusion. Guinea pigs were observed for 14 days. No deaths occurred and no other clinical signs were observed. Two guinea pigs lost weight.	21,37
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.	37,38

Table 8. Acute toxicity studies of monoalkylglycol dialkyl acid esters.

Ingredient	Animal (n)	Methods; Results	Reference
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.	13
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.	13
		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.	21,37,38
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.	37,38
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.	21,37,38
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.	13
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.	13
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}=> 2 000 mg/kg No mortalities or clinical signs of toxicity were observed.	17
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}=>2 000 mL/kg (>1880 mg/kg)	17
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.	16
		Inhalation	
Trimethyl Pentanyl Diisobutyrate	Rats (n=3)	Whole body apparatus at 120 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.	37,38
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.	21,37,38
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).	14,16

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

Table 9. 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.	13,38
Trimethyl Pentanyl Diisobutyrate	Not specified	OECD TG 476 (In Vitro Mammalian Cell Mutation Assay)	CHO cells	Negative with and without metabolic activation.	37
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.	13
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.	37
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.	21
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.	13
Trimethyl Pentanyl Diisobutyrate	Not specified	OECD TG 473 (In vitro Mammalian Chromosome Aberration Test)	CHO cells	Negative with and without metabolic activation.	37
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.	21
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.	13
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.	13
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;	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.	17

Table 9. In vitro genotoxicity studies of monoalkylglycol dialkyl acid esters.

Test Article	Concentration/Vehicle	Procedure	Test System	Results	Reference
	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.				
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.	[17]
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.	[17]
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.	[17]
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	[41]

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

Table 10. 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.	38
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).	38
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.	37,38
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.	13
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.	13
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.	13
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	17
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.	17
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.	59

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

Table 11. 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.	38
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.	37
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.	44
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.	43
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.	60
Propanediol Dicaprylate/Caprate	100%; 0.2 mL, 0.2 mg. Test substance was applied to upper back of subjects 3 times per week for3 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.	45
Propanediol Dipelargonate	100%; 0.2 mL, 0.2 mg. Test substance was applied to upper back of subjects 3 times per week for3 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.	46

HRIPT=Human repeated insult patch test

Table 12. 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.	[37,38]
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.	[13]
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.	[13]
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.	[17]
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.	[17]
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.	[59]

OECD TG=Organisation for Economic Co-operation and Development Test Guidelines

[a] Strain of rabbit not specified.

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1

Final Report on the Safety Assessment of Glycol Stearate, Glycol Stearate SE, and Glycol Distearate

Glycol Stearate, Glycol Stearate SE, and Glycol Distearate consist primarily of the mono- and diesters of triple-pressed stearic acid. They are used in numerous categories of cosmetic products at concentrations ranging from less than 0.1 to 10%.

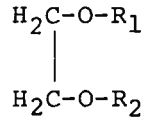
Animal data for acute oral toxicity, skin and eye irritation, and sensitization show that these ingredients have low acute toxicity. A repeated insult patch test with 50% Glycol Distearate on 125 subjects presented no evidence of skin irritation or hypersensitivity. Human studies using formulations containing Glycol Stearate at levels of 2–5% reported no skin irritation or sensitization.

Subchronic testing has not been adequately investigated in laboratory animals. Human test data for formulations containing > 4% Glycol Stearate or Glycol Distearate should be considered.

Based on the available information presented herein, it is concluded that Glycol Stearate, Glycol Stearate SE, and Glycol Distearate are safe as cosmetic ingredients in the present practices of use and concentration.

CHEMICAL AND PHYSICAL PROPERTIES

These ingredients are mixed esters of ethylene glycol and triple-pressed stearic acid. The latter consists of 42.5% stearic acid and about an equal amount of palmitic acid, along with lesser amounts of several other fatty acids. The general structural formula for these ingredients is:[1,2]



Glycol Stearate: The ingredient is comprised of 40–70% of the monoester in which R_1 is the acyl portion of triple-pressed stearic acid and R_2 is H. Glycol

Stearate also contains a significant portion, 30–58%, of the diester in which both R_1 and R_2 are the acyl moiety of triple-pressed stearic acid.[2]

Glycol Stearate SE: This ingredient is a self-emulsifying grade of Glycol Stearate containing free stearic acid and some sodium and/or potassium stearate.[1]

Glycol Distearate: This ingredient is the diester of ethylene glycol in which both R_1 and R_2 are the acyl moiety of triple-pressed stearic acid.[2]

Glycol Stearate, Glycol Stearate SE, and Glycol Distearate have similar physical properties. They are white to cream colored waxy solids. Their physical properties vary within specified limits according to their proportions of mono- and diesters and other components. Depending on the intended use, a purchasing specification is used to set specific limits on the physical characteristics of these ingredients.[2]

Analytical Methods

Glycol Stearate and Glycol Distearate can be analyzed by gas chromatography.[3] Mass spectrometric analysis of long-chain esters of ethanediol (ethylene glycol) has been described[4]; this allows for the identification of individual esters of the diol as well as of classes of diol monoesters. A method of gel-permeation chromatography for Glycol Distearate on Sephadex LH-20 has also been reported.[5] Standard methods have been suggested for determining the chemical properties of these ingredients.[2]

Impurities

Impurities such as free stearic acid (triple-pressed), the mono- or diesters, ethylene glycol, and corresponding derivatives of other fatty acids found in the stearic acid may be present in Glycol Stearate.[2]

Ethylene glycol and/or ethylene oxide are used as starting material for the synthesis of Glycol Stearate. Since the former is known to be contaminated with traces of 1,4-dioxane,[6] it is possible that such traces also appear in the synthesized material. Analytical data on traces of 1,4-dioxane in Glycol Stearate were not available to the Expert Panel.

When rats were given high doses of 1,4-dioxane in drinking water (~1.0%) for 13 months, liver lesions including hepatomas occurred.[7]

USE

Purpose and Frequency of Use in Cosmetics

These ingredients are used as emulsifiers, dispersants, opacifiers, and viscosity modifiers. As wax ingredients in stick preparations, they have served to control hardness, add slip, and increase opacity. They give lotion, cream, and detergent formulations an opaque or milky appearance.[8,9]

As shown in Table 1, these ingredients are used in a variety of categories of cosmetic products; their concentrations range from less than 0.1% to as high as 10%. The cosmetic product formulation computer printout which is made

TABLE 1. Prc

Cosmetic pro	*Ingred.*
Glycol Stearate	
Bath oils, tablet:	
Bubble baths	
Other bath prep	
Eyebrow pencil	
Eyeliner	
Eyeshadow	
Mascara	
Hair conditione	
Hair straightene	
Rinses (noncolo	
Shampoos (non-	
Tonics, dressing hair grooming	
Hair shampoos	
Blushers (all typ	
Foundations	
Lipsticks	
Makeup bases	
Rouges	
Other makeup p	
Bath soaps and	
Aftershave lotio	
Cleansing (cold cleansing lotic and pads)	
Face, body and (excluding sha preparations)	
Moisturizing	
Other skin care	
Suntan gels, cre liquids	
Glycol Stearate .	
Other skin care	
Glycol Distearat	
Hair conditione	
Permanent wav	
Shampoos (non-	
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TABLE 1. Product Formulation Data.[a]

Cosmetic product type/ Ingredient	*Concentration (%)*	*No. of product formulations*
Glycol Stearate		
Bath oils, tablets and salts	>0.1–1	6
Bubble baths	>1–5	3
	>0.1–1	44
Other bath preparations	>0.1–1	6
Eyebrow pencil	>1–5	3
Eyeliner	>1–5	9
Eyeshadow	>5–10	1
	>1–5	75
Mascara	>1–5	2
Hair conditioners	>5–10	2
Hair straighteners	>5–10	4
Rinses (noncoloring)	>0.1–1	3
Shampoos (noncoloring)	>5–10	1
	>1–5	46
	>0.1–1	28
	≤0.1	2
Tonics, dressings, and other hair grooming aids	>1–5	1
Hair shampoos (coloring)	>1–5	2
Blushers (all types)	>1–5	5
Foundations	>1–5	88
Lipsticks	>1–5	1
Makeup bases	>1–5	2
Rouges	>1–5	8
Other makeup preparations	>1–5	2
Bath soaps and detergents	>1–5	1
	>0.1–1	1
Aftershave lotions	>0.1–1	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1–5	3
	>0.1–1	5
Face, body and hand (excluding shaving preparations)	>1–5	9
	>0.1–1	2
Moisturizing	>5–10	1
	>1–5	8
	>0.1–1	3
Other skin care preparations	>5–10	2
	>1–5	2
	>0.1–1	1
Suntan gels, creams, and liquids	>1–5	1
Glycol Stearate SE		
Other skin care preparations	>0.1–1	1
Glycol Distearate		
Hair conditioners	>0.1–1	1
Permanent waves	>1–5	5
Shampoos (noncoloring)	>1–5	9
	>0.1–1	6
Hair dyes and colors (all types requiring caution statement and patch test)	>0.1–1	1

TABLE 1. (Continued.)

Cosmetic product type/ Ingredient	*Concentration (%)*	*No. of product formulations*
Deodorants (underarm)	>1–5	1
Other personal cleanliness products	>5–10	1
Other shaving preparation products	>1–5	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1–5	1

[a]Data from Ref. 10.

available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations (1979). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. According to FDA, Glycol Stearate SE is used in one unspecified skin-care product. Glycol Distearate is principally employed in hair-care preparations[10]; however, its use as a lyophilic component of self-emulsifying ointment bases has been described.[11]

Products containing these ingredients are used on all body orifices. Thus they may enter the body by several routes (though the inhalation of sprays appears to be minor as a mode of exposure and absorption).

These ingredients may be applied as often as several times a day (lipsticks and lotions) or as infrequently as once every one or two months (hair dyes and colors). The period of time for which they remain in contact may be conditioned by the frequency with which the affected part of the body is washed.

BIOLOGICAL PROPERTIES

General Effects

The addition of 12.5 percent Glycol Stearate as a surfactant to a vaseline-based ointment increased the cutaneous absorption of the following compounds through the shaved skin of rats by the factors shown: 10% potassium iodide (4X); 5% sodium salicylate (4.6X); and 5% ammonium thiocyanate (3.1X). A two-gram sample of each emulsion was rubbed into the skin for five minutes and then covered with a protective bandage. Absorption was determined by the analysis of urine specimens collected at 12 and 24 hours.[12]

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Animal Toxicology

Oral Toxicity: Glycol Stearate and Glycol Distearate have each been tested in five studies for acute oral toxicity in rats; the data from these studies are summarized in Table 2. During the various studies, doses of 13 or more g/kg body weight 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, the stomach contained residues which appeared to be the test material.[13]

For 91 days, four groups of weanling rats, each comprised of five males and five females, were fed a diet containing a dishwashing liquid one of whose ingredients was ethylene glycol distearate at a concentration range of between 1% and 5%. The equivalent dosing levels of the ethylene glycol distearate were 0, 0.0025–0.0125%, 0.005–0.025%, and 0.01–0.05%. Following both gross and histopathologic examination, no differences were observed between the controls and test groups.[14]

Primary Skin Irritation Studies: Draize type procedures were used to test Glycol Stearate, Glycol Stearate SE, and Glycol Distearate for primary irritation of albino rabbit skin; the ingredients were found to be nonirritating to slightly irritating (See Table 2). In addition, when Glycol Stearate and Glycol Distearate were tested for corrosivity according to the procedures of the U.S. Department of Transportation, they were found to be noncorrosive to rabbit skin.[13]

Sensitization: Sensitization studies were conducted in guinea pigs on Glycol Stearate and Glycol Distearate. 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.[13]

Subchronic: For 90 days, Glycol Stearate at 3% in a liquid foundation formulation was applied five times a week for 13 weeks to the clipped backs of 15 female rats. Observations were made for survival, body weight, appearance and behavior, hematology, clinical chemistry, organ weights, and gross and histopathologic changes. No effects were attributed to the repeated application of the test formulation.[13]

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.[14]

Two formulations were tested for 91 days. 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. The skin irritation that resulted was reported to be similar to that produced by other forms of shampoo.[14]

Table 2. Acute Animal Toxicity.[a]

Ingredient	File No.	LD50–Acute oral				Skin Irritation			Draize Woodard Calvary	Eye Irritation		Draize	
		Value	Conc.	Dosage	No. Rats/ Dose	Conc.	Animals	Irritation Index		Conc.	No. of Rabbits	Comment
Glycol Stearate	6.4b.i	>10 g/kg	50% in corn oil	0.464–10 g/kg	5	undiluted	6 rabbits	0.13		undiluted	6	mild transient irritant in 1/6
	6.4b.ii	>21.3 g/kg	1:2 in corn oil	0.7–21.3 g/kg	5	undiluted	6 rabbits	0.0		undiluted	9	no irritation
	6.4b.ii	[Dept. of Transportation Skin Irritation Test]				undiluted	6 rabbits	0.0				
	6.4b.iv	>10 g/kg	undiluted	10 g/kg	10	undiluted	6 rabbits	0.375				
	6.4b.iv	[Skin Sensitization Test]				i.c. inject. of 0.1% in saline	2 guinea pigs	not a sensitizer				
	6.4b.v	>5000 mg/kg	undiluted	5000 mg/kg	10	undiluted	3 rabbits	0.8		undiluted	3	practically non-irritating
Glycol Stearate SE	6.4d.i					5% in water	3 rabbits	0.0		5% in water	3	not an irritant
Glycol Distearate	6.4c.i	>10 g/kg	50% in corn oil	0.464–10 g/kg	5	undiluted	6 rabbits	0.04		undiluted	6	practically non-irritating
	6.4c.ii	>16 g/kg	1:4 in corn oil	0.5–16 g/kg	5	undiluted	6 rabbits	0.0		undiluted	9	no irritation
	6.4c.ii	[Dept. of Transportation Skin Irritation Test]				undiluted	6 rabbits	0.0				
	6.4c.iv	>10 g/kg	undiluted	10 g/kg	10	undiluted	6 rabbits	0.085				
	6.4c.iv	[Skin Sensitization Test]				i.c. inject. of 0.1% in saline	2 guinea pigs	not a sensitizer				
	4.4c.v	>5000 mg/kg	undiluted	5000 mg/kg	10	undiluted	3 rabbits	1.0		undiluted	3	practically non-irritating

[a]Data from Ref. 14.

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		[Skin Sensitization Test]			i.c. inject. of 0.1% in saline	2 guinea pigs	not a sensitizer					
6.4c.iv					undiluted	3 rabbits	1.0	undiluted	3	practically non-irritating		
4.4c.v	>5000 mg/kg	undiluted	5000 mg/kg	10								

[a]Data from Ref. 14.

Two formulations were tested for 28 days. The concentration of Glycol Distearate ranged from 0.05% to 0.5%. Following complete gross and microscopic examination, including hematologic, there was no evidence of systemic toxic effects. According to the report, the skin irritation that was caused by the surfactant ranged from slight to severe.[14]

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.[14]

A shampoo containing 1–3% Glycol Distearate was applied at concentrations of 0.05% and 0.3% to 10 animals (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. Slight transient skin irritation was observed in one rabbit at the 0.05% level and in most animals at the 0.3% level.[14]

Eye Irritation: The Draize procedure was used to evaluate the capacities of these three ingredients for irritating rabbits' eyes. The results showed the ingredients to be nonirritating or practically so. Table 2 gives details of these studies.

Potential Toxicity of Impurities: In any effort to assess the safety of Glycol Stearate, the toxicity of ethylene glycol must be considered, for this is present up to 4%, as an impurity. In addition, it is possible that Glycol Stearate will be hydrolyzed by skin bacteria or upon absorption, so that ethylene glycol will be released. A review of the extensive literature on the toxicity of ethylene glycol indicates that it has adverse effects only at dosage levels much higher than those which might be expected from cosmetics.

Clinical Assessment of Safety

Unpublished clinical data for the Glycol Stearates and their products were reviewed and are summarized below.

Skin Irritation and Sensitization: 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. Patches containing 0.25 g of sample were applied for 24 hours 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 hours. No visible skin changes characteristic of irritation or sensitization were observed in any subject; all scores were zero.[15]

Eyeshadow Containing 3.5% Glycol Stearate: Fifty female volunteers sequentially applied eyeliner, eyeshadow (known to contain 3.5 percent Glycol Stearate), blushing cream, and mascara once a day for 30 days. Approximately

one-half of the subjects were rated as hypersensitive prior to the start of the test. Dermatological examinations were made before the study began and at one-, two-, three-, and four-week intervals during the test period. The dermatologist reported that the products did not produce any reaction over the entire four-week period. It was concluded that "none of the products tested demonstrated any potential as allergic sensitizers or primary irritants."[16]

Eyeliner Containing 3.5% Glycol Stearate: In a 21-day cumulative irritancy assay (Maibach test) performed on seven individuals, eyeliner containing 3.5% Glycol Stearate was applied at full strength under an occlusive patch. A maximum individual subject value of 0.19 on a 4.0 maximum-effect basis was reported, and a cumulative value of 0.58 on a 28 maximum group value was noted. The average mean value for the entire group was 0.08.[16]

Eyecolor Cream Containing 4.0% Glycol Stearate: The formulation was subjected to a 21-day cumulative irritation assay on eight subjects. The average irritation score of 5.94 was obtained out of a maximum possible score of 84.0. Out of a 672 maximum total score for the eight subjects, a score of 47.5 was recorded. Twenty-two was the maximum score for a single individual.[16]

Cream Foundation Containing 3% Glycol Stearate: A repeated insult patch test was performed on 100 subjects, half of whom were considered sensitive. The undiluted formulation containing 3% of the ingredient did not evoke any reaction indicative of induced sensitization. No procedures were stated, and the duration of the study was not reported.

Sixty-two black males and females were tested with a cream containing 2.5% of the ingredient. An adaptation of the repeated insult patch test procedure was used. No skin irritation was reported, nor was there any indication of sensitization following a challenge test 14 days after the end of the repeated patch testing.[14]

Shampoo Containing 2–5% Ethylene Glycol Distearate: A repeated insult patch test was performed on 89 subjects. On Monday, Wednesday, and Friday of the first three weeks, an application of 0.5 ml of a 0.25% liquid solution of the formulation was made along the dorsal surface of the upper arm of each subject. (Since it was stated that the formulation contained 2–5%, the diluted test material would have contained 0.005–0.0125% ethylene glycol distearate.) Fourteen days after the final induction or insult application, the subject was challenged with a challenge patch at the insult site. The subjects were examined 48 and 96 hours after challenge. No evidence of sensitization was reported.[16]

Formulations Containing Ethylene Glycol Distearate: A repeated insult patch test was performed on 103 subjects using 0.5 ml of a 0.2% solution of a shampoo. It was stated that the formulation contained 2–5% ethylene glycol distearate, so that the diluted test material would have contained 0.004–0.01% ethylene glycol distearate. The test procedures were identical to those in the preceding study. No evidence of sensitization was reported.[16]

Four dishwashing liquids containing 1–5% ethylene glycol distearate were tested by means of the repeated insult patch test. Over a three-week period, patches were applied to the upper arm on three alternate days. Fourteen days after the final induction application, the subjects were given challenge patches.

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TABLE 3. Sensitization Tests on Dishwashing Liquids Containing Ethylene Glycol Distearate.[a]

Dishwashing liquid	*No. of subjects*	*Detergent conc. (%)*	*Range of conc. of ethylene glycol distearate (%)*
1	67	1	0.01–0.05
2	69	1	0.01–0.05
3	87	1.5	0.015–0.075
4	78	0.5	0.005–0.025

[a]Data from Ref. 14.

Table 3 shows the range of concentration of ethylene glycol distearate for each group of subjects.

No results were presented on irritation caused by the test compounds. In all cases, there was no reported evidence of sensitization after challenge.(14)

Consumer Information: Two companies reported on the incidence of consumer complaints related to their products containing Glycol Stearate. One indicated that it was unaware of any complaints having arisen over a 20-year period from the use of over two million units of products (various creams and lotions) containing 0.5–5% Glycol Stearate. According to the second company, the unscreened adverse reaction rate for shampoos containing 4.0% Glycol Stearate averaged 1.2 complaints per million.(14)

Occupational Exposure: Two manufacturers reported that they have been manufacturing Glycol Stearates and Glycol Distearates for between 20 and 30 years. 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.(14)

SUMMARY

Glycol Stearate, Glycol Stearate SE, and Glycol Distearate are comprised primarily of the mono- and diesters of triple-pressed stearic acid. They are used at concentrations ranging from less than 0.1% to 10% in numerous categories of cosmetic products. They function as emulsifiers, dispersants, opacifiers, and viscosity modifiers, and have been used as wax ingredients in stick preparations. Because they are used on all body surfaces, these ingredients may be absorbed through several routes; and their contact with the body may be frequent and prolonged. Animal studies indicate that Glycol Stearate serves as a surfactant and enhances percutaneous absorption.

The animal data indicate that these ingredients have low acute oral toxicity, skin and eye irritation, and sensitization. One subchronic skin painting study with a product formulation containing 3% Glycol Stearate showed no toxic effects throughout the 90-day test period and after necropsy.

A repeated insult patch test with 50% Glycol Distearate on 125 subjects presented no evidence of skin irritation or hypersensitivity. Human studies using formulations containing Glycol Stearate at levels of 2–5% reported no skin irritation or sensitization. Additional human studies using Glycol Distearate, at levels of the test compound 500 times lower than that which a consumer would actually use, showed no irritation or sensitization upon challenge. Prolonged repeated insult patch testing on the forearm was used to approximate the high-level exposure consumers would experience when they applied a shampoo containing Glycol Distearate to their scalps, under hot and wet conditions, for a very short period of time.

Subchronic testing has not been adequately investigated in laboratory animals. Human test data for formulations containing > 4% Glycol Stearate or Glycol Distearate should be considered.

CONCLUSION

On the basis of the available information presented herein, the Panel concludes that Glycol Stearate, Glycol Stearate SE, and Glycol Distearate are safe as cosmetic ingredients in the present practices of use and concentration.

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Annual Review of Cosmetic Ingredient Safety Assessments—2001/2002[1]

The Cosmetic Ingredient Review (CIR) Expert Panel has assessed the safety of over 1100 cosmetic ingredients since its inception in 1976. The very first safety assessments were published in earlier incarnations of this journal—the *Journal of Environmental Pathology and Toxicology* in 1980, and the *Journal of the American College of Toxicology* from 1982 to 1996.

Because information relevant to the safety of ingredients may have become available since these early safety assessments were published, the CIR Expert Panel has initiated a re-review process. If new information is thought to be available or if a long period of time has passed, the CIR Expert Panel may initiate a search for relevant new data.

In some cases, newly available data are largely redundant with the data available in the original safety assessment. In other cases, there is new safety data. If after considering any newly available information, the CIR Expert Panel decides not to reopen a safety assessment, this finding, along with any background material, is summarized and announced publicly. To assure that the scientific community is aware of any new information and the decision not to reopen, this *Annual Review of Cosmetic Ingredient Safety Assessments* is prepared. This is the first such annual review.

For each original safety assessment, the re-review addresses the import of new studies that were considered by the CIR Expert Panel, if any were available. A reference list is provided that updates the references provided in the original safety assessment. The re-review also captures information on the industry's current practices of ingredient use, updating the data available in the earlier report. Although this material provides the opinion of the CIR Expert Panel regarding the new data described, it does not constitute a full safety review.

The ingredients the CIR Expert Panel considered through June of 2002 and decided not to reopen are:

Aluminum Distearate
Aluminum Stearate
Aluminum Tristearate
Ammonium Stearate
Avocado Oil (aka Persea Gratissima (Avocado) Oil)
Calcium Stearate
Caprylic/Capric Triglyceride
Carbomers
Decyl Oleate
Glycol Stearate
Glycol Stearate SE
Glycol Distearate
Imidazolidinyl Urea
Isodecyl Oleate
Isopropyl Lanolate
Lithium Stearate
Magnesium Stearate
Potassium Stearate
Quaternium-18
Quaternium-18 Hectorite
Quaternium-18 Bentonite
Sodium Stearate
Squalene
Squalane
Stearalkonium Chloride
Wheat Germ Glycerides
Wheat Gluten (*aka* Triticum Vulgare (Wheat) Gluten)
Wheat Flour (*aka* Triticum Vulgare (Wheat) Kernel Flour)
Wheat Starch (*aka* Triticum Vulgare (Wheat) Starch)
Wheat Germ Oil (*aka* Triticum Vulgare (Wheat) Germ Oil)
Zinc Stearate

AVOCADO OIL (*aka* PERSEA GRATISSIMA (AVOCADO) OIL)

A safety assessment of Avocado Oil was published in 1980 with the conclusion "safe for use as presently incorporated into cosmetic formulations" (Elder 1980). Studies available since that safety assessment was completed, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel discussion focused on the new studies reporting the co-occurrence of latex and avocado allergies. Because the oil derived from the avocado has no protein component, Persea Gratissima (Avocado) Oil used in cosmetics is not expected to cross-react in individuals who are allergic to latex.

The Panel noted that a long history of reviewing plant-derived or "botanical" cosmetic ingredients has developed since these

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA

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TABLE 8
Isodecyl Oleate use

Product category	1976 use (CIR 1982)	2001 use (FDA 2001)	1976 concentrations (CIR 1982)	2001 concentrations (CTFA 2001)
Bath oils, tablets and salts	1	—	>5%–10%	—
Other bath preparations	1	—	>0.1%–1%	—
Eyeshadow	8	—	>1%–5%	2%
Eye makeup remover	—	1	—	2%
Hair conditioners	—	3	—	
Hair tonics, dressings, etc.	—	—	—	2%
Hair sprays	—	1	—	—
Blushers	1	—	>1%–5%	8%
Foundations	2	1	>1%–5%	5%
Lipstick	—	22	—	4%–8%
Other makeup preparations	2	2	>1%–5%	5%
Other manicuring preparations	—	1	—	—
Deodorants	1	—	>1%–5%	2%
Other personal cleanliness products	1	—	>1%–5%	—
Aftershave lotion	—	3	—	—
Other shaving preparation products	—	1	—	—
Skin cleansing preparations	1	2	>10%–25%	3%
Face and neck skin care preparations[a]	2	—	>5%–25%	2%–5%
Body and hand skin care preparations[a]		1		4%
Moisturizing preparations	4	5	>1%–10%	2%–3%
Night creams, lotions, etc.	—	1	—	5%
Other skin preparations	—	—	—	3%–4%
Suntan gels, creams, and liquids	—	—	—	3%
Totals/ranges	24	44	>0.1%–25%	2%–8%

[a]Originally, Face and Neck and Body and Hand were combined as one category, but now they are separated.

Isodecyl Oleate

Isodecyl Oleate was used in 24 cosmetic products in 1976, with the largest uses in eyeshadows in the >1% to 5% concentration range. In 2001, Isodecyl Oleate was used in 44 preparations, with the largest single use in lipsticks (FDA 2001). Concentration of use data from 2001 was provided (CTFA 2001). Complete Isodecyl Oleate information is shown in Table 8.

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GLYCOL STEARATE, GLYCOL STEARATE SE, AND GLYCOL DISTEARATE

A safety assessment of Glycol Stearate, Glycol Stearate SE, and Glycol Distearate was published in 1982 with the conclusion that these ingredients "are safe as cosmetic ingredients in the present practices of use and concentrations" (Elder 1982). New studies, along with the updated information below regarding types and concentrations of use were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Glycol Stearate

Glycol Stearate was used in 284 formulations in 1976, at concentrations from ≤0.1% to 10%. In 2001, there were 424 formulations reported to the FDA that contained Glycol Stearate (FDA 2001). Glycol Stearate was reported to be used in 16 new product categories and no longer used in 11 categories as compared to the 1976 FDA database. Concentration of use data from 2001 was provided (CTFA 2001). Table 9 presents the available use information for Glycol Stearate.

TABLE 9
Glycol Stearate use

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentrations (Elder 1982)	2001 concentrations (CTFA 2001)
Baby lotions, oils, powders, etc.	—	—	—	5%
Other baby products	—	1	—	—
Bath oils, tablets, and salts	6	4	>0.1%–1%	—
Bubble baths	47	20	>0.1%–5%	2%
Other bath preparations	6	12	>0.1%–1%	0.2%–5%
Eyebrow pencil	3	—	>1%–5%	5%
Eyeliner	9	—	>1%–5%	4%
Eye shadow	76	—	>1%–10%	6%
Mascara	2	—	>1%–5%	3%
Perfumes	—	—	—	4%
Powders (dusting and talcum)	—	—	—	4%
Sachets	—	—	—	4%
Other fragrance preparations	—	1	—	2%
Hair conditioners	2	17	>5%–10%	0.0001%–3%
Hair straighteners	4	—	>5%–10%	—
Permanent Waves	—	1	—	—
Rinses (noncoloring)	3	—	>0.1%–1%	—
Shampoos (noncoloring)	77	149	≤0.1%–10%	0.05%–4%
Hair tonics, dressings, etc.	1	2	>1%–5%	1%
Hair dyes and colors	—	32	—	2%–6%
Hair shampoos (coloring)	2	1	>1%–5%	—
Blushers (all types)	5	—	>1%–5%	2%
Foundations	88	2	>1%–5%	4%
Leg and body paints	—	—	—	2%
Lipstick	1	1	>1%–5%	—
Makeup bases	2	—	>1%–5%	—
Rouges	8	—	>1%–5%	2%
Makeup fixatives	—	—	—	2%
Other makeup preparations	2	—	>1%–5%	2%–3%
Cuticle softeners	—	1	—	—
Nail creams and lotions	—	1	—	—
Nail polish and enamel removers	—	1	—	—
Other manicuring preparations	—	—	—	0.02%
Bath soaps and detergents	2	40	>0.1%–5%	0.3%–5%
Deodorants (underarm)	—	2	—	—
Douches	—	1	—	—
Other personal cleanliness products	—	8	—	0.2%–6%
Aftershave lotions	1	—	>0.1%–1%	—
Shaving cream	—	3	—	1%
Skin cleansing preparations	8	21	>0.1%–5%	0.2%–5%
Face and neck skin preparations[a]	11	8	>0.1%–5%	5%
Body and hand skin preparations[a]		24		0.7%–5%
Foot powders and sprays	—	4	—	5%
Moisturizing preparations	12	27	>0.1%–10%	5%
Night preparations	—	4	—	3%
Paste masks (mud packs)	—	3	—	—
Other skin care preparations	5	26	>0.1%–10%	3%–4%
Suntan gels, creams, and liquids	1	5	>1%–5%	—
Indoor tanning preparations	—	1	—	—
Other suntan preparations	—	1	—	2%
Totals/ranges	284	424	≤0.1%–10%	0.0001%–6%

[a]Originally, Face and Neck and Body and Hand were combined as one category, but now they are separated.

TABLE 10
Glycol Stearate SE

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentrations (Elder 1982)	2001 concentrations (CTFA 2001)
Other bath preparations	—	—	—	0.2%
Other eye makeup preparations	—	2	—	—
Makeup bases	—	—	—	0.9%
Makeup fixatives	—	1	—	—
Other personal cleanliness products	—	—	—	0.2%
Skin cleansing preparations	—	1	—	0.2%
Body and hand skin preparations	—	3	—	—
Moisturizing preparations	—	6	—	—
Paste masks (mud packs)	—	—	—	12%
Other skin care preparations	1	—	>0.1%–1%	
Suntan gels, creams, and liquids	—	1	—	2%
Other suntan preparations	—	—	—	5%
Totals/ranges	1	14	>0.1%–1%	0.2%–12%

Glycol Stearate SE

There was one formulation reported to the FDA in 1976 that contained Glycol Stearate SE, in the >0.1% to 1% concentration range. In 2001, there were 14 formulations reported to the FDA that contained Glycol Stearate SE, in five new product categories (FDA 2001). Concentration of use data from 2001 was provided (CTFA 2001). Table 10 presents the available use information for Glycol Stearate SE.

Glycol Distearate

There were 26 formulations that contained Glycol Distearate at concentrations from >0.1% to 10% in 1976. In 2001, there were 28 formulations reported to the FDA that contained Glycol Distearate (FDA 2001). Glycol Distearate was reported to be used in three new product categories and no longer used in four categories as compared to the 1976 data. Concentration of use data from 2001 was provided (CTFA 2001).

TABLE 11
Glycol Distearate use

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentrations (Elder 1982)	2001 concentrations (CTFA 2001)
Other baby products	—	—	—	1%
Bath oils, tablets, and salts	—	—	—	0.4%
Bubble baths	—	—	—	2%
Other bath preparations	—	1	—	0.7%–3%
Mascara	—	—	—	3%
Hair conditioners	1	1	>0.1%–1%	2%–9%
Permanent waves	5	—	>1%–5%	—
Shampoos (noncoloring)	15	7	>0.1%–5%	—
Other hair preparations	—	1	—	2%
Hair dyes and colors	1	—	>0.1%–1%	0.2%
Other hair coloring preparations	—	—	—	0.5%
Bath soaps and detergents	—	15	—	2%–3%
Deodorants (underarm)	1	—	>1%–5%	—
Other personal cleanliness products	1	—	>5%–10%	0.5%–3%
Other shaving preparation products	1	1	>1%–5%	—
Skin cleansing preparations	1	2	>1%–5%	0.2%–3%
Body and hand skin preparations	—	—	—	6%
Foot powders and sprays	—	—	—	2%
Other skin care preparations	—	—	—	4%
Totals/ranges	26	28	>0.1%–10%	0.2%–9%

Table 11 presents the available use information for Glycol Distearate.

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IMIDAZOLIDINYL UREA

A safety assessment of Imidazolidinyl Urea was published in 1980 with the conclusion that this ingredient is "safe when incorporated in cosmetic products in amounts similar to those presently marketed" (Elder 1980). New studies, along with the updated information below regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

In 1976, Imidazolidinyl Urea was used in 1061 cosmetic products, with the largest single use in face powder products in the concentration range of ≤0.1% to 5%. In 2001, there were uses reported in 2025 products, with the largest single use in eye shadow (FDA 2001). In 2001, the maximum use concentration

TABLE 12
Imidazolidinyl Urea use

Product category	1976 use (Elder 1980)	2001 use (FDA 2001)	1976 concentrations (Elder 1980)	2001 concentrations (CTFA 2001)
Baby shampoos	2	1	≤0.1%–1%	0.5%
Baby lotions, oils, powders, etc.	1	2	>0.1%–1%	0.3%–0.6%
Other baby products	—	1	—	0.3%
Bath oils, tablets, and salts	12	—	>0.1%–1%	0.2%–0.5%
Bubble baths	15	26	≤0.1%–1%	0.3%–0.4%
Other bath preparations	12	60	≤0.1%–1%	0.5%
Eyebrow pencil	13	4	≤0.1%–1%	0.3%
Eyeliner	99	18	≤0.1%–5%	0.01%–0.6%
Eye shadow	—	301	—	0.2%–0.5%
Eye lotion	—	7	—	0.5%
Eye makeup remover	3	16	≤0.1%–1%	0.1%–0.5%
Mascara	46	59	≤0.1%–1%	0.3%–0.5%
Other eye makeup preparations	18	28	≤0.1%–1%	0.3%–0.5%
Colognes and toilet waters	1	3	≤0.1%	0.4%
Perfumes	—	11	—	0.4%–0.5%
Powders	52	19	≤0.1%–1%	0.2%–0.4%
Sachets	13	—	≤0.1%–1%	0.1%
Other fragrance preparations	2	17	≤0.1%	0.4%–0.5%
Hair conditioners	35	35	≤0.1%–5%	—
Hair sprays (aerosol fixatives)	—	1	—	0.4%
Permanent waves	1	6	≤0.1%–1%	—
Rinses (noncoloring)	6	2	≤0.1%–5%	0.2%
Shampoos (noncoloring)	43	46	≤0.1%–5%	0.2%–0.5%
Hair tonics, dressings, etc.	8	24	≤0.1%–1%	0.4%
Wave sets	4	3	≤0.1%–1%	0.3%
Other hair preparations	4	7	≤0.1%–1%	0.2%
Hair dyes and colors	—	3	—	—

(Continued on next page)

[2]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

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Final Report of the Cosmetic Ingredient Review Expert Panel on the Safety Assessment of Pelargonic Acid (Nonanoic Acid) and Nonanoate Esters

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Abstract

Pelargonic acid and its esters function as skin-conditioning agents in cosmetics. Molecular weight (mw) and octanol–water partition coefficient data suggest that dermal penetration is possible. The biohandling of branched-chain fatty acids is not the same as for straight-chain fatty acids, but the differences are not significant to the conclusion that they all are readily metabolized to nontoxic moieties. Limited data suggested that the penetration of other ingredients may be enhanced if these ingredients are present in the same formulation. These ingredients are not significant oral or dermal toxicants in animal studies. They are not reproductive/developmental toxicants or genotoxic/carcinogenic in animal studies. The available data suggested that product formulations containing these ingredients would be nonirritating and nonsensitizing to human skin, but formulators were cautioned to consider the penetration enhancement potential. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that these ingredients are safe in the present practices of use and concentration.

Keywords

pelargonic acid, safety, cosmetics

Introduction

Pelargonic acid (aka nonanoic acid) is a fatty acid that can function as a fragrance ingredient, surfactant-cleansing agent, and surfactant-emulsifying agent in cosmetics. In its soap form, it can function as a surfactant-cleansing agent. Many of the fatty acids that are used in cosmetics and their synthesized derivatives (primarily esters and diesters of the corresponding alcohol and pelargonic acid) have similar additional functions in cosmetics. An idiosyncrasy in the terminology used in the *International Cosmetic Ingredient Dictionary and Handbook* is that most of these derivatives are termed nonanoates, not pelargonates. This safety assessment includes the following ingredients:

- pelargonic acid
- butylene glycol diisononanoate
- cellobiose octanonanoate
- cetearyl isononanoate
- cetearyl nonanoate
- cetyl isononanoate
- cholesteryl nonanoate
- diethylene glycol diethylhexanoate/diisononanoate
- diethylene glycol diisononanoate
- dihydrocholesteryl nonanoate
- dipentaerythrityl pentaisononanoate
- ethylhexyl isononanoate
- glycereth-7 diisononanoate
- isodecyl isononanoate
- isononyl isononanoate
- isostearyl isononanoate
- isotridecyl isononanoate
- neopentyl glycol diisononanoate
- PEG-2 diisononanoate

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- PEG-5 isononanoate
- pentaerythrityl tetraisononanoate
- phytosteryl nonanoate
- polyglyceryl-20 octaisononanoate
- propylene glycol diisononanoate
- tridecyl isononanoate
- ethylhexyl pelargonate
- ethyl pelargonate
- isobutyl pelargonate
- methyl pelargonate
- neopentyl glycol dicaprylate/dipelargonate/dicaprate
- pentaerythrityl tetrapelargonate

The nonanoate or pelargonate esters and diesters are straight-chain compounds, whereas the isononanoate esters and diesters are branched-chain compounds. Propylene glycol dipelargonate would have been included in this safety assessment; however, the Cosmetic Ingredient Review (CIR) Expert Panel previously concluded that this ingredient is safe in the present practices of use in cosmetic products.[1]

Pelargonic acid is a reactant in the esterification process that yields all of the esters included in this safety assessment. While this fatty acid is not reported to be currently used in cosmetics, much of the data available for review relate to pelargonic acid. The CIR Expert Panel has published safety assessments on the following fatty alcohols and other reactants used to form some of the esters reviewed in this safety assessment, and other fatty acid esters: butylene glycol—safe in present practices of use and concentration (safe),[2,3] cetearyl, cetyl, and isostearyl alcohols—safe,[4,5] cholesterol—safe,[6,3] ethylene glycol—special report on reproductive and developmental toxicity—no conclusion,[7] ethylhexyl palmitate (previously incorrectly named octyl palmitate)—safe,[8,9] PEG-7 glyceryl cocoate—safe as used in rinse off products; safe up to 10% in leave on products,[10] PEGs-2 and -6 dilaurate—safe for use in cosmetics at concentrations up to 25%,[11] octyl stearate and isobutyl stearate—safe,[12,5] isodecyl oleate—safe,[13,14] and propylene glycol dipelargonate—safe,[1] as stated above. These conclusions may contribute to the safety assessment of ingredients in the current review for which little or no data have been identified in the published literature.

Similarly, there are ingredient moieties that have not been reviewed by the Expert Panel, and available data on these chemicals may be useful in the absence of safety test data on some of the esters that are being reviewed. Thus, data on or relevant to the following chemicals are also summarized in the current safety assessment: isononanoic acid, isononyl alcohol, isotridecyl alcohol, neopentyl glycol, isobutyl alcohol, and isodecyl alcohol. Excerpts from the summary and discussion from the CIR Final Safety Assessment on propylene glycol dipelargonate and other propylene glycol esters and diesters are also included, because these data may be useful in evaluating the safety of diesters included in the current review. Excerpts from the CIR Final Safety Assessments on isobutyl stearate and isodecyl oleate are also included, in lieu of data on isobutyl alcohol and isodecyl alcohol, respectively.

Chemistry

Definition and Structure

Chemical definitions, other chemical names, and cosmetic ingredient functions for the ingredients reviewed in the safety assessment are included in Table 1. The International Nomenclature Cosmetic Ingredient (INCI) name appears first in each series of chemical names; "iso" in an INCI name denotes methyl branching/substitution and does not necessarily imply substitution on the second to last carbon atom (omega-2 substitution).[15] Chemical structures/formulas are included in Figure 1. The inclusion of [sic] after a technical name or CAS No. in Table I denotes those instances wherein the authors of the dictionary associated a specific branched chemical entity other than an omega-2 methyl substituted isomer with an "iso" INCI name. According to the dictionary *proviso* regarding "iso"-named ingredients, all branched isomers are potentially included by an "iso" INCI ingredient name. For simplicity, only omega-2 isomers are shown in Figure I. However, in one exception, the [sic] notation is included after "octyl isononanoate," in the ethylhexyl isononanoate box of Table I, in that octyl isononanoate is included in the *International Cosmetic Ingredient Dictionary and Handbook* because it is a former INCI name for this ingredient.

Chemical and Physical Properties

Available chemical and physical properties are included in Table 2.

UV Absorption

Data provided by a manufacturer[33] indicated that the following chemicals did not absorb significantly in the 250 to 400 nm range: neopentyl glycol diisononanoate, cetyl nonanoate + stearyl nonanoate, trideceth-9 + PEG-5-isononanoate + water, glyceryl triisononanoate + glyceryl diisononanoate, and ethylhexyl isononanoate.

Analytical Methods

Pelargonic acid, cholesteryl nonanoate, ethyl pelargonate, and methyl pelargonate have been analyzed by nuclear magnetic resonance (NMR), infrared (IR), and mass spectrometry; and pentaerythrityl pelargonate has been analyzed by IR spectrometry.[17] Methyl pelargonate and pelargonic acid have also been analyzed by gas chromatography–mass spectrometry,[34] and the same is true for ethyl pelargonate.[35]

Methods of Production

In general, the alkyl esters can be produced industrially via the esterification of carboxylic acids with the corresponding alcohols (with or without a metal catalyst).[36] The sources of these carboxylic acids and alcohols are often natural or are derived from natural sources. Alcohols with chains longer than ethanol

Table 1. Pelargonic Acid and Its Nonanoate Esters[15]

Chemical Names	Definition	Functions in Cosmetics
Pelargonic acid; nonanoic acid; nonoic acid; nonylic acid; 1-octanecarboxylic acid; pelargic acid; pergonic acid; CAS No. 112-05-0	An acid that conforms to the formula in Figure 1	Fragrance ingredients; surfactants—cleansing agents; surfactants—emulsifying agents
Butylene glycol diisononanoate; trade name: cetiol FC	The diester of butylene glycol and branched-chain nonanoic acids	Skin-conditioning agents—emollient; skin-conditioning agents—occlusive; viscosity increasing agents—nonaqueous
Cellobiose octanonanoate; α-o-glycopyranose, 4-O-[2,3,4,6-tetrakis-O-(1-oxononyl)-β-D- glucopyranosyl]-tetranonanoate; CAS No. 172585-66-9; trade name: α-o-cellobiose octanonanoate	The octaester formed by the reaction of α-D-cellobiose and nonanoic anhydride	Viscosity increasing agents—nonaqueous
Cetearyl isononanoate; isononanoic acid, cetyl/stearyl ether; trade names: AEC cetearyl isononanoate; cetiol SN; dub IN 1618; saboderm CSN; and tegosoft CI	The ester of cetearyl alcohol and a branched-chain nonanoic acid	Hair-conditioning agents; skin-conditioning agents—emollient
Cetearyl nonanoate; trade name: SymMollient 5 181598	The organic compound that conforms to the formula in Figure 1, where R represents the cetearyl group	Skin-conditioning agents—emollient
Cetyl isononanoate; isononanoic acid, hexadecyl ester; CAS No. 84878-33-1	The ester of cetyl alcohol with a branched-chain nonanoic acid	Skin-conditioning agents—emollient
Cholesteryl nonanoate; cholesterin pelargonate; cholesteryl nonylate; cholesteryl pelargonate; CAS No. 1182-66-7; trade name: yofco LC-CN	The ester of cholesterol and nonanoic acid	Not reported
Diethylene glycol diethylhexanoate/diisononanoate	The diester of a mixture of 2-ethylhexanoic acid and isononanoic acids and diethylene glycol	Hair-conditioning agents; plasticizers; skin-conditioning agents – emollient
Diethylene glycol diisononanoate; isononanoic acid, oxydi-2,1-ethanediyl ester; PEG-2 diisononanoate; CAS Nos. 106-01-4;190282-37-2	The diester of diethylene glycol and isononanoic acid	Hair-conditioning agents; plasticizers; skin-conditioning agents—emollient
Dihydrocholesteryl nonanoate	The ester of dihydrocholesterol and nonanoic acid	Skin-conditioning agents—emollient
Dipentaerythrityl pentaisononanoate; CAS No. 84418-63-3; trade name: dub vinyl	The pentaester of isononanoic acid with a dimer of pentaerythritol	Skin-conditioning agents—emollient; viscosity increasing agents—nonaqueous
ethylhexyl isononanoate; 2-ethyl-hexyl isononanoate; 2-ethylhexyl isopelargonate; 2-ethylhexyl 3,5,5-trimethyl-hexanoate; isononanoic Acid, 2-ethylhexyl ester; octyl iso-nonanoate [sic], former INCI ingredient name; CAS Nos.70969-70-9; 71566-49-9; trade names: AEC ethylhexyl isononanoate; dermol 89; dub INO; ES 108109; HallStar octyl isononanoate; isolanoate; pelemol 89; schercemol OISN	The ester of 2-ethyl-hexyl alcohol and a branched-chain nonanoic acid	skin-conditioning agents—emollient
Glycereth-7 diisononanoate; PEG-7 glyceryl ether diisononanoate; poly-ethylene glycol (7) glyceryl ether diisononanoate; polyoxyethylene (7) glyceryl ether diisononanoate; CAS No. 125804-15-1; trade name: dermol G-7DI	The diester of isononanoic acid and glycereth-7	Skin-conditioning agents—emollient; solvents
Isodecyl isononanoate; hexanoic acid, 3,5,5,-trimethyl-, isodecyl ester; isodecyl 3,5,5-trimethylhexanoate; isononanoic acid, isodecyl ester; 3,5,5-trimethylhexanoic acid, isodecyl ester; CAS Nos. 41395-89-5 and 59231-35-5; trade names: AEC isodecyl isononanoate; dermol 109; dub INID; KAK 109	The ester of branched-chain decyl alcohols and branched-chain nonanoic acid that conforms to The structure in Figure 1	Skin-conditioning agents – emollient

(continued)

Table 1. (continued)

Chemical Names	Definition	Functions in Cosmetics
Isononyl isononanoate; hexanoic acid, 3,5,5-trimethyl-, 3,5,5-trimethylhexyl ester; isononanoic acid, isononyl ester; 3,5,5-trimethylhexa-noic acid, 3,5,5-trimethylhexyl ester; 3,5,5-trimethylhexyl-3,5,5-trimethyl-hexanoate; CAS Nos. 42131-25-9 and 59219-71-5; trade names: AEC isononyl isononanoate; dermol 99; dub ININ; hatcol 5131; KAK 99; lanol 99; pelemol IN-2; saboderm 15N; salacos 99	The ester of a branched-chain nonyl alcohol with a branched-chain nonanoic acid	Skin-conditioning agents—emollient
Isostearyl isononanoate; hexanoic acid, 3,5,5-trimethyl-, isooctadecyl ester; CAS Nos. 90967-66-1and 163564-45-2; trade name: lanol 189	The ester of isostearyl alcohol and isononanoic acid	Skin-conditioning agents—emollient
Isotridecyl isononanoate; hexanoic acid, 3,5,5-trimethyl-, isooctadecyl ester; isononanoic acid, isotridecyl ester; isotridecyl 3,5,5-trimethylhexanoic acid; CAS Nos. 42131-27-1 and 59231-37-7; trade names: AEC isotridecyl isononanoate; dub INI; KAK 129; OriStar ITIN; salacos 913	The ester of isotridecyl alcohol and isonona-noic acid	Skin-conditioning agents—emollient
Neopentyl glycol diisononanoate; CAS No. 137636-04-5; trade names: NPDIN; SymMollient L 177205	The organic compound that conforms to the structure in Figure 1	Skin-conditioning agents—emollient
PEG-2 diisononanoate; polyethylene glycol 100 diisononanoate; polyoxy-ethylene (2) diisononanoate;	The polyethylene glycol diester of isononanoic acid that conforms to the structure in Figure 1, where n has an average value of 2	Surfactants—emulsifying agents
PEG-5 isononanoate	The organic compound that conforms generally to the structure in Figure 1, where n has an average value of 5	Surfactants—emulsifying agents
Pentaerythrityl tetraisononanoate; 2,2-bis[[(1-oxoisononyl)oxy]methyl]-1,3-propanediyl isononanoate; isononanoic acid, 2,2-bis[[(1-oxoisononyl)oxy]methyl]-1,3-propanediyl ester; CAS No. 93803-89-5; trade name: pelemol P-49	The tetraester of pentaerythritol and a branched-chain nonanoic acid. It conforms generally to the structure in Figure 1, where RCO represents the isononanoic acid radical	skin-conditioning agents—occlusive; viscosity increasing agents—nonaqueous
Phytosteryl nonanoate; trade name: yofco LC-PN	The ester of phytosterol and nonanoic acid	Hair-conditioning agents; skin-conditioning agents—miscellaneous
Polyglyceryl-20 octaisononanoate; trade name: sunsoft Q-98U	The octaester of isononanoic acid and polyglycerin-20	Surfactants—cleansing agents; surfactants—emulsifying agents; surfactants—solubilizing agents
Propylene glycol diisononanoate; isononanoic acid, 1-methyl-1,2-ethanediyl ester; CAS No. 125804-17-3; trade names: AEC propylene glycol diisononanoate; dermol PGDI	The diester of propylene glycol and branched-chain nonanoic acids	Skin-conditioning agents—occlusive; viscosity increasing agents—nonaqueous
Tridecyl isononanoate; hexanoic acid, 3,5,5-trimethyl-, tridecyl ester; isononanoic acid, tridecyl ester; 3,5,5-trimethylhexanoic acid, tridecyl ester; CAS No. 125804-18-4; trade name: dermol 139	The ester of tridecyl alcohol and isononanoic acid that conforms to the structure in Figure 1	Skin-conditioning agents—emollient

(continued)

Table 1. (continued)

Chemical Names	Definition	Functions in Cosmetics
Ethylhexyl pelargonate; 2-ethylhexyl pelargonate; nonanoic acid, w-ethylhexyl ester; octyl pelargonate; CAS No. 59587-44-9; trade names: AEC ethylhexyl pelargonate; bernel ester OPG; crodamol OPG; dub PEO; jeechem OPG; pelemol OPG; schercemol OPG ester	Ester of 2-ethylhexyl alcohol and pelargonic acid that conforms to the structure in Figure 1	Skin-conditioning agents—emollient
Ethyl pelargonate; ethyl nonanoate; nonanoic acid, ethyl ester; CAS No. 123-29-5	Ester of ethyl alcohol and pelargonic acid that conforms to the structure in Figure 1	Fragrance ingredients; hair-conditioning agents; skin-conditioning agents—emollient
Isobutyl pelargonate; isobutyl nonanoate; 2-methylpropyl nonanoate; nonanoic acid, isobutyl ester; nonanoic acid, 2-methypropyl ester; CAS No. 30982-03-7; trade name: AEC isobutyl pelargonate	Ester of isobutyl alcohol and pelargonic acid that conforms to the structure in Figure 1	Fragrance ingredients; skin-conditioning agents—emollient
Methyl pelargonate; methyl nonanoate; nonanoic acid, methyl ester; pelargonic acid methyl ester; CAS No. 1731-84-6	Ester of methyl alcohol and pelargonic acid that conforms to the structure in Figure 1	Fragrance ingredients; skin-conditioning agents—emollient
Neopentyl glycol dicaprylate/dipelargonate/dicaprate	Diester of neopentyl glycol and a blend of caprylic, pelargonic, and capric acids	Skin-conditioning agents—emollient; viscosity increasing agents—nonaqueous
Pentaerythrityl tetrapelargonate; 2,2-bis[[(1-oxononyl)oxy]methyl]-1,3-propanediyl nonanoate; nonanoic acid, 2,2-bis[[(1-oxononyl)oxy]methyl]-1,3-propanediyl ester; CAS No. 14450-05-6; trade name: pelemol PTP	Tetraester of pentaerythritol and pelargonic acid that conforms to the structure in Figure 1	Binders; skin-conditioning agents—occlusive; viscosity increasing agents—nonaqueous

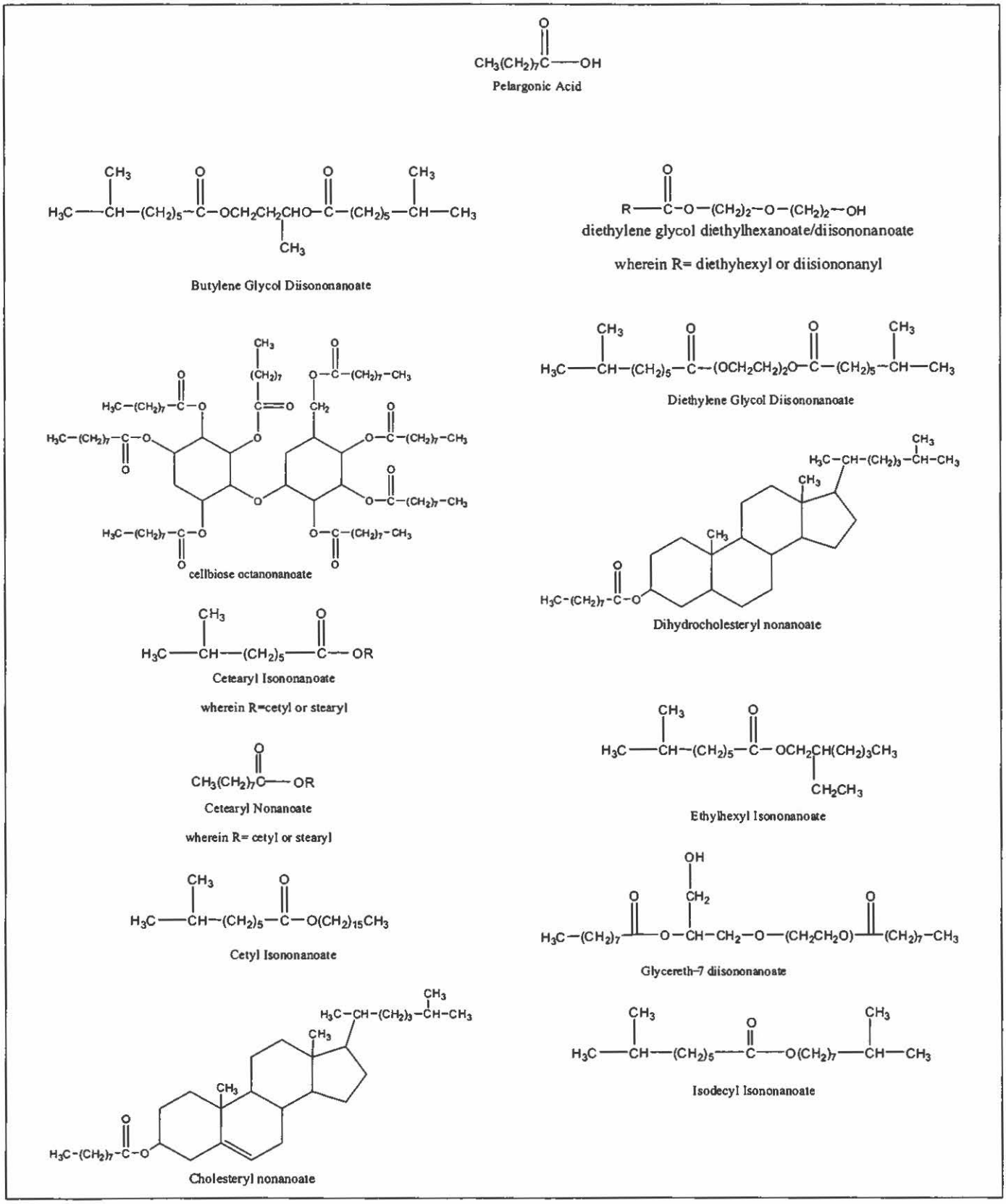

Figure 1. Structures/formulas of nonanoates/pelargonates.

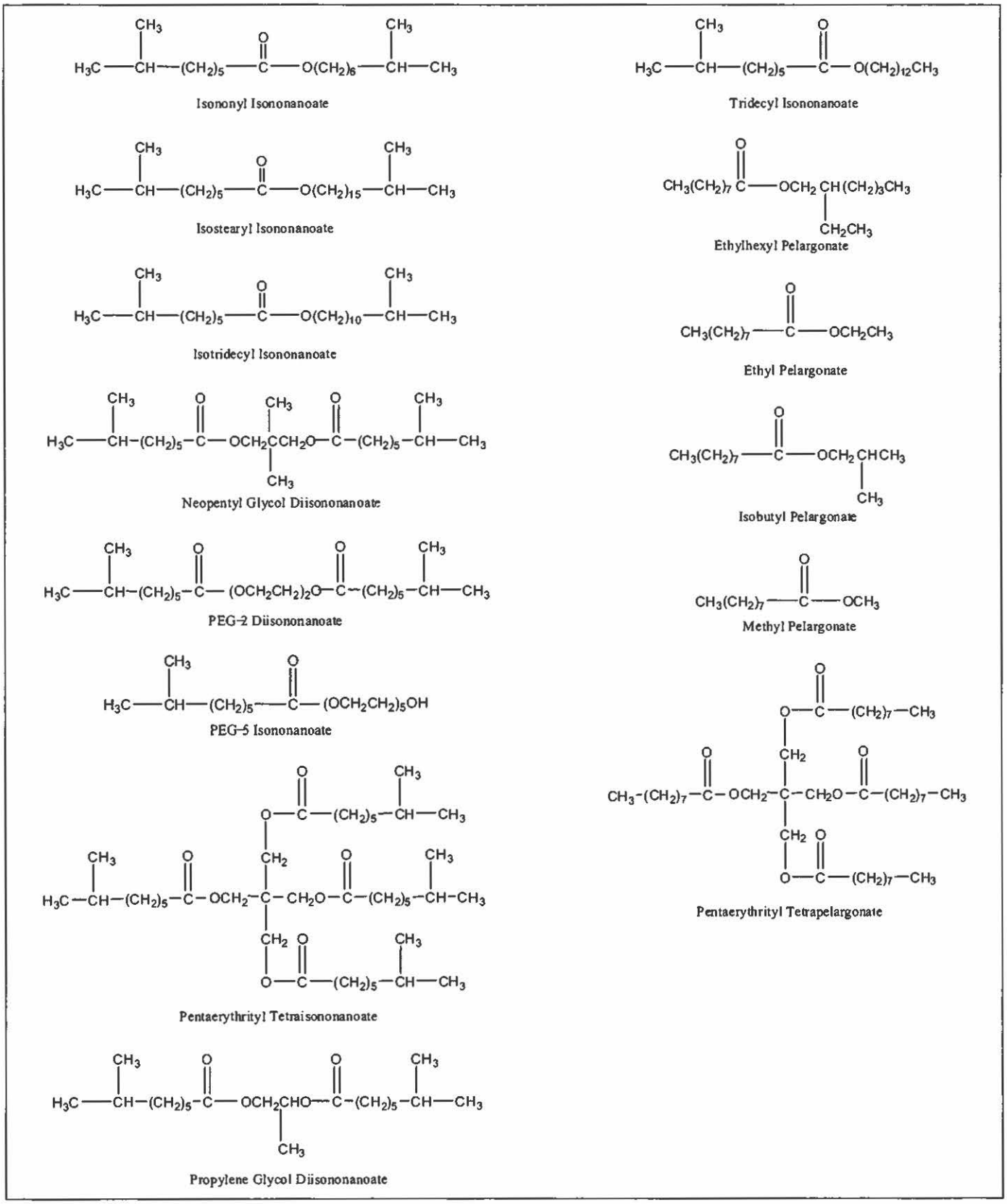

Figure 1. (Continued).

Table 2. Chemical and Physical Properties

Property	Value	Reference
Pelargonic acid		
Form	Oily, colorless liquid	Lewis[16]
Molecular weight	158.24	STN[17]
Density	0.9055 @ 20°C/40°C	Lewis[16]
		STN[17]
	0.9839 g/cm^3 @ 20°C	
	0.921 ± 0.06 g/cm^3 @ 20°C (calculated value)	
Solubility	Miscible with water and methanol	Committee of Revision of the United States Pharmacopeial Convention[18]
	Very slightly soluble in water	Lewis[16]
Refractive index	1.4456 @ 20°C and 589.3 nm	STN[17]
Vapor pressure	8.67E-03 Torr (calculated)	ACD Labs[19]
Melting point	12°C	Lewis[16]
		STN[17]
	12.3°C	
Freezing point	12.24°C	Lewis[16]
Boiling point	254.4°C @ 760 Torr	ACD Labs[19]
	254.9°C ± 3°C @ 760 Torr (calculated)	
Flash point	100.0°C ± 0°C (calculated)	ACD Labs[19]
Enthalpy of vaporization	52.03 ± 3.0 kJ/mol (calculated)	ACD Labs[19]
pKa	4.78 ± 0.10 (calculated)	ACD Labs[19]
logP	3.434 ± 0.184 @ 25°C (calculated)	ACD Labs[19]
Butylene glycol diisononanoate		
Molecular weight	370.57	ChemDraw[20]
Melting point	391.86°K (118.71°C (calculated)	ChemDraw[20]
Boiling point	818.52°K (545.37°C) (calculated)	ChemDraw[20]
logP	6.37 (calculated)	ChemDraw[20]
Cetearyl isononanoate (Tegosoft CI)		
Form	Yellowish liquid	Evonik Industries[21]
Refractive index	1.4450-1.4500 (specification)	Evonik Industries[22]
Density	0.854 to 0.858 g/mL (specification); ≈ 0.85 g/cm^3 @ 68°F	Evonik Industries[21,22]
Solubility	Insoluble in water	Evonik Industries[21]
Viscosity, according to Höppler (mPas)	≈ 16 @ 25°C	Evonik Industries[23]
Volatility	0% in water	Evonik Industries [21]
Melting temperature	<59°F (15°C)	Evonik Industries[21]
Flash point	>212°F (100°C)	Evonik Industries[21]
Solidifications point	≤15.0°C (specification)	Evonik Industries[22]
Hydroxyl value	≤1.0 mg KOH/g (specification)	Evonik Industries[22]
Iodine value	≤1.0 g L/100g (specification)	Evonik Industries[22]
Acid value	≤0.2 mg KOH/g (specification)	Evonik Industries[22]
Saponification value	140.0-146.0 mg KOH/g (specification)	Evonik Industries[22]
Heavy metals content	20 ppm maximum (Cu; Pb; Sn; Pt; Pd; Hg; As; Cd; Ni); <1 ppm (Hg; As; Cd; Ni respectively)	Evonik Industries[24]
Cellobiose octanonanoate		
Molecular weight	1464.08	STN[17]
Density	1.05 ± 0.1 g/cm^3 @ 20°C (calculated)	STN[17]
Vapor pressure	0 Torr @ 25°C (calculated)	STN[17]
Boiling point	1115.1°C ± 65°C@ 760 Torr (calculated)	STN[17]
Flash point	371.9°C ± 34.3°C (calculated)	STN[17]
Enthalpy of vaporization	164.52 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
log P	32.470 ± 0.860 @ 25°C (calculated)	STN[17]
Cetyl isononanoate		
Molecular weight	382.66	ChemDraw[20]
Melting point	398.34°K (125.19°C) (calculated)	ChemDraw[20]
Boiling point	829.38°K (556.23°C) (calculated)	ChemDraw[20]
logP	9.28 (calculated)	ChemDraw[20]
Cholesteryl nonanoate		
Molecular weight	526.88 (calculated)	STN[17]
Density	0.97 ± 0.1 g/cm^3 @ 20°C and 760 Torr (calculated)	STN[17]

(continued)

Table 2. (continued)

Property	Value	Reference
Optical rotation	−30°@ concentration of 1.0 g/100 mL in chloroform	STN[17]
Vapor pressure	2.77E-13 Torr @ 25°C (calculated)	STN[17]
Melting point	80°C (calculated)	STN[17]
Boiling point	576.3 ± 29°C @ 760 Torr (calculated)	STN[17]
Flash point	300.8 ± 11.8 ?C (calculated)	STN[17]
Enthalpy of vaporization	86.30 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
logP	14.4245 ± 0.299 @ 25°C (calculated)	STN[17]
Diethylene glycol diethylhexanoate/diisononanoate		
Molecular weight	576.85	ChemDraw[20]
Diethylene glycol diisononanoate		
Molecular weight	386.57	ChemDraw[20]
Melting point	414.09°K (140.94°C) (calculated)	ChemDraw[20]
Boiling point	890.94°K (617.79°C) (calculated)	ChemDraw[20]
logP	5.65 (calculated)	ChemDraw[20]
Dihydrocholesteryl nonanoate		
Molecular weight	528.89	ChemDraw[20]
Dipentaerythrityl pentaisononanoate		
Molecular weight	922.38	ChemDraw[20]
Ethylhexyl Isononanoate		
Molecular weight	270.45	ChemDraw[20]
Melting point	293.18°K (20.03°C) (calculated)	ChemDraw[20]
Boiling point	645.9°K (372.75°C) (calculated)	ChemDraw[20]
logP	5.91 (calculated)	ChemDraw[20]
Isodecyl isononanoate		
Molecular weight	298.50	ChemDraw[20]
Refractive index	1.437 to 1.439 @ 25°C (specification)	Nikitakis and McEwen[25]
Specific gravity	0.852 to 0.858 @ 25°/25°C (specification)	Nikitakis and McEwen[25]
Acid value	1.0 maximum (specification)	Nikitakis and McEwen[25]
Saponification value	175-192 (specification)	Nikitakis and McEwen[25]
Iodine value	0.5 maximum (specification)	Nikitakis and McEwen[25]
Melting point	315.72°K (42.57°C) (calculated)	ChemDraw[20]
Boiling point	691.66°K (418.51°C) (calculated)	ChemDraw[20]
logP	6.68 (calculated)	ChemDraw[20]
Isononyl isononanoate		
Molecular weight	284.48	ChemDraw[20]
Refractive index	1.4340-1.4360 @ 25°C (specification)	Nikitakis and McEwen[25]
Specific gravity	0.849 to 0.855 @ 25°C/25° (specification)	Nikitakis and McEwen[25]
Acid value	1.0 maximum (specification)	Nikitakis and McEwen[25]
Saponification value	192-202 (specification)	Nikitakis and McEwen[25]
Iodine value	0.5 maximum (specification)	Nikitakis and McEwen[25]
Melting point	304.45°K (31.3°C)	ChemDraw[20]
Boiling point	668.78°K (395.63°C)	ChemDraw[20]
logP	6.27 (calculated)	ChemDraw[20]
Isononyl isononanoate (Tegosoft INI)		
Form	Colorless to slightly yellow liquid	Evonik Industries[26]
Density	0.865 g/cm^3 at 71.60°F (22°C)	Evonik Industries[26]
Solubility	Insoluble in water	Evonik Industries[26]
Viscosity, dynamic	5.5 mPa.s @ 20°C	Evonik Industries[26]
Boiling temperature	273.20°F -280.40°F (138°C) @ 1.3 hPa	Evonik Industries[26]
Flash point	305.60°F (152°C)	Evonik Industries[26]
Hydroxyl value	≤5.0 mg KOH/g (specification)	Evonik Industries[27]
Iodine value	≤0.50 g I/100 g (specification)	Evonik Industries[26]
Acid value	≤0.20 mg KOH/g (specification)	Evonik Industries[26]
Saponification value	185-200 mg KOH/g (specification)	Evonik Industries[26]
Water content	≤0.30 % (specification)	Evonik Industries[26]
Heavy metals content	20 ppm maximum (Cu; Pb; Sn; Pt; Pd; Hg; As; Cd; Ni); < 1 ppm (Hg; As; Cd; Ni respective)	Evonik Industries[28]
Isostearyl isononanoate		
Molecular weight	410.72	ChemDraw[20]
Melting point	405.88°K (132.73°C) (calculated)	ChemDraw[20]

(continued)

Table 2. (continued)

Property	Value	Reference
Boiling point	874.7°K (601.55°C) (calculated)	ChemDraw[20]
logP	10.02 (calculated)	ChemDraw[20]
Isotridecyl isononanoate		
Molecular weight	340.58	ChemDraw[20]
Refractive index	1.433-1.445 @ 25°C (specification)	Nikitakis and McEwen[25]
Specific gravity	0.859-0.861 @ 25°C /25°C (specification)	Nikitakis and McEwen[25]
Acid value	1.0 maximum (specification)	Nikitakis and McEwen[25]
Saponification value	155-165 (specification)	Nikitakis and McEwen[25]
Iodine value	0.5 maximum (specification)	Nikitakis and McEwen[25]
Melting point	349.53°K (76.38°C) (calculated)	ChemDraw[20]
Boiling point	760.3°K (487.15°C) (calculated)	ChemDraw[20]
logP	7.94 (calculated)	ChemDraw[20]
Neopentyl glycol diisononanoate		
Molecular weight	384.59	ChemDraw[20]
Melting point	405.55°K (132.4°C) (calculated)	ChemDraw[20]
Boiling point	838.17°K (565.02°C) (calculated)	ChemDraw[20]
logP	7.03 (calculated)	ChemDraw[20]
Pentaerythrityl tetraisononanoate		
Molecular weight	697.04	ChemDraw[20]
Propylene glycol diisononanoate		
Molecular weight	356.54	ChemDraw[20]
Melting point	365.59°K (92.44°C) (calculated)	ChemDraw[20]
Boiling point	795.2°K (522.05°C) (calculated)	ChemDraw[20]
logP	6.13 (calculated)	ChemDraw[20]
Tridecyl isononanoate		
Molecular weight	340.58	ChemDraw[20]
Melting point	364.53°K (91.38°C) (calculated)	ChemDraw[20]
Boiling point	760.74°K (487.59°C) (calculated)	ChemDraw[20]
logP	8.02 (calculated)	ChemDraw[20]
Ethylhexyl pelargonate		
Molecular weight	270.45	STN[17]
Density	0.864 ± 0.06 g/cm^3 @ 20°C	STN[17]
Mass intrinsic solubility	0.0022 g/L @ 25°C (calculated)	5TN[17]
Molar intrinsic solubility	0.0000081 mol/L @ 25°C (calculated)	STN[17]
Boiling point	311.8 ± 10.0°C @ 760 Torr (calculated)	STN[17]
Melting point	308.18°K (35.03°C) (calculated)	ChemDraw[20]
Vapor pressure	5.49E-04 Torr @ 25°C (calculated)	STN[17]
Enthalpy of vaporization	55.28 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
Flash point	144.1 ± 8.8°C (calculated)	STN[17]
logP	7.432 ± 0.212 @ 25°C (calculated)	STN[17]
Ethyl pelargonate		
Molecular weight	186.29	STN[17]
Density	0.872 ± 0.06 g/cm^3 @ 20°C (calculated)	STN[17]
Refractive index	1.43367 @ 15°C	STN[17]
Mass intrinsic solubility	0.17 g/L @ 25°C (calculated)	STN[17]
Molar intrinsic solubility	0.0092 mol/L @ 25°C (calculated)	STN[17]
Boiling point	225.5°C-227.5°C; 220.0°C ± 0°C @ 760 Torr (calculated)	STN[17]
Melting point	−36.7°C (calculated)	STN[17]
Vapor pressure	1.16E-01 Torr @ 25°C (calculated)	STN[17]
Enthalpy of vaporization	45.64 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
Flash point	94.4 ± 0°C (calculated)	STN[17]
logP	4.428 ± 0.206 @ 25°C (calculated)	STN[17]
Isobutyl pelargonate		
Molecular weight	214.34 (calculated)	STN[17]
Density	0.867 ± 0.06 g/cm^3 @ 20°C (calculated)	STN[17]
Mass intrinsic solubility	0.041 g/L @ 25°C (calculated)	STN[17]
Molar intrinsic solubility	0.00019 mol/L @ 25°C (calculated)	STN[17]
Boiling point	248.9 ± 8°C @ 760 Torr (calculated)	STN[17]
Melting point	263.1°K (−10.05°C) (calculated)	ChemDraw[20]

(continued)

Table 2. (continued)

Property	Value	Reference
Vapor pressure	2.36E-02 Torr @ 25°C (calculated)	STN[17]
Enthalpy of vaporization	48.61 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
Flash point	104.7 ± 8.3°C (calculated)	STN[17]
logP	5.307 ± 0.212 @ 25°C (calculated)	STN[17]
Methyl pelargonate		
Molecular weight	172.26 (calculated)	STN[17]
Density	0.8655 g/ cm^3 @ 25°C; 0.874 ± 0.06 g/cm^3 @ 20°C and 760 Torr (calculated)	STN[17]
Refractive index	1.4205 @ 20°C and 589.3 nm; 1.41395 @ 25°C and 589.3 nm	STN[17]
Mass intrinsic solubility	0.36 g/L @ 25°C (calculated)	STN[17]
Molar intrinsic solubility	0.0021 mol/L @ 25°C (calculated)	STN[17]
Boiling point	213.5°C and 122.0°C; 210.3 ± 3°C @ 760 Torr (calculated)	STN[17]
Melting point	244.29°K (−28.86°C) (calculated)	ChemDraw[20]
Vapor pressure	1.93E-01 Torr @ 25°C (calculated)	STN[17]
Enthalpy of vaporization	44.66 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
Flash point	84.4°C ± 0°C (calculated)	STN[17]
logP	3.896 ± 0.205 @ 25°C (calculated)	STN[17]
Neopentyl glycol dicaprylate/dipelargonate/dicaprate		
Molecular weight	1017.55	ChemDraw[20]
PEG-2 diisononanoate		
Molecular weight	574.75	ChemDraw[20]
PEG-5 isononanoate		
Molecular weight	199.35	ChemDraw[20]
Pentaerythrityl tetrapelargonate		
Molecular weight	697.04 (calculated)	STN[17]
Density	0.969 ± 0.06 g/cm^3 @ 20°C and 760 Torr (calculated)	STN[17]
Mass intrinsic solubility	0.00000077 g/L @ 25°C (calculated)	STN[17]
Molar intrinsic solubility	0.000000001 1 mol/L @ 25°C (calculated)	STN[17]
Boiling point	699.1°C ± 50°C @ 760 Torr (calculated)	STN[17]
Melting point	12°C (calculated)	STN[17]
Vapor pressure	2.16E-19 Torr @ 25°C (calculated)	STN[17]
Enthalpy of vaporization	102.35 ± 3.0 kJ/mol @ 760 Torr (calculated)	STN[17]
Flash point	273.5°C ± 30.2°C (calculated)	STN[17]
logP	14.879 ± 0.360 @ 25°C (calculated)	STN[17]
Isononanoic acid		
Molecular weight	158.24	STN[17]
Density	0.919 ± 0.06 g/cm^3 @ 20°C and 760 Torr (calculated)	STN[17]
Refractive index	1.4304 @ @ 21°C and 589.3 nm	STN[17]
Mass intrinsic solubility	0.52 g/L @ 25°C (calculated)	STN[17]
Molar intrinsic solubility	0.0033 mol/L @ 25°C (calculated)	STN[17]
Boiling point	248°C @ 765 Torr and 253.4 ± 8°C @ 760 Torr (calculated)	STN[17]
Melting point	3°C to 5°C (calculated)	STN[17]
Vapor pressure	5.70E-03 Torr @ 25°C (calculated)	STN[17]
Enthalpy of vaporization	54.04 ± 6.0 kJ/mol @ 760 Torr (calculated)	STN[17]
Flash point	129.7°C ± 6.9°C (calculated)	STN[17]
logP	3.250 ± 0.194 @ 25°C (calculated)	STN[17]
Isononyl alcohol		
Molecular weight	144.25	ChemDraw[20]
Boiling point	100°C @ 13 Torr	STN[17]
Melting point	64°C -65°C	STN[17]
logP	3.22	SRC[29]
Isotridecyl alcohol		
Molecular weight	200.36	ChemDraw[20]
Melting point	281.59°K (8.44°C) (calculated)	ChemDraw[20]
Boiling point	588.78°K (315.63°C) (calculated)	ChemDraw[20]
logP	5.19 (calculated)	SRC[29]

(continued)

Table 2. (continued)

Property	Value	Reference
Neopentyl glycol		
Molecular weight	104.149	STN[30]
Density	1.1 g/cm^3	National Institute for Occupational Safety and Health (NIOSH)[31]
Impurities	Neopentyl glycol formic acid ester and neopentyl glycol isolactic acid ester	Organisation for Economic Cooperation and Development (OECD)[32]
Water solubility	190 g/100 mL @ 25°C (65%)	Organisation for Economic Cooperation and Development (OECD)[32]
Melting point	127 °C (solvent = benzene)	STN[30]
Boiling point	206°C @ 747 Torr	STN[30]
Flash point	107°C	NIOSH 2010[31]
Autoignition temperature	388°C	NIOSH 2010[31]
Explosive limits	1.1 to 11.4 vol% in air	NIOSH 2010[31]
Vapor pressure	0.00217522-0.0551305 Torr @ 10.74-38.14°C	NIOSH 2010[31]
	30 mm Hg @140°C and 760 mm Hg @ 211°C	OECD [32]
Enthalpy of fusion	4590 J/mol	OECD [32]
Enthalpy of vaporization	87 320 J/mol @ 25.24°C	OECD [32]
Enthalpy of phase transition	14 100 J/mol	OECD [32]
Heat capacity	193.48-202.21 J/mol *K @ 31.85°C-39.35°C	OECD [32]
Thermal decomposition	Occurs at >120°C in strong base	OECD [32]
Thermal decomposition products	Methanol, isobutanol, isobutyl aldehyde, formaldehyde, etc	OECD [32]
logP	0.12 @25°C	OECD [32]

(C_2) are sometimes produced synthetically, but natural sources are more common. Acids and alcohols from natural sources are often mixtures. This is especially true in the case of branched acids and alcohols. Accordingly, the resulting esters are also mixtures. An important method for producing C_3-C_{20} industrial alcohols involves a process known as oxo-synthesis (a process for the production of aldehydes which occurs by the reaction of olefins (which can be natural or petroleum sourced) with carbon monoxide, hydrogen, and a catalyst (typically colbalt based), followed by the hydrogenation of the aldehyde products, to form the alcohols.[37] An industry shift began a couple of years ago toward a green, biocatalytic process developed specifically for the manufacture of esters for use in the formulation of cosmetic and personal care ingredients (ie, for producing cosmetic grade esters).[38]

Pelargonic acid is prepared from unsaturated hydrocarbons by the oxo process, or by the oxidation of oleic acid, and from tall oil unsaturated fatty acids or rice bran oil fatty acid.[39] In the oxo process, pelargonic acid is prepared synthetically. Preparation from tall oil unsaturated fatty acids or rice bran oil fatty acid occurs naturally via splitting/separation.

The production methodology for cetearyl isononanoate and isononyl isononanoate includes the use of a typical mineral salt/nonorganic catalyst for ester formation in the reaction; the catalyst is filtered off upon completion of the reaction.[40]

Impurities

Specifications on pelargonic acid from a chemical supplier include pelargonic acid (90% minimum), iron (1.0 ppm max), moisture (0.2% max), and the following monoprotic acids: other C9 acids (93%; eg, isononanoic acid) and other length monoprotic acids (2%; eg, octanoic acid).[41]

The heavy metal content of both cetearyl isononanoate (Tegosoft CI) and isononyl isononanoate (Tegosoft INI) is described as follows: 20 ppm maximum (copper, lead, tin, platinum, palladium, mercury, arsenic, cadmium, and nickel); <1 ppm (mercury, arsenic, cadmium, and nickel).[24,28]

Typical impurities include olefin, acid, and alcohol starting materials; water; and residual metals (from catalysts). Neopentyl glycol formic acid ester and neopentyl glycol isolactic acid ester are impurities that have been detected in neopentyl glycol.[32]

Use

Purpose in Cosmetics

The majority of the ingredients reviewed in this safety assessment function as skin-conditioning agents in cosmetics. Cholesteryl nonanoate is the only ingredient for which an ingredient function in cosmetics is not listed in the *International Cosmetic Ingredient Dictionary and Handbook*. Ingredient functions in cosmetics are included in Table 1.[42]

Scope and Extent of Use in Cosmetics

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary

Cosmetic Registration Program (VCRP) in 2009,[43] the following ingredients reviewed in this safety assessment are being used in cosmetic products: cetearyl isononanoate, cholesteryl nonanoate, diethylene glycol diethylhexanoate/diisononanoate, ethylhexyl isononanoate, isodecyl isononanoate, isononyl isononanoate, isotridecyl isononanoate, tridecyl isononanoate, and ethylhexyl pelargonate. Use data for these ingredients are summarized in Table 3. Independent of these data, the results of a survey of current ingredient use concentrations conducted by the Personal Care Products Council (Council) in 2009 are also summarized in Table 3.[44] Cetearyl isononanoate is used in 5 of the 1196 eye shadow products reported to the VCRP, and results from the Council survey indicate the use of this ingredient at a concentration of 0.05% in these products. In other cases, for example for cetearyl isononanoate, uses are reported to the VCRP, but its use concentration data are not available. Current use concentration data from the Council also indicate that, while not reported to the VCRP, the following ingredients are also being used in cosmetic products: butylene glycol diisononanoate, cetearyl nonanoate, cetyl isononanoate, dipentaerythrityl pentaisononanoate, neopentyl glycol diisononanoate, PEG-2 diisononanoate, PEG-5 isononanoate, pentaerythrityl tetraisononanaote, polyglyceryl-20 octaisononanoate, and pentaerythrityl tetrapelargonate.

Based on the data included in Table 3 (use frequency and use concentration data), there is no indication that the following ingredients are being used in cosmetics: cellobiose octanonanoate, diethylene glycol diisononanoate, dihydrocholesteryl nonanoate, glycereth-7 diisononanoate, isostearyl isononanoate, phytosteryl nonanoate, propylene glycol diisononanoate, ethyl pelargonate, isobutyl pelargonate, methyl pelargonate, neopentyl glycol dicaprylate/dipelargonate/dicaprate, and pelargonic acid.

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

Noncosmetic Use

Pelargonic acid is included on the list of food additives (synthetic flavoring substances and adjuvants) permitted for direct addition to food for human consumption, as stated in 21 CFR 172.515.[45] Mixtures containing pelargonic acids may be used in other food preparation or processing uses (21 CFR 173.315, 21CFR 178.1010).[45] Pelargonic acid is registered by the US Environmental Protection Agency (EPA) for use as a blossom thinner and as an herbicide.[46,47] It is exempt from the requirement of a tolerance for pesticide residues in or on all foods, when used as a component of a food contact surface sanitizing solution in food handling establishments.[48]

General Biology

Metabolism

Pelargonic acid. The oxidative degradation of fatty acids, such as pelargonic acid, into 2-carbon fragments through enzymatically catalyzed reactions is a well-documented central metabolic pathway in animals and plants. Pelargonic acid, a straight-chain carbon molecule, would be metabolized by β-oxidation to form acetate molecules, which enter the citric acid cycle and are metabolized to carbon dioxide, water, and energy.[46,49]

Ethyl pelargonate. Straight-chain aliphatic acid esters are thought to be readily hydrolyzed into their component acids and alcohols, which would then be expected to follow their normal metabolic pathways.[50]

Branched-chain fatty acids. Mammalian metabolism of some lipids, including 3-methyl (eg, phytanic acid) and 2-methyl (eg, pristanic acid) branched-chain fatty acids, occurs in peroxisomes.[51] Because of the location of a methyl group at the β-carbon of phytanic acid, degradation of the acid via the β-oxidation pathway cannot occur. Instead, the α-methylene group of phytanic acid is oxidatively excised, yielding pristanic acid, which can be metabolized via the β-oxidation pathway.

Percutaneous Absorption

Isononyl alcohol. The results of an acute dermal toxicity study[52] on undiluted isononyl alcohol (rabbits, abraded skin) are summarized later in the report text. When the occlusive binders were observed after 24 hours of contact in this study, percutaneous absorption was evident. Details relating to this finding were not included.

Skin Penetration Enhancement

The skin penetration enhancement effects of fatty acids on p-aminobenzoic acid (PABA) penetration through sheets of human stratum corneum (surgically removed human breast or abdominal skin) were studied.[53] The stratum corneum sheet was pretreated with the penetration enhancer. The permeation of PABA increased with increasing chain length of straight-chain saturated fatty acid, from 6 to 9 carbons (hexanoic, heptanoic, octanoic, and pelargonic acids, respectively). A sharp increase in PABA permeability occurred at fatty acid chain lengths of between 8 and 9 carbons. The mean steady state flux for PABA was 837.84 $\pm$ 190.30 $\mu g/cm^2$ per h in the presence of pelargonic acid, compared to 2.57 $\pm$ 0.19 $\mu g/cm^2$ per h in the presence of water, and 0.28 $\pm$ 0.14 $\mu g/cm^2$ per h in the presence of propylene glycol.

A study on the release profile of melatonin from drug-in-adhesive type transdermal patches (prepared using Eudragit E 100 as adhesive polymer) containing pelargonic acid or other penetration enhancers, and the in vitro penetration of melatonin through hairless rat skin in the presence of the enhancer was

Table 3. Current Cosmetic Product Uses and Concentrations of Nonanoates and Pelargonic Acid[43,44]

Product Category (FDA 2009)	2009 Uses (Total Number of Products in Category; FDA 2009)	2009 Concentrations (Personal Care Products Council 2009), %
Butylene glycol diisononanoate		
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	–	17
Total uses/ranges for butylene glycol diisononanoate	–	17
Cetearyl isononanoate		
Eye makeup		
Eyeliner	2 (684)	–
Eye shadow	5 (1196)	0.05
Eye lotion	4 (177)	–
Eye makeup remover	1 (131)	–
Other	3 (288)	–
Fragrance products		
Other	3 (399)	27-50
Noncoloring hair products	1 (1097)	
Tonics, dressings, etc		–
Makeup		
Blushers	1 (539)	8
Face powders	2 (613)	0.05-11
Foundations	4 (635)	10
Lipstick	1 (1912)	–
Makeup bases	1 (164)	–
Other	3 (406	12
Nail care products		
Creams and lotions	1 (17)	–
Other	1 (124)	–
Personal hygiene products		
Other	2 (514)	–
Shaving products		
Aftershave lotion	1 (395)	3-6
Preshave lotions	1 (27)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	10 (1368)	2-3
Face and neck lotions	12 (1195)	0.07-8
Body and hand lotions	14 (1513)	3-5
Foot powders and sprays	1 (48)	–
Moisturizers	29 (2039)	2
Night creams and lotions	6 (343)	2
Paste masks (mud packs)	1 (418)	–
Other	9 (1244)	–
Suntan products		
Indoor tanning preparations	3 (200)	–
Other	1 (62)	–
Total uses/ranges for cetearyl isononanoate	123	0.05-50
Cetearyl nonanoate		
Skin care products		
Body and hand lotions	–	3
Total uses/ranges for cetearyl nonanoate	–	3
Cetyl isononanoate		
Eye makeup		
Eye lotion	–	1
Noncoloring hair products		
Tonics, dressings, etc.	–	1
Skin care products		
Body and hand lotions	–	3
Moisturizers	–	5
Other	–	1
Total uses/ranges for cetyl isononanoate	–	1-5

(continued)

Table 3. (continued)

Product Category (FDA 2009)	2009 Uses (Total Number of Products in Category; FDA 2009)	2009 Concentrations (Personal Care Products Council 2009), %
Cholesteryl nonanoate		
Eye makeup		
Eye lotion	2 (117)	–
Other	1 (288)	–
Noncoloring hair products		
Conditioners	–	0.01
Shampoos	–	0.01
Makeup		
Lipstick	–	20-30
Skin care products		
Face and neck lotions	–	0.04
Moisturizers	–	0.06
Paste masks (mud packs)	–	0.03
Hair-coloring products		–
Dyes and colors	13 (2481)	–
Makeup		
Lipstick	1 (1912)	–
Makeup bases	1 (164)	–
Skin care products		
Face and neck lotions	8 (1195)	–
Moisturizers	3 (2039)	–
Paste masks (mud packs)	6 (418)	–
Skin fresheners	1 (285)	–
Other	2 (1244)	–
Total uses/ranges for cholesteryl nonanoate	38	0.01-30
Diethylene glycol diethylhexanoate/diisononanoate		
Fragrance products		
Powders	5 (278)	19
Makeup		
Foundations	1 (635)	18
Lipstick	9 (1912)	–
Other	1 (406)	–
Total uses/ranges for diethylene glycol diethylhexanoate/ diisononanoate	16	18-19
Dipentaerythrityl pentaisononanoate		
Makeup		
Lipstick	–	9
Nail care products		
Nail polish and enamel	–	13
Total uses/ranges for dipentaerythrityl pentaisononanoate	–	9-13
Ethylhexyl isononanoate		
Eye makeup		
Eye shadow	3 (1196)	7-65
Eye lotion	2 (177)	0.8
Eye makeup remover	1 (131)	–
Other	2 (288)	12
Fragrance products		
Other	3 (399)	2-5
Noncoloring hair products		
Conditioners	–	1
Rinses	–	0.8
Tonics, dressings, etc	3 (1097)	–
Other	1 (716)	8
Makeup		
Blushers	1 (539)	7
Face powders	–	3

(continued)

Table 3. (continued)

Product Category (FDA 2009)	2009 Uses (Total Number of Products in Category; FDA 2009)	2009 Concentrations (Personal Care Products Council 2009), %
Foundations	2 (635)	3
Lipstick	9 (1912)	–
Fixatives	1 (38)	–
Other	2 (406)	31 (in a face highlighter)
Personal hygiene products		
Other	1 (514)	–
Shaving products		
Aftershave lotion	2 (395)	1
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	1 (1368)	0.8-2
Face and neck lotions	5 (1195)	0.04-6
Body and hand lotions	31 (1513)	0.04-74
Body and hand sprays	–	18
Moisturizers	14 (2039)	2
Night creams and lotions	5 (343)	0.02
Other	3 (1244)	0.08
Suntan products		
Suntan gels, creams, and liquids	1 (156)	7
Indoor tanning preparations	22 (200)	0.07-1
Other	1 (62)	0.03
Total uses/ranges for ethylhexyl isononanoate	116	0.02-74
Isodecyl isononanoate		
Eye makeup		
Eye shadow	2 (1196)	21
Eye lotion	–	6
Eye makeup remover	–	10
Noncoloring hair care products		
Conditioners	–	2
Other	1 (406)	–
Makeup		
Blushers	6 (539)	22-26
Foundations	1 (635)	59
Lipstick	–	0.05-18
Rouges	–	13
Skin care products		
Face and neck lotions	5 (1195)	–
Moisturizers	4 (2039)	–
Night creams and lotions	1 (343)	–
Paste masks (mud packs)	2 (418)	2
Other	2 (1244)	–
Suntan products		
Suntan gels, creams, and liquids	1 (156)	–
Other	1 (62)	5
Total uses/ranges for isodecyl isononanoate	26	0.05-59
Isononyl isononanoate		
Bath products		
Oils, tablets, and salts	–	15
Soaps and detergents	–	8-10
Eye makeup		
Eyebrow pencil	–	2
Eye shadow	24 (1196)	2-18
Eye lotion	8 (177)	3-26
Eye makeup remover	2 (131)	–
Other	13 (288)	6-12 (12% in a concealer)
Fragrance products		
Perfumes	4 (569)	26-42
Other	2 (399)	21-46

(continued)

Table 3. (continued)

Product Category (FDA 2009)	2009 Uses (Total Number of Products in Category; FDA 2009)	2009 Concentrations (Personal Care Products Council 2009), %
Noncoloring hair care products		
Other	1 (716)	–
Conditioners	–	0.08
Sprays/aerosol fixatives	–	0.4
Rinses	–	0.03-1
Tonics, dressings, etc	–	7
Hair-coloring products		
Bleaches	–	33
Makeup		
Blushers	23 (539)	4-17
Face powders	12 (613)	2-15
Foundations	28 (635)	3-27
Leg and body paints	3 (29)	4-57
Lipstick	28 (1912)	8-50
Makeup bases	3 (164)	3-7
Rouges	3 (99)	12
Makeup fixatives	3 (38)	–
Other	12 (406)	4-6 (4% in a concealer)
Nail care products		
Nail extenders	–	0.4
Nail polish and enamel removers	–	5
Personal hygiene products		
Deodorants (underarm)	1 (540)	3
Other	1 (514)	–
Shaving products		
Aftershave lotion	2 (395)	3-4
Preshave lotions	–	22
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	11 (1368)	0.04-21
Face and neck lotions	39 (1195)	0.05-17
Face and neck sprays	–	6
Body and hand lotions	29 (1513)	5-50
Foot powders and sprays	–	3
Moisturizers	48 (2039)	3-13
Night creams and lotions	10 (343)	2-11
Paste masks (mud packs)	2 (418)	2-64
Skin fresheners	1 (285)	–
Other	16 (1244)	1-21
Suntan products		
Suntan gels, creams, and liquids	2 (156)	2-9
Indoor tanning preparations	8 (200)	0.3-3
Other	4 (62)	0.08-21
Total uses/ranges for isononyl isononanoate	343	0.03-64
Isotridecyl isononanoate		
Eye makeup		
Eye shadow	–	0.7
Noncoloring hair products		
Conditioners	–	3
Makeup		
Blushers	15 (539)	4
Face powders	6 (613)	10
Foundations	10 (635)	0.8-9
Lipstick	19 (1912)	10
Makeup bases	–	5-7
Rouges	–	4
Other	3 (406)	5

(continued)

Table 3. (continued)

Product Category (FDA 2009)	2009 Uses (Total Number of Products in Category; FDA 2009)	2009 Concentrations (Personal Care Products Council 2009), %
Skin care products		
Face and neck lotions	2 (1195)	–
Body and hand lotions		1
Moisturizers	4 (2039)	11
Night creams and lotions	2 (343)	–
Other	1 (1244)	5-51
Suntan products	–	
Suntan gels, creams, and liquids	–	0.8
Total uses/ranges for isotridecyl isononanoate	62	0.7-51
Neopentyl glycol diisononanoate		
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	–	1
Total uses/ranges for neopentyl glycol diisononanoate	–	1
PEG-2 diisononanoate		
Nail care products		
Creams and lotions	–	2
Total uses/ranges for PEG-2 diisononanoate	–	2
PEG-5 isononanoate		
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	–	1
Total uses/ranges for PEG-5 isononanoate	–	1
Pentaerythrityl tetraisononanoate		
Eye makeup		
Eye lotion	–	2
Skin care products		
Body and hand lotions	–	1
Total uses/ranges for pentaerythrityl tetraisononanoate	–	1-2
Polyglyceryl-20 octaisononanoate		
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	–	3
Total uses/ranges for polyglyceryl-20 octaisononanoate	–	3
Tridecyl isononanoate		
Makeup		
Foundations	1 (635)	9
Total uses/ranges for tridecyl isononanoate	1	9
Ethylhexyl pelargonate		
Hair-coloring products		
Dyes and colors	–	5
Eye makeup		
Eye shadow	–	2
Makeup		
Blushers	1 (539)	–
Foundations	1 (635)	25
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	1 (1368)	2
Body and hand lotions	–	4
Total uses/ranges for ethylhexyl pelargonate	3	2-25
Pentaerythrityl tetrapelargonate		
Noncoloring hair care products		
Tonics, dressings, etc	–	2
Total uses/ranges for pentaerythrityl tetrapelargonate	–	2

conducted.[54] Melatonin release was studied using the US Pharmacopoeia dissolution test apparatus in conjunction with high-performance liquid chromatography. The release profiles of melatonin from the patches with enhancers were similar when compared to the control patch release profile.

In skin penetration experiments, each penetration enhancer was added to the patch at a concentration of 2.5% or 5%. Skin samples from at least 3 rats were used in each experiment, and each mean value for skin penetration represented 3 replicates. The presence of enhancers in the patches resulted in an increase

in the permeation of melatonin through hairless rat skin. The mean melatonin flux values for patches containing octanol, pelargonic acid, or myristic acid (each at both concentrations) were higher when compared to the control patch; however, the differences were not statistically significant ($P > .05$).[54]

Endocrine Disruption

According to EPA,[49] it would be unlikely for straight-chain carbon molecules, as in the C9 carbon chain of pelargonic acid, to be associated with a risk of endocrine disruption.

Animal Toxicology

Acute Inhalation Toxicity

Pelargonic acid. EPA[46] placed pelargonic acid in toxicity category III (>0.5 through 2 mg/L), primarily based on the results of the following study. The acute inhalation toxicity of pelargonic acid was evaluated using groups of 10 (5 males, 5 females/group) albino rats.[55] The 4 groups were exposed (4-hour exposure) to aerosol generated from undiluted pelargonic acid, delivering concentrations of 0.510, 0.710, 2.20, and 3.31 mg/L, respectively. The following mortalities were reported: 1 rat (at 0.510 mg/L), 1 rat (at 0.710 mg/L), 8 rats (at 2.20 mg/L), and 10 rats (at 3.31 mg/L). Gross necropsy was performed on animals that died, and the following findings were considered unusual and possibly related to exposure: nasal discharge, polyuria, salivation, and discolored and swollen lungs, and variations thereof. Acute inhalation lethal concentration 50s (LC50s) of 0.87 mg/L (95% confidence limits = 0.50-1.51 mg/L) and 2.10 mg/L (95% confidence limits = 1.71-2.58 mg/L) were reported for males and females, respectively. The overall LC50 was 1.24 mg/L (95% confidence limits undefined).

Isononanoic acid. The respiratory effects of isononanoic acid using groups of 4 specific pathogen-free, male Swiss-Webster mice were evaluated.[56] The animals were exposed to nebulized isononanoic acid (concentration range: 172-755 mg/m^3) in a 2.5-L exposure chamber for 180 minutes. Sensory and pulmonary irritation was reported, and recovery immediately post exposure was described as poor. The test substance concentration that was capable of evoking a 50% decrease in the mean respiratory frequency (RD50) was 420 mg/m^3. The decreases in respiratory frequency induced by isononanoic acid were described as concentration dependent and due to a combination of sensory and pulmonary irritation.

Isononyl alcohol. The inhalation toxicity of isononyl alcohol using groups of 10 Swiss mice, Wistar rats, and English Short Hair guinea pigs was studied.[52] Each group received a single 6-hour vapor exposure under dynamic conditions; exposure was followed by a 14-day observation period. The concentration of isononyl alcohol in the exposure chamber was calculated to be 21.7 mg/L. None of the animals died during exposure; however, 1 mouse and 2 rats died within the first 14-hour post exposure. Signs of systemic toxicity consisted primarily of central nervous system depression but were not pronounced. Local irritation involving mucous membranes of the eyes and nose was observed to a variable extent, and all animals had recovered within 1 hour after termination of exposure. Histopathological examinations were not performed.

Acute Oral Toxicity

Pelargonic acid. EPA[46] placed pelargonic acid in toxicity category IV (>5000 mg/kg), primarily based on the results of the following study. The acute oral toxicity of nonanoic acid was evaluated using 2 groups of 10 specific pathogen-free Sprague-Dawley ([SD] Crl:CD) rats (5 males, 5 females/group).[57] One group was dosed orally with nonanoic acid in corn oil (dose = 5000 mg/kg). The control group was dosed with vehicle only. None of the animals died and no abnormal clinical signs were noted during the 14-day observation period. There was no evidence of macroscopic abnormalities at necropsy. The LD50 was >5000 mg/kg, and nonanoic acid was considered nontoxic.

Cetearyl nonanoate. The acute oral toxicity of cetearyl nonanoate (97% pure) was evaluated using groups of 4 SD CD rats.[58] 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. Signs of systemic toxicity were observed in the 300 mg/kg dose group but not in the 2000 mg/kg dose group. Necropsy did not reveal any abnormal findings, and an LD50 of >2000 mg/kg body weight was reported.

Cetearyl isononanoate. According to a manufacturer,[59] an LD50 of >5000 mg/kg was reported for cetearyl isononanoate in a study involving mice. Study details were not provided.

Isononyl isononanoate. According to a manufacturer,[60] an LD50 of >5000 mg/kg was reported for isononyl isononanoate in a study involving rats. Study details were not provided.

Ethyl pelargonate. Acute oral LD50 values of >43 000 mg/kg and 24 190 mg/kg have been reported for rats and guinea pigs, respectively.[50]

Ethylhexyl pelargonate. The acute oral toxicity of undiluted ethylhexyl pelargonate was evaluated using 10 albino rats (5 males and 5 females).[61] A single oral dose of 5 g/kg body weight was administered to each animal. Dosing was followed by a 14-day observation period, and gross necropsy was performed on animals that survived. The LD50 was >5 g/kg.

Isononyl alcohol. The acute oral toxicity of isononyl alcohol using 5 fasted, male SD rats was evaluated.[52] An acute oral LD50 of 2.98 g/kg was reported.

Isotridecyl alcohol. The acute oral LD50 for isotridecyl alcohol[62] in rats is 17 000 mg/kg.

Neopentyl glycol diisononanoate. The acute oral toxicity of undiluted neopentyl glycol diisononanoate was evaluated using groups of 4 SD CD rats.[63] 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 LD50 of >2000 mg/kg body weight was reported.

PEG-5 isononanoate. The acute oral toxicity of PEG-5 isononanoate was evaluated using 2 groups of 3 fasted SD CD rats.[64] Animals of both groups were dosed orally with 2000 mg/kg. None of the animals died and necropsy did not reveal any abnormal findings. An LD50 of >2500 mg/kg body weight was reported.

Neopentyl glycol. The Organisation for Economic Co-operation and Development (OECD)[32] reported an acute oral LD50 of 3200 mg/kg (rats) for neopentyl glycol; others have reported the acute oral LD50 for neopentyl glycol[62] in rats is 3259 mg/kg.

Acute Dermal Toxicity

Pelargonic acid. In a study involving rabbits,[50] the acute dermal LD50 was greater than 5 g/kg (number of animals not stated). Results relating to the skin irritation potential of pelargonic acid in this study are included later in the report text. The US Environmental Protection Agency placed pelargonic acid in toxicity category III (>2000-5000 mg/kg) based on the results of the following acute dermal toxicity studies that were published in a *Federal Register* notice.[49] The application of pelargonic acid to intact and abraded skin of mice induced moderate-to-severe skin irritation, and an acute dermal LD50 of 9000 mg/kg was reported in this study. An acute dermal LD50 of 5000 mg/kg (rabbits) for undiluted pelargonic acid also has been reported.

The acute dermal toxicity of nonanoic acid was evaluated using 2 groups of 10 specific pathogen-free SD (Crj:CD) rats (5 males, 5 females/group).[65] The test substance, in deionized water, was placed on filter paper that was applied to clipped, shaved skin (4 × 5 cm site) of the back for 24 hours. Deionized water (0.5 mL) was applied to control animals according to the same procedure. None of the animals died during the 21-day observation period. Scales/scabs in the dorsal region (test substance related) were observed only in treated females (days 3-17 post application). Macroscopic abnormalities were not observed in any of the animals (test or controls) at necropsy. It was concluded that the LD50 for nonanoic acid in males and females was >2000 mg/kg.

Cetearyl nonanoate. The acute dermal toxicity of cetearyl nonanoate (97% pure) was evaluated using 10 SD CD strain rats (5 males and 5 females).[58] The test substance was applied to intact skin (24-hour semiocclusive application) at a dose of 2000 mg/kg body weight. 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 LD50 of >2000 mg/kg body weight was reported.

Ethyl pelargonate. The acute dermal LD50 in rabbits[50] exceeded 5 g/kg.

Isononyl alcohol. The acute dermal toxicity of undiluted isononyl alcohol was evaluated in a study using 4 rabbits.[52] The test substance was applied (under occlusive binding) to clipped, abraded abdominal skin at the following doses: 0.500, 0.200, 0.794, and 3.16 g/kg. An acute dermal LD50 of 3.2 g/kg was reported. Signs of percutaneous toxicity were not observed.

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).[63] A dose of 2000 mg/kg body was applied according to the procedure in the preceding section on cetearyl nonanoate. 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 LD50 of >2000 mg/kg was reported.

Acute Intravenous Toxicity

The acute intravenous (iv) toxicity of pelargonic acid using 10 mice was studied.[66] An LD50 of 224 ± 6 mg/kg was reported. Similarly, an LD50 of 224 mg/kg was reported for mice dosed iv with undiluted pelargonic acid.[49]

Acute Intraperitoneal Toxicity

In a study involving rats, intraperitoneal (ip) dosing with undiluted pelargonic acid resulted in death and the lowest lethal dose (LDLo) was 3200 mg/kg.[49] The dosing (ip) of mice with a 10% solution of pelargonic acid in corn oil resulted in death, and an LDLo of 1600 mg/kg was reported.[49]

Short-Term Oral Toxicity

Pelargonic acid. A study was conducted to determine the appropriate dose level of pelargonic acid for a teratology screening study.[67] Groups of 6 cesarean-derived, SD rats (sexually mature; weights = 177-285 g) were used. The test substance was administered (via oral intubation) in corn oil, at 3 dose levels (200, 1000, and 2000 mg/kg per d; 6 inseminated females/dose level) from 6 to 15 days of gestation. The dose volumes corresponding to the administered doses (lowest to highest) were 1.0, 5.0, and 10.0 mL/kg. The control group (6 inseminated females) was dosed with corn oil according to the same procedure. All surviving rats were killed after gestation day 15 and necropsied.

There were no remarkable clinical signs in any of the rats dosed with pelargonic acid, and none of the rats died. Mean feed consumption in the 200 mg/kg dose group was significantly higher, up to gestation day 14, when compared to the control group. Gross pathology findings were observed principally in the lungs, kidneys, or stomach. The numbers of rats with gross lesions included 2 rats at the 200 mg/kg dose level and 1 rat each at the 1000 and 2000 mg/kg levels. It was agreed

that the only pelargonic acid-induced effect was on body weight. Study results relating to reproductive and developmental toxicity are included in the Section on Reproductive and Developmental Toxicity later in the report text.[67]

In another short-term study,[68] the oral toxicity of pelargonic acid was evaluated using groups of 6-week-old albino rats (Crl:CD (SD) BR strain). Four groups (15 males and 15 females per group) were fed pelargonic acid in the diet at concentrations of 10, 100, 1000, and 5000 ppm, respectively. Ten rats per sex in each group received their respective diet for 28 days and until necropsy; a fifth group received basal diet only. After 28 days of pelargonic acid (in diet) feeding, the remaining rats (5 males and 5 females per group) in the 4 groups were switched to a basal diet, and feeding was continued for an additional 56 days (recovery phase). The fifth group was allowed to continue on the basal diet. Necropsy was also performed at the end of the recovery phase.. Compared to the control group, male rats in the 5000 ppm dietary group had significantly lower ($P < .05$) group mean body weights during weeks 1 through 4. The same was true for female rats in this group during weeks 3 through 6. Changes in mean body weights, body weight gains, and food consumption in the 100 and 1000 ppm dietary groups were influenced by an approximately 30-hour water deprivation, which occurred during week 3. Reversible changes in clinical pathology variables (blood/urine) following dietary administration of 5000 ppm pelargonic acid were noted.

Treatment-related morphologic changes were noted in the hearts and livers of rats killed after 28 days. Changes in the heart were also observed in male rats during the recovery phase but at a lower incidence and severity. Liver lipid content was greater in female rats on diets containing 100, 1000, and 5000 ppm pelargonic acid. The lower body weights in rats killed after 28 days resulted in greater relative weights in a number of organs. Absolute liver weights were greater in male rats that received 5000 ppm pelargonic acid and in female rats that received 1000 and 5000 ppm pelargonic acid in the diet. All other changes that were observed were considered to have been of no toxicological importance. It was concluded that pelargonic acid appeared to have increased the risk of cardiac changes in treated male and female rats and hepatic changes in female rats that received 5000 ppm in the diet. Changes in the liver were not observed at 56 days posttreatment, while cardiac changes persisted at a reduced intensity.

The lowest observable effect level (LOEL) for pelargonic acid was 100 ppm for antemortem data (lower body weights) and 5000 ppm for clinical pathology in rats of both sexes. Taking into consideration the increased liver weights observed after dosing with pelargonic acid, the LOEL was 5000 ppm for male rats and 100 ppm for female rats; the LOEL for macroscopic effects on the liver was 1000 ppm in rats of both sexes. Regarding both cardiac and hepatic effects, the LOEL for macroscopic changes was 1000 ppm (male rats) and 100 ppm (female rats). However, because histopathology was not performed on livers from lower dose rats from the scheduled sacrifice, the LOEL for microscopic liver changes may actually be lower than these values.[68]

A short-term oral toxicity study was conducted using groups of 6 SD albino rats (3 males, 3 females/group).[69] Six groups were fed pelargonic acid in the diet at concentrations ranging from 1500 ppm to 20 000 ppm (1 dietary concentration per group) for 2 full weeks. A seventh group (control) was fed untreated feed. Feeding with pelargonic acid did not induce any adverse effects over the range of concentrations evaluated. Body weight gain and food consumption were normal throughout the study. Other than piloerection (not dose related), no clinical signs were observed. All animals appeared healthy and normal at the time of necropsy. Hematology parameters were all within normal limits, and the same was true for most of the serum clinical chemistry parameters.

Except for the lowest dose group, mean serum alkaline phosphatase (ALP) activity was significantly greater than the control value. Effects on ALP activity were not considered toxicologically significant relative to liver function, taking into consideration the absence of an effect of pelargonic acid on serum alanine aminotransferase (ALT) and serum protein content. Total bilirubin was elevated in some of the groups, controls included high values correlated primarily with the presence of hemolysis in individual blood samples. It was concluded that pelargonic acid did not induce overt signs of toxicity in albino rats, when fed in the diet at concentrations up to 20 000 ppm (2%) for 2 weeks.[69]

In another study,[49] 8 male rats (weights not stated) were fed 4.17% pelargonic acid in the diet (2100 g/kg per d) for 4 weeks. A slight decrease (4%, not statistically significant) in mean growth was observed. No effects on survival were noted.

Isononyl Isononanoate

The short-term oral toxicity of isononyl isononanoate was evaluated using 4 groups of SD rats (10 males, 10 females/group) of the *Caesarian Obtained, Barrier Sustained-Virus Antibody Free* (*COBS-VAF*) strain.[70] One group served as the vehicle control (corn oil) group, and the 3 test groups received the following doses of isononyl isononanoate (in corn oil) by gavage daily for 4 weeks: 100, 300, and 1000 mg/kg per d. Test substance-related mortalities were associated with 1 female in the 300 mg/kg per d dose group and 4 females in the 1000 mg/kg per d dose group. Ptyalism was the only test substance-related clinical sign, and there were no remarkable hematological findings. A correlation between lower body weight gain and lower food consumption was evident only in the highest dose group.

Doses of 300 and 1000 mg/kg per d were associated with higher enzyme activities, namely aspartate aminotransferase (AST), ALT, and/or ALP. Also, compared to controls, the blood urea level was higher in males and females of all dose groups; these changes were attributed to pathological changes in the liver and kidneys, which will be mentioned later. Additionally, it was suggested that the high urine volume associated with animals of the highest dose group was related to kidney

damage noted at microscopic examination. Higher absolute and relative liver and kidney weights were noted in animals of all dose groups, and lower absolute and relative spleen and thymus weights were observed in 300 and 1000 mg/kg per d dose groups.

The treatment-related macroscopic findings included enlargement and an accentuated lobular pattern and/or paleness of the liver and a gray/green color of the kidneys in some of the animals from each dose group. Other relevant findings were described as a reduction in size of the spleen and/or thymus in some of the animals from the 300 and 1000 mg/kg per d dose groups. These findings correlated with contracted spleen and lymphoid depletion in the thymus at microscopic examination and were considered secondary to the poor physical condition of several treated animals. The treatment-related microscopic findings were described as follows: hepatocellular hypertrophy of the liver (300 and 1000 mg/kg per d dose groups); liver steatosis (all dose groups); acidophilic globules in cortical tubular epithelium (kidneys), associated with cellular damage in males (all dose groups); vacuolated cortical tubular epithelium in females (300 and 1000 mg/kg per d dose groups); and contracted spleen and thymic lymphoid depletion (1000 mg/kg per d dose group).

Isononyl isononanoate induced mortality at doses of 300 and 1000 mg/kg per d and liver and kidney (target organs) toxicity in rats at all doses administered. Under the conditions of this experiment, it was not possible to establish a no observed effect level (NOEL) for isononyl isononanoate.[70]

Comments received on the preceding study suggest that the findings from the study may not be relevant to humans.[71] High-fat diets produce adaptive changes in the liver and kidneys of rodents, and, if maintained on high-fat diets for long periods, these changes may develop into a pathologic condition such as fatty liver or steatosis. Steatosis at an isononyl isononanoate dose of 100 mg/kg per d and higher doses in the preceding study should not be considered a toxicological adverse end point, but an exacerbation of an adaptive response to administration of a fatty material. Regarding changes in the kidneys, the authors suggested that mineral and other oils are likely to induce acidophilic globules in the kidneys (hyaline droplet nephropathy), due to the sex-linked production of α-2-microglobulin, and, understandably, this effect was observed in male rats of all isononyl isononanoate treatment groups. However, because the α-2-microglobulin protein (under androgen control) is absent from man and many species, this sex- and species-specific hyaline droplet nephropathy is not considered relevant to man.

Isononyl alcohol. Isononyl alcohol (in polyethylene glycol 300) was administered by gavage to 5 male rats (Alderly Park Wistar-derived) for 14 days at a dose level that was equivalent to 1 mmol/kg per d.[72] Control animals (10 rats) were dosed with polyethylene glycol 300 (10 mL/kg per d). Livers were removed, weighed, and homogenized for enzyme assays. Testis weights were also determined. No major pathological signs of hepatotoxicity resulted from oral dosing with isononyl alcohol. Minor histological changes consisted of slight centrilobular hypertrophy and fat type vacuolation in control and test animals. No effects on body weight gain or testis weight were noted. Isononyl alcohol also did not induce peroxisome proliferation, hypocholesteremic/hypotriglyceridemic effects, or effects on catalase. However, compared to controls, isononyl alcohol dosing resulted in slight elevation of palmitoyl CoA oxidase (marker enzyme for peroxisome proliferation).

Neopentyl glycol. A combined repeated dose and reproductive/developmental toxicity study on neopentyl glycol was performed using groups of male and female rats of the Slc: SD strain.[32] The test substance, in distilled water, was administered by gavage at doses of 100, 300, or 1000 mg/kg per d. Control rats were dosed with distilled water. Male rats were dosed over a 42-day period, and female rats were dosed from 14 days before mating to day 3 of lactation. There were no dead or abnormal animals with clinical signs related to dosing. Body weight and food consumption data were not indicative of consistent or treatment-related differences between test and control groups. Liver and kidney weights (absolute and relative) were increased in male and female rats of the 300 and 1000 mg/kg dose groups. Necropsy revealed hypertrophy of the liver in 2 males dosed with 1000 mg/kg; definite lesions were not found at microscopic examination. A high incidence of protein casts, hyaline droplets, and basophilic change was reported for renal tubules in males dosed with 1000 mg/kg. The no observed adverse effect level (NOAEL) for this study was of 100 mg/kg.

Short-Term Dermal Toxicity

Pelargonic acid. A 28-day dermal toxicity study[73] was conducted using groups of New Zealand White rabbits (5 males, 5 females/group). Pelargonic acid (25% weight/weight [w/w] mixture in mineral oil) was applied to the skin at doses of 500 mg/kg per d (dose volume = 2 mL/kg) daily for a total of 10 applications. The test substance was applied directly to the skin and spread evenly over the test site; patches were not applied. The skin of half of the rabbits per group (3 males and 2 females) was abraded prior to application. The control group was dosed with mineral oil according to the same procedure. For necropsy, 6 rabbits per group (3 with abraded skin and 3 with intact skin) were killed at 2 weeks and surviving animals were killed at 4 weeks.

Slight weight loss (0.1-0.4 kg) was noted in most of the rabbits dosed with pelargonic acid after 1 and/or 2 weeks of the study. Weight gain was noted in rabbits that were held for a 2-week recovery period. Slight-to-moderate weight gains were also noted in vehicle control rabbits. None of the rabbits dosed with pelargonic acid died. Skin reactions are summarized in the section on Skin Irritation later in the report text. Discoloration of the gastric mucosa was observed in treated animals; other gross morphologic findings in treated and/or control animals were not considered treatment related. Inflammatory changes observed in the kidneys, lungs, and brain and, less frequently, in other organs were not considered treatment related.[73]

Undiluted pelargonic acid (25 µL) was applied to both ears (dorsum) of inbred CBA/Ca mice (groups of 4) once per day for 3 consecutive days.[74] None of the animals died.

Following intermittent dermal application of pelargonic acid to the skin of mice over a 3-day period, the 3 mL/kg dose was the lowest dose that caused a toxic effect (TDLo). In a similar study involving mice, a TDLo of 3000 mg/kg was reported.[75]

Isononyl isononanoate. The short-term dermal toxicity of isononyl isononanoate was evaluated using 4 groups of SD rats (5 males, 5 females/group) of the *COBS-VAF* strain with healthy, intact skin.[76] One group served as the vehicle (corn oil) control, and the test groups received cutaneous doses of isononyl isononanoate in corn oil daily for 8 days (860 mg/kg per d dose group) or for 2 weeks (100 and 300 mg/kg per d dose groups). Doses of the test substance or control were applied for 6 hours to a 45 to 50 cm^2 area (males) or a 30 to 35 cm^2 area (females) on backs that had been clipped free of hair. A constant dose volume of 1 mL/kg per d was used. None of the animals died. Slight cutaneous reactions were observed in the 100 and 300 mg/kg per d dose groups (1 animal/group). However, severe skin irritation and necrosis were observed at the application sites of animals of the 860 mg/kg per d dose group and treatment was discontinued after day 8 of dosing.

A correlation between decreased body weight gain and decreased feed consumption was evident only in the highest dose group. Low white blood cell counts were also noted in the highest dose group; however, these changes were considered related to inflammatory reactions and the tissue distribution of inflammatory cells at the application site. Changes in blood biochemistry were noted in each dose group, all of which were treatment related. A high urea level and high ALP enzyme activity were noted in 300 and 860 mg/kg per d dose groups. High AST enzyme activity was noted only in the highest dose group, but neither ALP nor AST activity was high in the lowest dose group.

A gray/green coloration of the kidneys was observed in the mid- and high-dose groups, and this finding was correlated with acidophilic globules in the cortical tubular epithelium of high-dose male rats. An accentuated lobular pattern in the liver was noted in all dose groups, and this finding was correlated with steatosis and hepatocellular hypertrophy noted at microscopic examination and considered related to 300 and 860 mg/kg per d doses. Cortical cell hypertrophy in the adrenal glands ranging in severity from minimal to moderate was observed in the highest dose group. Whether this finding was considered treatment related was not stated specifically. The adrenal glands and the liver were considered target organs for isononyl isononanoate toxicity. Under the conditions of this experiment, it was not possible to establish an NOEL for isononyl isononanoate. [76]

Comments on the preceding study were received suggesting that since it is unlikely that isononyl isononanoate penetrates the skin, the steatosis was caused by significant oral exposure secondary to grooming and licking of the application site.[71] As stated above, study results indicate that steatosis was observed in all isononyl isononanoate dose groups and that acidophilic globules were observed in the kidneys of high-dose male rats. Furthermore, some of the effects observed in this dermal study were of a similar order of incidence and severity as those observed at the same dose levels in the short-term oral toxicity study on isononyl isononoate (summarized earlier in report text)..

Subchronic Oral Toxicity

Cetearyl isononanoate. A summary of a 1993 subchronic oral toxicity study on Cetiol SN (cetearyl isononanoate, percentage not stated)) was provided by the Council.[77] Three groups of Wistar rats of both sexes received oral doses of 100, 300, and 1000 mg/kg body weight, respectively, over a period of 90 days. A fourth group served as the untreated control. Reversible fatty alterations of the liver were observed in the 1000 mg/kg dose group and in females of the 300 mg/kg dose group. Based on these results, it was determined that the NOAEL should be 100 mg/kg per d. The authors suggested that branched acids, like isononanoic acid, undergo a specific type of metabolism in rodents, and that the fatty alterations in the liver reflect an adaptive response due to increased metabolic activity. The relevance of these changes in the liver of humans was placed in doubt, and, thus, it was anticipated that the NOAEL for human-relevant effects would be >100 mg/kg body weight.

Ethyl pelargonate. No effects were observed at microscopic examination of the following tissues from rats (5 males and 5 females) fed 1% ethyl pelargonate in the diet for 16 weeks: liver, kidney, heart, spleen, testes, viscera, and hind limb.[50] Terminal hematological examinations and gross pathology and weights of the liver, kidney, heart, spleen, and testes did not differ from the findings in control rats.

Ocular Irritation/Toxicity

Pelargonic acid. The EPA[46] placed pelargonic acid in toxicity category II (corneal involvement or other eye irritation clearing in 8-21 days), based primarily on the results from the following primary ocular irritation study involving 6 Hra: (NZW)SPF adult albino rabbits.[78] The undiluted test substance (0.1 mL) was instilled into the right eye of each animal, and untreated left eyes served as controls. Instillation was followed by a 21-day observation period. Pelargonic acid induced corneal and iridial involvement and severe conjunctival irritation. All reactions had cleared by day 21 postinstillation. The average primary irritation score (5-animal mean) was 40.6 at 1 hour and 0 at day 21.

Pelargonic acid was a mild irritant when instilled into the rabbit eye at a dose of 0.1 mL.[75]

Cetearyl nonanoate. The ocular irritation potential of cetearyl nonanoate (97% pure) was evaluated using 3 male New Zealand white rabbits.[58] The test substance (0.1 mL) was instilled into the right eye of each animal and reactions were scored at

approximately 1, 24, 48, and 72 hours post instillation. Moderate conjunctival irritation was observed; however, there were no changes in the cornea or iris. All eyes appeared normal at 48 hours post instillation. Cetearyl nonanoate was classified as minimally irritating to the rabbit eye.

Cetearyl isononanoate. A summary of a 1970 study evaluating the ocular irritation potential of Cetiol SN (cetearyl isononanaote, percentage not stated) was provided by the Council.[77] Cetiol SN (10% active matter, 0.05 mL) was instilled into the eyes of 2 rabbits, and reactions were scored for up to 72 hours post instillation. The test substance was classified as a nonirritant. In a 1991 study summary provided by the Council, a homologue, cetyl ethylhexanoate, was applied undiluted (0.1 mL) to the eyes of 3 rabbits and remained for 24 hours. Mild conjunctival reactions (erythema, edema, and lacrimation) were observed, all of which had cleared by 72 hours post instillation. Cetyl ethylhexanoate was classified as slightly irritating to the eyes of rabbits.[77]

Isononyl isononanoate. A manufacturer reported that isononyl isononanoate was not irritating to the eyes of rabbits.[60] Study details were not provided.

Ethylhexyl pelargonate. The ocular irritation potential of undiluted ethylhexyl pelargonate was evaluated using 6 New Zealand white rabbits.[61] Eyes were not rinsed following the instillation of the test substance (0.1 mL). Contralateral eyes served as controls. Reactions were scored up to 72 hours post instillation. Ethylhexyl pelargonate was not irritating to the eyes of rabbits.

Neopentyl glycol diisononanoate. A study evaluating the ocular irritation potential of neopentyl glycol diisononanoate in rabbits was conducted according to the procedure in the preceding section on cetearyl nonanoate.[63] Neopentyl glycol diisononanoate (0.1 mL) produced similar results and also was classified as a minimal ocular irritant.

PEG-5 isononanoate. The ocular irritation potential of PEG-5 isononanoate was evaluated using 3 female SPF albino rabbits,[64] according to the procedure in the preceding section on cetearyl nonanoate. Conjunctival redness and edema had cleared within 14 days, and PEG-5 isononanoate was classified as a nonirritant.

Isononyl alcohol. In a study, undiluted isononyl alcohol was instilled (0.1 mL) into the left conjunctival sac of each of 6 rabbits.[52] Untreated eyes served as controls. Ocular irritation reactions were scored using the Draize scale (0-110). Draize median irritation scores of 30 (at 24 hours) and 2 (at day 7) were reported. The ocular irritation induced by isononyl alcohol was classified as marked. The test substance did not produce severe opacity or other comeal effects, such as sloughing or vascularization.

Skin Irritation

Pelargonic acid. Pelargonic acid (concentration not stated) was classified as a strong skin irritant in guinea pigs, and a moderate irritant when applied undiluted (under occlusion) to abraded or intact skin of rabbits[50] for 24 hours.

In a 28-day dermal toxicity study (in the section on short-term dermal toxicity earlier in report text),[73] slight-to-severe erythema and edema without necrosis or eschar formation were observed in most of the rabbits during the first week of the study. Generally, during the second week, necrosis and eschar formation were observed in all rabbits. Atonia, desquamation, fissuring, and exfoliation were also observed. In rabbits held for recovery, dermal responses subsided. At microscopic examination, epidermal necrosis, hyperplasia, and hyperkeratosis were noted at the application site. Diffuse and perifollicular dermal inflammation was also common. The skin application sites in all surviving animals appeared healed by 2 weeks posttreatment.

The EPA[46] placed pelargonic acid in toxicity category II (severe irritation at 72 hours [severe erythema or edema]), based primarily on results from the following skin irritation study involving 6 adult female albino rabbits of the Hra: (NZW) SPF strain.[79] The test substance (undiluted) was applied to intact skin of the back (0.5 mL, exposure area $\approx$6.25 cm^2), and the site was covered with a semiocclusive patch for 4 hours. Reactions were scored up to day 21 post removal. Skin irritation was observed in all animals; reactions ranged from moderate-to-severe erythema and edema. The average of the 4-, 24-, 48-, and 72-hour scores was 5.6 (severely irritating). The following observations were also made at application sites: subcutaneous hemorrhaging, blanching, desquamation, fissuring, possible necrotic areas, denuded areas, and possible scar tissue. With the exception of a denuded area in 1 animal, all irritation reactions had cleared by day 21.

In a study, undiluted pelargonic acid (25 µL) was applied to both ears (dorsum) of inbred CBA/Ca mice (groups of 4) once per day for 3 consecutive days.[74] Skin irritation (erythema and edema) was not observed at the test sites. LLNA results are included in the section on skin irritation and sensitization later in the report text.

According to Scientific and Technical Information Network (STN),[75] pelargonic acid (500 mg dose) was moderately irritating, following application to rabbit skin for 24 hours. Undiluted pelargonic acid was classified as a severe irritant, following application to guinea pig skin.

Cetearyl nonanoate. The skin irritation potential of cetearyl nonanoate (97% pure) was evaluated using 3 male New Zealand white rabbits.[58] The test substance (0.5 mL) was applied to skin clipped free of hair and the application site was covered with a semiocclusive patch for 4 hours. Reactions were scored 1 hour after patch removal and 24, 48, and 72 hours later. Cetearyl nonanoate was classified as a nonirritant.

Cetearyl isononanoate. A manufacturer reported that cetearyl isononanoate was not irritating to the skin of rabbits.[59] Study

details were not provided. Repeated applications of undiluted Cetiol SN (cetearyl isononanoate, percentage not stated) were made to the skin of 5 hairless mice for a total of 5 days. It was concluded that the test substance was slightly irritating to the skin.[77] A homologue, cetyl ethylhexanoate, was applied undiluted (0.5 mL) to dorsal shaved skin of 3 rabbits under semiocclusive conditions for 4 hours. Slight-to-moderate erythema and edema were observed for up to 72 hours post application, and eschar was observed at 1 week post application. All reactions cleared within 14 days, and cetyl ethylhexanoate was classified as a slight-to-moderate skin irritant.[77]

Isononyl isononanoate. A manufacturer reported that isononyl isononanoate[60] was slightly irritating to the skin of rabbits tested according to OECD method 404. Additional study details were not provided.

PEG-5 isononanoate. The skin irritation potential of undiluted PEG-5 isononanoate was evaluated using 3 male New Zealand white rabbits.[64] The test substance (0.5 mL) was applied to skin clipped free of hair and the application site was covered with a semiocclusive patch for 4 hours. Reactions were scored 1 hour after patch removal and 24, 48, and 72 hours later. The test substance induced well-defined erythema and very slight edema; no corrosive effects were observed. PEG-5 isononanoate was classified as a mild irritant (primary irritation index [PII] = 2).

Ethyl pelargonate. Moderate skin irritation was observed after undiluted ethyl pelargonate was applied, under occlusion, to intact or abraded skin of rabbits for 24 hours.[50]

Ethylhexyl pelargonate. The skin irritation potential of undiluted ethylhexyl pelargonate was evaluated using 6 New Zealand white rabbits.[61] The test substance (0.5 mL) was applied to intact and abraded skin sites that remained occluded for 24 hours. Reactions were scored at 24 and 72 hours post-application. Ethylhexyl pelargonate did not induce skin irritation in any of the rabbits (PII = 0.40).

Isononyl alcohol. The results of an acute dermal toxicity study[52] on undiluted isononyl alcohol (4 rabbits, abraded skin) are summarized earlier in the report text. The test substance was applied under an occlusive binding for 24 hours, and the doses administered ranged from 0.500 to 3.16 g/kg. In this study, dermal irritation (erythema and edema) was classified as marked overall. Both the intensity and duration of skin irritation were dose related. Atonia and desquamation, with some necrosis or eschar, were persistent findings. Some of the irritation observed was associated with the trapping of liquid under the occlusive binder at a point where the binder was bound to the animal. These areas of intimate contact and pressure gave rise to some of the reported necrosis and eschar.

Inflammation

A study to examine the tissue response of pelargonic acid in the buccal mucosa of the rat was conducted.[80] Both the methyl ester and propyl ester of pelargonic acid (both in acetone) were tested using groups of 6 SD rats (3 months old). The protocol used consisted of sensitization (dorsal skin) with 2% pelargonic acid (both solutions; dose volume = 100 µL) and challenge in the buccal mucosa (dose volume = 50 µl) with different concentrations of the sensitizing solution (0.2% and 2.0%). The area of the application site (cm^2) was not stated. Allergenic potential, as evidenced by the tissue response in the buccal mucosa, was investigated using a skin-sensitization procedure and elicitation with 2% or 0.2% solutions. Control rats were exposed to acetone only. The animals were killed 48 hours after the last application, and the right buccal mucosa was excised and prepared for microscopic examination. Cellular infiltrates in the buccal mucosa were recorded and compared to normal rat buccal mucosal.

Both test substances (at both concentrations) caused increased cellularity, mainly of the mononuclear cell type. The low concentration of the methyl ester of pelargonic acid (0.2%) induced stronger inflammatory reactions than the high concentration (2.0%). This finding was the opposite of that reported for the propyl ester of pelargonic acid. Both substances were said to have shown a sensitization tendency. Repeated applications of the propyl ester of pelargonic acid (2%) decreased the inflammatory response, when compared to 1 application. However, for the methyl ester of pelargonic acid, a clear irritative potential was noted with repeated applications. Pre-exposure of dorsal skin prior to buccal painting resulted in an enhanced reaction to pelargonic acid in methyl ester and pelargonic acid in propyl ester.[80]

Comedogenicity

Cetearyl isononanoate. Repeated applications of Cetiol SN (cetearyl isononanoate, percentage not stated) to the rabbit ear at concentrations ranging from 10% to 100% did not cause any alterations or produce structures typical of comedogenicity in the infrainfundibulum of hair follicles.[77] The positive control, isopropyl myristate, was comedogenic at a concentration of 10% and non-comedogenic at a concentration of 2%.

Skin Irritation and Sensitization

Pelargonic acid. The skin sensitization potential of pelargonic acid was evaluated in a repeated insult patch test using 24 male albino guinea pigs.[81] The test group consisted of 10 animals, and negative (corn oil) and positive (2,4-dinitrochlorobenzene [DNCB]) control groups contained 10 and 4 animals, respectively. During induction, pelargonic acid (50% weight/volume [w/v] mixture in corn oil, 0.5 mL) was placed on an adhesive patch (Hill Top Chamber, 25-mm diameter) that was applied to shaved skin of the anterior left flank for 6 hours per application. Following a nontreatment period, a 6-hour challenge

application of the test mixture (0.4 mL) was made to the anterior right flank of each test animal and corn oil was also applied to a new site on the anterior left flank. The 10 negative control animals were not treated during induction but received challenge applications of the test mixture and corn oil alone. The positive control was applied during induction and challenge phases.

Pelargonic acid (50% w/v mixture in corn oil) induced moderate-to-strong dermal reactions (erythema/edema) in all 10 guinea pigs during the induction phase. Dermal reactions to the mixture were not observed in the negative control animals during the challenge phase. The test mixture also did not elicit any dermal reactions in test animals during the challenge phase and was considered a nonsensitizer in guinea pigs. The positive control induced sensitization.[81]

Three female BALB/c mice or female CBA/J mice (6 weeks old; Harlan) were treated with pelargonic acid for 3 consecutive days.[82] The test substance was applied topically (25 µL total/ear; application area not stated) to both ears at concentrations ranging from 20% to 80% pelargonic acid in 1-propanol (volume/volume [v/v]) and an LLNA was performed.[83]

Compared to the vehicle control, pelargonic acid produced slight increases in the percenatge of $B220^+$ lymphocytes at all doses. These findings were not dose related. Even at high concentrations, the cell number per node and the percentage of $B220^+$ cells never approached the values that were associated with allergens such as 1-chloro-2,4,6-trinitrobenzene (TNCB) and DNCB.[82]

Pelargonic acid, neat or in dimethylformamide, in the LLNA. Pelargonic acid showed a dose–response relationship and positive results when tested at concentrations of ≥50% and was classified as a potential sensitizer.[74]

Pelargonic acid was administered to the dorsal and ventral surfaces of each ear of groups of 5 female B6C3F1 mice (C57BL/6 × C3HHeN at concentrations ranging from 5% to 60% in acetone) for 4 consecutive days.[85] Compared to the vehicle control, pelargonic acid produced a dose-dependent and statistically significant increase in lymph node cell proliferation at concentrations of 20%, 40%, and 60%. The no-effect-level was at a concentration of 10%. Known sensitizers (ie, oxazolone, 2,4-dinitrofluorobenzene, and toluene diisocyanate) evaluated in the assay produced marked lymph node cell proliferation.

Ceteoryl nonanoate. The skin sensitization potential of cetearyl nonanoate (89% pure) in sesame oil was evaluated in a maximization test using 15 male guinea pigs.[58] Of the 15, 5 comprised the vehicle control group. Because topical induction with 50% cetearyl nonanoate in sesame oil did not induce skin irritation in a preliminary experiment, the skin was treated with sodium lauryl sulfate (SLS) in order to induce local irritation. Cetearyl nonanoate (10% in sesame oil) was administered during the first (intracutaneous) induction stage, and reactions were evaluated after 24 and 48 hours. During the second (topical) induction stage, cetearyl nonanoate (50% in sesame oil, 2 mL) was applied and reactions were scored 48 and 72 hours after the initiation of exposure. At day 21, the animals were challenged with 10% cetearyl nonanoate in sesame oil (2 mL). Skin changes were not observed following intracutaneous induction or during the challenge phase, and the same was true for the vehicle control. Cetearyl nonanoate was classified as a nonsensitizer.

Cetearyl isononanoate. Anon-GLP-sensitization study was conducted on Cetiol SN (cetearyl isononanoate, percentage not stated).[77] During induction and challenge phases, the test substance (25%) was injected intracutaneously (10 injections within 14 days) into 5 male guinea pigs of the Pirbright White strain. The skin reactions observed in test animals did not differ from those observed in the control group.

Neopentyl glycol diisononanoate. A maximization test on neopentyl glycol diisononanoate was performed according to a slight modification of the preceding test procedure.[63] Undiluted test material was applied during the second induction and challenge phase. Initially, the skin was treated with SLS 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.

PEG-5 isononanoate. The skin sensitization potential of PEG-5 isononanoate in CBA/Ca mice (groups of 4) following topical application was evaluated in the local lymph node assay.[64] The undiluted test substance and concentrations of 25% and 50% in acetone/olive oil were applied to the dorsal surface of the ear. The control group was treated with vehicle only. The stimulation index (SI) was expressed as the mean radioactive incorporation for each treatment group divided by the mean radioactive incorporation of the vehicle control group. The SI values of 1.70 (25% concentration), 2.42 (50%), and 1.85 (100%) were reported, and PEG-5 isononanoate was classified as a nonsensitizer.

Reproductive and Developmental Toxicity

Pelargonic Acid

A study was conducted to determine the appropriate dose level of pelargonic acid for a teratology screening study involving cesarean-derived, SD rats.[49] Details relating to the conduct of this study are included in the section on short-term oral toxicity earlier in the report text. The number of corpora lutea per ovary and the number and placement of uterine implantations, resorptions, and live and dead fetuses were recorded. Mean ovarian and uterine weight data were comparable between treated and control groups. No treatment-related reproductive effects were noted over the range of administered doses (1.0-10.0 mL/kg).

A study to evaluate the embryo/fetal toxicity and teratogenic potential of pelargonic acid was conducted using groups of 22 mated female Crl:COBS, CD (SD)BR rats (14 weeks old).[86] Females of the test group were dosed orally (by gavage) with

pelargonic acid (in corn oil; dose = 1500 mg/kg) on gestation days 6 through 15. The control group received corn oil according to the same procedure. Pregnant females were killed on day 20 and fetuses were delivered by cesarean section. Neither test substance-related maternal toxicity nor effects on food and water consumption were observed in the test or control group. Additionally, there was no definitive evidence of teratogenic effects in the test or control group.

The EPA[46] reported the results of a developmental toxicity study involving rats. Treatment of the animals with pelargonic acid had no adverse effects on clinical signs, body weight gain, or food/water consumption. Fetal toxicity was not observed in treated rats or in untreated control rats, and the following parameters were comparable between treated and control rats: mean number of viable fetuses, early or late resorptions, implantation sites, corpora lutea, pre- and postimplantation losses, sex ratios, and fetal body weights. The NOEL for maternal and developmental toxicity was 1500 mg/kg per d, and the LOEL was greater than 1500 mg/kg per d.

Cetearyl Isononanoate

In a teratogenicity study on Cetiol SN (cetearyl isononanoate, percentage not stated), 3 groups of pregnant CD rats received oral doses (gavage; dose volume = 10 mL/kg) of 100, 300, and 1000 mg/kg body weight, respectively, from day 6 to 15 of gestation.[77] A fourth group served as the untreated control. None of the animals died and maternal body weight gain was not affected by treatment. All of the females had viable fetuses, and preimplantation loss and mean numbers of resorptions were not affected by treatment. Nondose-related postimplantation loss was observed in treatment groups. All parameters were said to have been comparable to those of the control group. The results of skeletal and visceral examinations did not provide evidence of any treatment-related malformations. The NOAEL for maternal toxicity and embryotoxicity/fetotoxicity was 1000 mg/kg body weight.

Isononyl Isononanoate

The developmental toxicity of isononyl isononanoate (in corn oil) was evaluated using groups of 10 mated female SD rats.[87] The 3 test groups received doses of 30, 100, and 300 mg/kg per d, respectively, by gavage on day 6 to day 17 post coitum. The control group was dosed with corn oil. There was no evidence of treatment-related, macroscopic postmortem findings in any of the females, and none of the animals died. There was also no evidence of total resorption or abortion. The number of implantation sites and corpora lutea per female was similar in all dose groups, and, compared to controls, the number of resorptions (early and late) and postimplantation loss per female in either dose group were similar. Additionally, there were no differences in the number of live fetuses in either dose group when compared to controls, and neither external anomalies nor malformations were observed. It was concluded that isononyl isononanoate did not induce direct embryotoxicity or fetotoxicity at doses up to 300 mg/kg per d.

Isononyl Alcohol

The developmental toxicity of isononyl alcohol using sexually mature, virgin Wistar rats of outbred strain Chbb/THOM was studied.[88] The 2 types of isononyl alcohol, both identified as CAS No. 68515-81-1, tested were isononanol type 1 (purity ≥99%) of commercial origin, consisting of roughly equivalent amounts of 3,4-, 4,6-, 3,6-, 3,5-, 4,5-, 5,6-dimethylheptanol-1; and Isononanol type 2 (purity ≥99%) produced at BASF with 4,5-diemthylheptanol-1 (~23%), 4-methyloctanol-1 (29%), 3-ethylheptanol-1 (3%), 6-methyloctanol-1 (15%), and 3-ethyl-4-methylhexanol (1%) as main components. (Note: Based on these chemical composition data, there is reason to believe that neither chemical [type 1 or 2) is isononanol. However, it is evident that both are branched-chain nonanols.). The test substances were diluted (twice-distilled water, employing ~0.005% Cremophor EL [PEG-35 Castor Oil] as emulsifier) to a standard dose volume of 5 mL/kg body weight. Each test substance was administered by gavage (doses ranging from 1 to 10 mmol/kg per d) to pregnant females (10/group) on days 6 to 15 post coitum. Two control groups were treated with either double-distilled water alone (control group 1) or water plus ~0.005% Cremophor EL (control group 2).

Both isononanols (types 1 and 2) exhibited a marked degree of maternal and fetal toxicity at daily doses of 7.5 and 10 mmol/kg per d, and slight fetal effects at 5 mmol/kg per d doses. Of the fetal findings (malformations, variations, or retardations), the only ones that were significantly different from controls were the number of fetuses with skeletal retardations in the 5 mmol/kg per d dose group ($p < .1$, both control groups) and the number with skeletal variations in this group ($p < .05$; 1 control group). Dosing at 1 mmol/kg per d did not cause adverse effects. When pregnant females were dosed with 7.5 mmol/kg per d (isononanol type 1) in a supplementary experiment, the incidence of malformations (mainly related to the heart) was statistically significantly increased ($P < .01$; 1 control group). Resorptions and postimplantation loss were also significantly increased ($P < .01$; 1 control group) at this dose level. For isononanol type 2, the only significant fetal findings (7.5 mmol/kg per d doses) were the number of fetuses with skeletal retardations ($P < .01, .05$, 1 control group—both values), number of fetuses with skeletal variations ($P < .051$, 1 control group), number of fetuses with variations ($P < .05$, 1 control group), and number of fetuses with malformations ($P < .05$, 1 control group). Resorptions were also significantly increased ($P < .05$; both control groups).

Neopentyl Glycol

A combined repeated dose and reproductive/developmental toxicity study on neopentyl glycol was performed using groups of male and female rats of the Slc: SD strain.[32] The test substance, in distilled water, was administered by gavage at doses

of 100, 300, or 1000 mg/kg per d. Control rats were dosed with distilled water. Male rats were dosed over a 42-day period and female rats were dosed from 14 days before mating to day 3 of lactation.

There were no test substance-related effects on copulation, fertility, or the estrous cycle of rats, and the same was true during the lactation period. With the exception of 1 control rat, delivery was normal for all dams. There were no test substance-related abnormal findings in any of the pups delivered. The body weight gain of pups was normal up to day 4 of lactation. Test substance-related, abnormal gross findings were not reported for stillborn, dead pups, or pups killed at day 4 of lactation. Additionally, no developmental toxic effects were associated with test substance administration. The NOAEL for neopentyl glycol (P and F_1 generations) was 1000 mg/kg.

Genotoxicity

Pelargonic Acid

In an Ames test,[89] the mutagenicity of pelargonic acid was evaluated with and without metabolic activation using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The test substance (in dimethyl sulfoxide [DMSO]) was evaluated at doses ranging from 100 to 5000 µg/plate in this reverse mutation assay. Pelargonic acid did not cause a positive increase in the number of histidine revertants per plate in any of the tester strains, with or without metabolic activation, and, therefore, was nonmutagenic.

The mutagenicity of pelargonic acid was evaluated in a forward mutation assay, using the L5178Y mouse lymphoma cell line.[90] In preliminary cytotoxicity assays, pelargonic acid (in DMSO) induced dose-related cytotoxicity and was completely toxic at a concentration of 4000 µg/mL (without metabolic activation) and at a concentration of 2000 µg/mL (with metabolic activation). In forward mutation assays without metabolic activation (concentrations of 150-1600 µg/mL), pelargonic acid did not induce repeatable increases in the mutant frequency. In assays with metabolic activation, dose-related increases in the mutation frequency that exceeded the minimum criterion for a positive response were observed at concentrations ranging from 50 to 600 µg/mL. These increases were primarily due to increases in small colonies considered to reflect gross chromosomal changes rather than small changes within a gene. Results for pelargonic acid were positive with metabolic activation but negative without metabolic activation.

The mutagenicity of pelargonic acid was evaluated in the in vivo micronucleus assay.[91] Three groups of ICR mice (5 males, 5 females/group) received pelargonic acid, in corn oil, at oral doses of 1250, 2500, and 5000 mg/kg, respectively. After dosing, the animals were killed and bone marrow was extracted. Pelargonic acid did not induce a significant increase in micronuclei in bone marrow polychromatic erythrocytes and was considered nonmutagenic in this assay.

The National Toxicology Program[92] evaluated the mutagenicity of pelargonic acid (in dimethylsulfoxide) in *Salmonella typhimurium* strains TA 98 and TA 100 using the Ames preincubation assay. Pelargonic acid was tested at doses up to 5000 µg/plate with and without metabolic activation, and results were negative in each strain.

Cetearyl Nonanoate

The mutagenicity of cetearyl nonanoate (in acetone; doses up to 5000 µg/plate) was evaluated in the Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA102, TA98, and TA100.[58] Results were negative with and without metabolic activation.

Cetearyl Isononanoate

A genotoxicity study evaluated Cetiol SN (cetearyl isononanoate, percentage not stated) at concentrations up to 5000 µg/plate with and without metabolic activation.[77] Neither toxicity nor reverse mutations were observed over the range of concentrations tested, and Cetiol SN was classified as nonmutagenic.

Ethylhexyl Isononanoate

The mutagencity of ethylhexyl isononanoate (in acetone; doses up to 5000 µg/plate) was evaluated in the Ames test using the bacterial strains stated immediately above.[93] Results were negative with and without metabolic activation.

Isononyl Isononanoate

The mutagenicity of isononyl isononanoate (in ethanol) was evaluated using the following *Salmonella typhimurium* strains with and without metabolic activation: TA1535, TA1537, TA98, TA100, and TA102.[94] Anthramine served as the positive control for assays with metabolic activation and the following chemicals served as positive controls for nonactivation assays: sodium azide, 9-aminoacridine, 2-nitrofluorene, and mitomycin C. Isononyl isononante was not mutagenic at doses up to 5000 µg/plate with or without metabolic activation. All positive controls were mutagenic.

Neopentyl Glycol Diisononanoate

The Ames test was also used to evaluate the mutagenicity of neopentyl glycol diisononanoate (in acetone; doses up to 5000 µg/plate) in the *Salmonella typhimurium* strains mentioned in the preceding study.[63] Results were negative with and without metabolic activation.

PEG-5 Isononanoate

A battery of mutagenicity tests on PEG-5 isononanoate was performed.[64] Ames test results (doses up to 5000 µg/plate ± metabolic activation) were negative in the *Salmonella typhimurium* strains mentioned in the preceding section on cetearyl nonanoate. The mutagenicity of a formulation containing water, trideceth-9, and 29% PEG-5 isononanoate was

evaluated in a chromosomal aberration assay involving human lymphocytes in vitro. The highest test concentration of the formulation was 5000 µg formulation/mL (1450 µL PEG-5 isononanoate/mL). Dose-dependent increases in chromosomal aberrations, with metabolic activation, were within the range of the laboratory's historical control data and, thus, considered biologically irrelevant. Clastogenicity was not observed with or without metabolic activation. The mutagenicity of the same formulation and maximum test concentration was evaluated in the mammalian cell gene mutation test (mouse lymphoma assay) using the L5178Y/TK$^{+/-}$ cell line with and without metabolic activation. Results were negative with and without metabolic activation.

Neopentyl Glycol

The mutagenicity of neopentyl glycol was evaluated using *Salmonella typhimurium* strains TA100, TA 1535, TA98, and TA1537 and *Escherichia coli* strain WP2 uvrA.[32] Mutagenicity was evaluated at doses up to 5000 µg/plate with and without metabolic activation. The minimum dose at which toxicity to bacteria was observed, with and without metabolic activation, was >5000 µg/plate. Results for neopentyl glycol were classified as negative in this assay. The mutagenicity of neopentyl glycol was also evaluated in an assay involving Chinese hamster CHL cells. Test substance (in distilled water) doses up to 1.0 mg/mL were evaluated and results were classified as negative.

An Ames test and a chromosomal aberration test, using Chinese hamster lung (CHL/IU) cells, on neopentyl glycol were conducted on neopentyl glycol.[95] In the latter assay, proliferating cells were treated with neopentyl glycol for 6 hours (short term) with and without metabolic activation. These cells were also treated with neopentyl glycol for 24 and 48 hours continuously without metabolic activation. Ames test results were negative. In the chromosomal aberrations test, results for neopentyl glycol were negative at doses manifesting 50% or <50% cytotoxicity (or at 5 mg/mL or 10 mmol/L). Negative chromosomal aberration test results (with and without metabolic activation) were associated with short-term as well as continuous treatment assays.

Methyl Pelargonate

The anticlastogenic potential of methyl esters of fatty acids was evaluated in vivo in the chromosomal aberration assay using Chinese hamster bone marrow cells.[96] Chinese hamsters of both sexes were gavaged (single oral dose) with the methyl ester of pelargonic acid, followed immediately by dosing with the mutagenic alkylating agent, busulfan (1,4- butandiolbismethane sulphonate). The chromosome-breaking activity of bisulfan was not modulated by the methyl ester of pelargonic acid (C_9) and other short-chain fatty acids. However, the methyl esters of fatty acids ranging from lauric acid (C_{12}) up to nonadecanoic acid (C_{19}) reduced the rate of aberrant metaphases from 9.4% to ~3% at doses of 100 mg/kg and less.

Carcinogenicity

The dermal carcinogenicity of undiluted pelargonic acid was evaluated using groups of 50 male C3H/HeJ mice.[97] Pelargonic acid (dose = 50 mg/kg) was applied twice weekly to interscapular skin (clipped free of hair) on the back for 80 weeks or until a neoplasm was grossly diagnosed as an advanced tumor. All surviving mice were killed between 80 and 83 weeks. Other groups included in the study were an untreated control group, a group treated with mineral oil, and a positive control group (0.05% benzo(a)pyrene in mineral oil). Sixty-six percent of the mice in the pelargonic acid-treated group survived to week 78, compared to 52% and 64% for untreated and mineral oil controls, respectively. None of the positive control mice receiving applications of 0.05% benzo(a)pyrene survived to week 78. Forty-two mice treated with pelargonic acid lived long enough to have sufficient exposure to develop a tumor within the average latent period.

The following nonneoplastic skin lesions were observed in pelargonic acid-treated mice: ulcer (7 mice), skin pigmentation (41 mice), fibrosis (48 mice), scar formation (14 mice), acanthosis (48 mice), and hyperkeratosis (40 mice). The authors noted that hyperplasia of the dermis (fibrosis), acanthosis, and hyperkeratosis are common findings in areas of mouse skin that have been clipped free of hair. There was no evidence of gross skin tumors in pelargonic acid-treated mice or in the 2 control groups. Gross skin tumors were reported for 46 positive control mice. The incidence of hepatocarcinomas in the test group was at least as high as that in the negative control groups after 80 weeks.[97]

Clinical Assessment of Safety

Skin Irritation and Sensitization

Data from predictive and provocative human skin irritation and sensitization testing on pelargonic acid and related ingredients are summarized in Table 4.

Pelargonic acid is a known skin irritant, based on the results of both predictive and provocative human skin irritation studies. In predictive tests, pelargonic acid-induced skin irritation at concentrations ranging from 5% to 80%; ethyl pelargonate was a skin irritant at a concentration of 20% but not 12%. Predictive human skin irritation test results for undiluted cetearyl nonanoate, Cetiol SN (cetearyl isononanoate, percentage not stated) at a concentration of 20%, and undiluted neopentyl glycol diisononanoate were negative, and the same was true for predictive human skin irritation and sensitization studies on cetearyl nonanoate, ethylhexyl isononanoate, and neopentyl glycol diisononanoate, all undiluted, and product formulations containing isodecyl isononanoate (51.35%) and isononyl isononanoate (3.552%). Similarly, predictive human skin sensitization studies on 12% pelargonic acid, 12% ethyl pelargonate, and formulations containing the following pelargonic acid esters were negative: cetearyl isononanoate (1.5%), cholesteryl nonanoate (20.86%), isotridecyl isononanoate (4.3%), isodecyl isononanoate (2.6%), isononyl isononanoate (24.66%), and PEG-5

Table 4. Skin Irritation and Sensitization Studies on Pelargonic Acid, Nonanoate Esters, and Related Chemicals

Test Substance	Participants Tested	Test Protocol	Results	References
Predictive Tests—skin irritation				
Pelargonic acid				
0.01, 0.1, 0.5, and 1.0 mol/L (in propanol)	20 male participants: 0.5 mol/L application (10 participants) and 1.0 mol/L (10 participants); 0.01 and 0.1 mol/L intradermal injections (5 participants)	24 hours Al-test patch application to interscapular area, 10 applications total/dose (0.04 mL volume; application area [cm^2] not stated); 10 intradermal injections (0.1 mL/injection) total /dose	Erythematous reactions: 7 participants (0.5 mol/L), 10 participants (1.0 mol/L), and 5 participants (0.01 and 0.1 mol/L)	Stillman et al[98]
5%, 10%, 20%, and 39.9% (in propanol)	116 male participants	48-hour patch (Al-test disc) application to upper back; 0.04 mL/dose (application area [cm^2] not stated)	Skin irritation in > 90% of participants at 48 and 96 hours post application (20% and 39.9% concentrations); skin irritation in 54.3% of participants at 48 hours and in 48.5% of participants at 96 hours (10% concentration); skin irritation in 12.9% of participants at 48 hours and in 13.9% of participants at 96 hours (5% concentration)	Wahlberg and Maibach[99]
20% (in propanol; pH of 4.3)	16 participants (10 males, 6 females)	24-hour closed patch (12 mm-diameter Finn chamber) application to anterolateral surface of both upper arms; dose volume/cm^2 not stated	Erythema and slight infiltration at 24 hours; occasional slight crusting at 48 hours	Agner and Serup[100]
40%, 60%, 70%, and 80% (in propanol)	42 male participants 40% (12 participants), 60% (32 participants), 70% (32 participants), and 80% (28 participants)	48-hour patch (8 mm diameter Finn chamber) application to volar forearm (30 μL/cm^2)	Positive reactions: 2 of 12 participants (40% concentration); 20 of 32 participants (60%); 2 of 32 participants (70%); and 28 of 28 participants (80%)	Willis et al[101]
20% (in propanol)	16 participants	24-hour closed patch (12 mm diameter Finn chamber) application to anterolateral surface of both upper arms; dose volume/cm^2 not stated	Mean irritation score of 2 (moderate positive reaction) at 24 hours; mean score of 1 (weak positive reaction) at 96 hours	Agner and Serup[102]
Pelargonic acid				
80% (in propan-1-(w/w) 100% propylene glycol)	10 male participants	48-hour patch (8 mm diameter Finn chamber) application to volar forearm (30 μL/cm^2)	Mild to moderate skin irritation at 1 hour post removal	Willis et al[103]
20% (in propanol)	20 participants (12 males , 8 females;)	24-hour closed patch (12 mm diameter Finn chamber) application to flexor side of both upper arms (0.06 mL/dose; application area [cm^2] not stated)	Skin irritation in all participants at 24 h.	Agner and Serup[104]
80% (in propanol, 100% propylene glycol)	10 male participants	48 h patch (8 mm-diameter Finn chamber) application to volar forearm (30 μl/cm^2)	Most of the irritation reactions were mild to moderate at 1 h post-removal	Willis et al[105]

(continued)

Table 4. (continued)

Test Substance	Participants Tested	Test Protocol	Results	References
10%, 20%, 40%, and 80% (in propanol)	152 female participants; 37 were atopic	47-hour patch (8 mm diameter Finn chamber) application to right and left lower back	Erythema was more severe at 48 hours than at 96 hours at sites on the left and right lower back ($P < .001$). Except for the 20% concentration (on left lower back),decreased erythema with time was noted at each concentration	Reiche et al[106]
Cetearyl isononanoate				
20% Cetiol SN	21 participants	24-hour occlusive application (Finn chambers)	No skin irritation	Kleber and Hoffmann-Dörr[77]
Cetearyl nonanoate				
Undiluted chemical	52 participants (males and females)	48-hour occlusive patch application (0.2 g) to upper back; application area [cm^2] not stated	No skin irritation	Symrise GmbH & Co. KG[58]
Neopentyl glycol diisononanoate				
Undiluted chemical	52 participants (males and females)	Preceding patch test procedure; application area [cm^2] not stated	No skin irritation	Symrise GmbH & Co. KG 2010c[63]
PEG-5 isononanoate				
Experimental formulation containing 14.5% PEG-5 isononanoate	53 participants	48-hour occlusive patch application (0.2 g) to upper back; application area [cm^2] not stated	No skin irritation	Symrise GmbH & Co. KG[64]
Ethyl pelargonate				
Concentration not stated	—	5-minute to 5-hour application period	No skin irritation	Opdyke [50]
12% in petrolatum)	—	48-hour closed patch test	No skin irritation	Opdyke [50]
20% (w/w) in petrolatum	10 healthy participants (4 males, 6 females;)	24-hour occlusive patch test	No skin irritation	Smith et al[107]
Provocative tests—skin irritation				
Pelargonic acid				
5%, 10%, 20%, and 100% (in propanol)	75 participants with allergic contact dermatitis patients (males and females)	48 h patch (Al-test disc) application (0.04 mL) to upper back; application area [cm^2] not stated	Dose related skin irritation observed. in 100% of all participants tested and with 100% concentration; 98.3% of all participants with 20% concentration.	Wahlberg and Maibach[108]
1%, 5%, 10%, 20%, and 39.9% (in propanol)	100 hospitalized participants with skin disease (54 males, 46 females;)	48 h patch (Al-test disc, saturated with solution) application to upper back; dose volume/cm^2 not stated	Irritation reactions (lowest test concentration producing a reaction): 1.0% pelargonic acid (1 male; 2 females), 5.0% (23 males; 9 females), 10.0 % (18 males; 22 females), 20.0% (12 males; 13 females), and 39.9% (all patients)	Wahlberg et al[109]
Skin irritation and sensitization				
Predictive tests				
Cetearyl nonanoate				

(continued)

Table 4. (continued)

Test Substance	Participants Tested	Test Protocol	Results	References
Undiluted chemical	106 participants (males and females)	RIPT. 24-hour occlusive patch applications, 0.2 g per patch, to upper back (induction and challenge); application area [cm^2] not stated	No skin irritation or sensitization	Symrise GmbH & Co. KG[58]
Ethylhexyl isononanoate				
Undiluted chemical	52 participants (males and females)	RIPT same as in preceding study, except semiocclusive patches used	Skin irritation in 10 participants. No allergic contact sensitization	Symrise GmbH & Co. KG[64]
Isodecyl isononanoate				
Makeup product containing 51.35%	101 normal participants (18 to 65 years old)	RIPT. 24-hour semiocclusive patch applications to upper back (induction and challenge); dose volume/cm^2 not stated	6 participants with ± or 1+ reaction during induction. 3 participants with ± reaction after challenge. Makeup product had no dermal irritation or sensitization potential.	Clinical Research Laboratories, Inc.[110]
Isononyl isononanoate				
Lipstick containing 3.55%	53 participants	RIPT. 24-hour semiocclusive patch applications,0.2 g per patch, to back (induction and challenge); dose volume/cm^2 not stated	No skin reactivity	Consumer Product Testing Company [111]
Lipstick containing 3.13%	97 participants	RIPT. 24-hour semiocclusive patch applications,0.2 g per patch, to back (induction and challenge); dose volume/cm^2 not stated	No skin reactivity	Consumer Product Testing Company [112]
Neopentyl glycol diisononanoate				
Undiluted chemical	106 participants (males and females)	RIPT. 24-hour occlusive patch applications, 0.2 g per patch to upper back (induction and challenge); application area [cm^2] not stated	No skin irritation or sensitization	Symrise GmbH & Co. KG[63]
Predictive tests—skin sensitization				
Pelargonic acid				
12% in petrolatum	25 normal participants	Maximization test	No sensitization	Opdyke [50]
Cetearyl isononanoate				
Liquid makeup remover containing 1.5%	25 normal participants (18 to 65 years old)	Maximization test	No contact allergy	KGL, Inc.[113]
Cholesteryl nonanoate				
Lipstick containing 20.86%	28 normal participants (21-57 years old)	Maximization test	No contact allergy	KGL, Inc.[114]
Isotridecyl isononanoate				
Facial cream containing 4.3%	28 normal participants (19 to 63 years old)	Maximization test	No contact allergy	KGL, Inc.[115]
Isodecyl isononanoate				

(continued)

Table 4. (continued)

Test Substance	Participants Tested	Test Protocol	Results	References
Day cream containing 2.6%	26 normal participants (26 to 65 years old)	Maximization test	No contact allergy	KGL, Inc.[116]
Isononyl isononanoate				
Eye shadow containing 24.66%	26 normal participants (18 to 65 years old)	Maximization test	No contact allergy	KGL, Inc.[117]
PEG-5 isononanaote				
Experimental formulation containing 14.5% PEG-5 isononanoate	53 normal participants	RIPT. Patch applications, 0.2 g per occlusive patch, to upper back (induction and challenge); application area [cm^2] not stated	No allergic contact sensitization	Symrise GmbH & Co. KG[64]
Ethyl pelargonoate				
12% in petrolatum	25 normal participants	Maximization test	No sensitization	Opdyke[50]
Provocative test—skin sensitization				
Cetearyl isononanoate				
Undiluted Cetiol SN	20 participants with eczema	RIPT. 24-hour applications under Beiersdorf test plaster	No irritation/sensitization	Herzberg[118]
Isotridecyl alcohol				
5% in petrolatum	229 participants with dermatitis	24-hour or 48-hour patch applications	No sensitization	Geier et al[119]

isononanoate (14.5%). Results were negative for undiluted Cetiol SN (cetearyl isononanoate, percentage not stated) and 5% isotridecyl alcohol in provocative human skin sensitization studies.

Epidermal Proliferation and Apoptosis

Alterations in the proliferative capacity of human epidermis following topical exposure to pelargonic acid (80% [v/v] in propan-1-ol) were investigated [120]. Finn chambers containing the test substance were applied to the volar aspect of the forearm of each of 10 healthy, nonatopic male participants for 48 hours. Punch biopsies were removed from each application site. Samples of normal skin were also obtained. Compared to the vehicle control, pelargonic acid induced a statistically significant ($P < .05$) increase in the density of proliferating keratinocytes (ie, increase in mitotic activity).

The effect of 80% pelargonic acid (in propan-1-ol) on Langerhans cells and on epidermal proliferation and apoptosis was studied.[121] Punch biopsies were obtained from the volar forearm of 46 participants with irritant contact dermatitis (25 males and 21 females) and 10 healthy participants, following application of the test substance (Finn chambers) and vehicle control to the skin for up to 48 hours. A higher number of Langerhans cells/mm basement membrane in the patients, compared to controls, was reported. However, there was no difference in the number of dendrites/Langerhans cell or in dendrite length. Pelargonic acid caused a decrease in keratinocyte proliferation after 24 hours of exposure, but a return to basal levels was observed after 48 hours. Pelargonic acid induced epidermal cell apoptosis after only 6 hours of exposure and dramatically decreased the Langerhans cell number after 24 and 48 hours of exposure. Apoptosis was induced in over half of the Langerhans cells that were present after 24 and 48 hours.

Effect on CD1a and Intercellular Adhesion Molecule 1 Expression

The possibility of differences in the interaction between different irritants (pelargonic acid and SLS) and immunological parameters in the epidermis were investigated in 9 healthy participants.[122] The reactions were evaluated by immunohistochemistry using monoclonal antibodies directed against CD1a, CD3, and intercellular adhesion molecule 1 (ICAM-1) molecules. Initially, occlusive patch tests (Finn chambers) involving the following 3 groups were conducted. In group 1 (2 males and 1 female), 2% SLS and 4% SLS in distilled water (w/v) and distilled water alone were applied under occlusion for 24 hours, and biopsies were obtained at 48 hours. In group 2 (3 males), 20% pelargonic acid and 80% pelargonic acid in isopropanol (v/v), and isopropanol alone were applied under occlusion for 24 hours, and biopsies were obtained at 48 hours. In group 3 (3 males), 4% SLS in water and 80% pelargonic acid in isopropanol were applied under occlusion for 24 hours; biopsies were obtained immediately after Finn chamber removal.

At 48 hours (groups 1 and 2), marked edema was observed at the 4% SLS site; this reaction was greater in severity when compared to those induced by 20% and 80% pelargonic acid. At 24 hours (group 3), the reactions to 4% SLS and 80% pelargonic acid were similar. Reactions were not induced by the distilled water or isopropanol vehicle. At both 24 and 48 hours, an exposure-related (SLS and pelargonic acid) increase in the number of CD3+ cells in the upper part of the dermis was observed. A minor increase in CD3+ cells following exposure to distilled water, but not isopropanol, was also observed at 48 hours. Few CD3+ cells were also identified in the epidermis following SLS and pelargonic acid exposure.

Differences in ICAM-1 expression in the epidermis following SLS and pelargonic acid exposure were observed. Following SLS exposure, an increase in ICAM-1+ keratinocytes at 24 and 48 hours was noted. A tendency toward increased numbers of CD1a+ cells was noted at 48 hours after treatment with 4% SLS. A definite decrease in the number of CD1a+ cells was observed following exposure to 80% pelargonic acid. Reactivity of ICAM-1 was not detected in the epidermis following exposure to 20% or 80% pelargonic acid. Increased levels of ICAM-1 expression were observed in the epidermis following exposure to both water and isopropanol controls. In the control biopsies, 3 of 9 specimens had ICAM-1 reactivity (single cells or few keratinocytes). It was concluded that different irritants applied to the skin surface may induce different responses in epidermis measured with markers for immunological components, although the clinical picture indicates primary irritancy.[122]

Case Reports

Cetearyl Isononanoate

In a case report,[123] a 23-year-old female with a history of allergic contact dermatitis developed acute dermatitis after application of a urea-based moisturizing cream containing cetearyl isononanoate. The participant was patch tested (repeated open application test) with ingredients of the cream, each diluted to a concentration identical to that in the product. Allergic reactions to the cream (day 2: ++; day 4: ++) and cetearyl isononanoate (day 2: negative; day 4: ++), both diluted to concentration of 4% in liquid mineral oil were reported. Patch test results for 4% cetearyl isononanoate were negative in 10 voluntary control participants on days 2, 3, and 4.

Isononyl Isononanoate

In a case report,[124] a 40-year-old, nonatopic female presented with contact cheilitis following application of a lipstick product containing isononyl isononanoate in 2002. In 2007, she presented with severe contact dermatitis on the eyelids following application of a new lipstick product containing isononyl isononanoate to the eyelids. Patch test results for isononyl isononanoate were positive. Additional patch testing (patch test chambers on forearm) was performed, and reactions were

scored according to International Contact Dermatitis Research Group criteria on days 2 and 4 and later. Strong (vesicular) positive reactions were observed at all tested ethanolic dilutions of isononyl isononanoate, from 20% (actual use concentration in product) to 1%. The patient developed severe edema of the entire test site. Patch test results for isononyl isononanoate (5% in ethanol) were negative in 20 control participants. Further patch testing in 2008 to identify possible cross-reactions did not yield further positive reactions.

Summary of Information From Earlier CIR Safety Assessments

Propylene Glycol Esters and Diesters—Including Propylene Glycol Dipelargonate

There were limited data on many of the propylene glycol esters and diesters. There were data indicating that propylene glycol dicaprylate/dicaprate was a minimal dermal irritant and was not comedogenic. In the discussion, it was noted that the caprylic (8-carbon chain)/capric (10-carbon chain) moiety is similar to the dipelargonate (9-carbon chain) moiety. Propylene glycol dipelargonate enhanced the skin penetration of caffeine and testosterone through human stratum corneum in vitro.

Overall, the Panel relied substantially on the prior reviews of the following ingredients previously reviewed to demonstrate overall safety of this group:

- propylene stearate for mutagenicity, chronic toxicity, and skin sensitization;
- caprylic/capric triglyceride for reproductive toxicity, chronic toxicity, and skin sensitization;
- coconut acid for chronic toxicity, tumor promotion, skin sensitization, phototoxicity, and photosensitization;
- isostearic acid for skin sensitization, photosensitization, and phototoxicity;
- lauric, myristic, and oleic acids for reproductive toxicity, carcinogenicity, skin sensitization, and photosensitization;

In the original safety assessment of isostearic acid, two reports that discussed metabolism were noted. One study concluded that rat liver homogenate acyl coenzyme A synthetase was found to activate isostearic acid. In another study that focused specifically on metabolism of iso-fatty acids versus straight-chain fatty acids, it was reported that metabolism is similar by the mitochondrial and microsomal fractions of rat liver homogenate. The straight-chain fatty acids are successively oxidized at the β carbon to yield 2-carbon fractions. The iso-fatty acids also follow that path but, in addition, are oxidized at the ω carbon to ultimately form 3-carbon dicarboxylic acids. The enzymes catalyzing the ω-hydroxylation are present in the mitochondrial and microsomal fractions, whereas the enzymes catalyzing further oxidation into carboxylic acids are in the soluble fractions of rat liver homogenate.

In the discussion, the Panel did note a concern about dermal penetration enhancement with propylene glycol dipelargonate. It has been shown that propylene glycol dipelargonate enhances the skin penetration of caffeine through human stratum corneum in vitro.

Butyl, Cetyl, Isobutyl, Isocetyl, Isopropyl, Myristyl, and Octyl (Now Ethyhexyl) Stearate

Few data were available that demonstrated the metabolic fate of the iso forms compared to straight-chain forms beyond noting that aliphatic esters are hydrolyzed to the corresponding alcohol and fatty acid and further metabolized. One study was provided in which isopropyl stearate, diluted in 9,10-$^{3}H_2$-labeled oleic acid, was given by gavage to thoracic duct fistula rats. Radiolabel was found in lymph lipids, suggesting a dietary origin. Less than 10% of the recovered radiolabel was in the form of the isopropyl ester and, conversely, over 95% of the radiolabel was in triglycerides, leading to the suggestion that the isopropyl ester is hydrolyzed in the intestine and that the fatty acids thus liberated are reesterified before distribution to lymph lipids.

Safety test data indicated low acute oral toxicity, no reproductive toxicity, and minimal skin irritation but no skin sensitization, phototoxicity, or photosensitization. The discussion noted the absence of data on comedogenicity.

Decyl and Isodecyl Oleate

These fatty acid esters have low acute oral toxicities, but few other toxicity data were available. They can be minimal-to-moderate dermal irritants but are not sensitizers in human and animal tests. No metabolic fate information relevant to the esters was available.

Summary

Pelargonic acid and nonanoate esters are cosmetic ingredients that function as skin-conditioning agents in cosmetics. The following ingredients are reported as being used: butylene glycol diisononanoate, cetearyl isononanoate, cetearyl nonanoate, cetyl isononanoate, cholesteryl nonanoate, diethylene glycol diethylhexanoate/diisononanoate, dipentaerythrityl pentaisononanoate, ethylhexyl isononanoate, isodecyl isononanoate, isononyl isononanoate, isotridecyl isononanoate, tridecyl isononanoate, ethylhexyl pelargonate, neopentyl glycol diisononanoate, cetearyl nonanoate, cetyl isononanoate, dipentaerythrityl pentaisononanoate, neopentyl glycol diisononanoate, PEG-2 diisononanoate, PEG-5 isononanoate, pentaerythrityl tetraisononanaote, polyglyceryl-20 octaisononanoate, and pentaerythrityl tetrapelargonate. Current ingredient use concentrations range from 0.01% (cholesteryl nonanoate) to 74% (ethylhexyl isononanoate).

The following chemicals do not absorb significantly in the 250 to 400 nm range: neopentyl glycol diisononanoate, cetyl nonanoate + stearyl nonanoate, trideceth-9 + PEG-5-isononanoate + water, glyceryl triisononnoate + glyceryl diisononanoate, and ethylhexyl isononanoate.

Straight-chain pelargonic acid esters are likely hydrolyzed to component alcohols and pelargonic acid, which is further metabolized by β-oxidation. Iso-fatty acids and straight-chain fatty acids both are metabolized at the β-carbon to yield 2-carbon fractions by mitochondrial and microsomal fractions of rat liver homogenate. Additionally, iso-fatty acids are oxidized at the ω carbon to ultimately form 3-carbon dicarboxylic acids. The enzymes catalyzing the ω-hydroxylation are present in the mitochondrial and microsomal fractions, whereas the enzymes catalyzing further oxidation into carboxylic acids are in the soluble fractions of rat liver homogenate. With the exception of pelargonic acid and ethyl pelargonate, specific information relating to the metabolism of the remaining ingredients reviewed in this safety assessment was not identified in the published literature. Branched-chain fatty acid metabolism involves initial α-oxidation, which is followed by the β-oxidation pathway.

Octanol–water partition coefficient (logP) and mw data included in the safety assessment may be used to predict the skin penetration potential of pelargonic acid and its esters/ester moieties. Most of the ingredients reviewed in this safety assessment have a logP of >5 and a mw of <500. Compounds with a logP of >5 and a mw of >500 are less likely to penetrate the skin. For example, cholesteryl nonanoate has a logP of 10 and a mw of >500, suggesting that dermal absorption is unlikely. The skin penetration enhancement effect of pelargonic acid on other chemicals has been demonstrated in vitro using human stratum corneum and hairless rat skin. The percutaneous absorption of isononyl alcohol was reported in an acute dermal toxicity study using rabbits with abraded skin and occlusion of the site.

An acute inhalation LC50 of 1.34 mg/L was reported for pelargonic acid in a study involving rats. Inhalation exposure to isononanoic acid caused a concentration-dependent decrease in respiratory frequency in mice, and an RD50 of 420 mg/m^3 was reported. Few and no deaths were reported for mice/rats and guinea pigs, respectively, following inhalation exposure to isononyl alcohol at a concentration of 21.7 mg/L.

Pelargonic acid and the esters for which data are available are not significant acute oral toxicants (LD50s > 1 g/kg) or acute dermal toxicants (lowest LD50 reported = 5 g/kg).

Short-term oral dosing with pelargonic acid (in diet) yielded LOELs of 5000 ppm (for clinical pathology) and 100 ppm (for antemortem data) in rats. Overt signs of toxicity were not associated with higher doses in other short-term oral toxicity studies. Short-term oral dosing with isononyl isononanoate induced liver and kidney toxicity in rats at doses up to 1000 mg/kg per d. Limited numbers of rats given isononyl alcohol at 1 mmol/kg per d had no overt signs of toxicity. The NOAEL for neopentyl glycol in rats was 100 mg/kg. Subchronic oral dosing with 1% ethyl pelargonate (in diet) did not result in any remarkable gross or microscopic findings in rats. However, subchronic oral dosing with Cetiol SN (cetearyl isononanoate, percentage not stated) induced reversible fatty alterations in the liver of rats, and an NOAEL of 100 mg/kg per d was reported.

Repeated applications of pelargonic acid (25% in mineral oil) to the skin of rabbits in a 28-day study did not cause death, and the random inflammatory changes observed in various organs were described as spontaneous. In other studies, dermal application of pelargonic acid to mice over a 3-day period did not cause death and a TDLo of 3000 mg/kg was reported. Short-term cutaneous dosing with isononyl isononanoate induced liver and adrenal toxicity in rats at doses up to 860 mg/kg per d.

The ocular changes observed in a 28-day oral toxicity study (rats) on pelargonic acid were considered sporadic and unrelated to treatment. In studies involving rabbits, pelargonic acid (0.1 mL) was severely irritating or mildly irritating. Neither isononyl isononanoate, ethylhexyl pelargonate (0.1 mL), nor Cetiol SN (cetearyl isononanoate, percenatge not stated) at a concentration of 10% (0.5 mL) induced ocular irritation in rabbits; however, both cetearyl nonanoate and neopentyl glycol diisononanoate (0.1 mL) induced minimal ocular irritation, and isononyl alcohol (0.1 mL) induced marked ocular irritation. PEG-5 isononanoate (0.1 mL) induced transient ocular reactions but was not classified as an ocular irritant.

Undiluted pelargonic acid was a mild-to-severe skin irritant in rabbits and a severe skin irritant in guinea pigs but was not irritating to the skin of mice. However, undiluted cetearyl isononanoate was nonirritating to the skin of rabbits, but, as undiluted Cetiol SN (cetearyl isononanoate, percentage not stated), was slightly irritating to the skin of mice. The remaining studies involved rabbits only. Isononyl isononanoate (unknown concentration) and undiluted PEG-5 isononanoate were slightly/mildly irritating, and undiluted ethyl pelargonate was moderately irritating to the skin; however, undiluted isononyl alcohol induced marked skin irritation. Skin irritation was not observed following the application of undiluted cetearyl nonanoate, cetearyl isononanoate, or undiluted ethylhexyl pelargonate. Repeated applications of Cetiol SN (cetearyl isononanoate, percentage not stated) to the rabbit ear at concentrations ranging from 10% to 100% did not cause any alterations or produce structures typical of comedogenicity in the infrainfundibulum of hair follicles.

In an RIPT, pelargonic acid (50% in corn oil) induced skin irritation, but not sensitization, in guinea pigs. Sensitization test results for guinea pigs injected intracutaneously with Cetiol SN (cetearyl isononanoate, percentage not stated) at a concentration of 25% did not differ from those of control guinea pigs. In guinea pig maximization tests, cetearyl nonanoate (10% in sesame oil) and undiluted neopentyl glycol diisononanoate were nonsensitizers; results for 50% cetearyl nonanoate in sesame oil and undiluted neopentyl glycol diisononanoate (for induction) were negative in preliminary skin irritation tests. Both the methyl ester and propyl ester of pelargonic acid (both at 0.2% and 2.0%) were said to have shown a sensitization tendency in a study examining the tissue response to pelargonic acid in the buccal mucosa of the rat. In mouse LLNAs (for sensitization potential), results were positive at pelargonic acid concentrations of ≥50% and ≥20% (no effect level = 10%) and negative for PEG-5 isononanoate at concentrations up to 100%.

Daily doses of pelargonic acid up to 1500 mg/kg per d did not induce reproductive effects in inseminated female rats.

Results from other studies support pelargonic acid daily doses of 1500 mg/kg per d as the NOEL for maternal/developmental toxicity in rats, and isononyl isononanoate daily doses of 300 mg/kg per d as the NOEL for developmental toxicity in rats. In a teratogenicity study on Cetiol SN (cetearyl isononanoate, percenatge not stated), the NOAEL for maternal toxicity and embryotoxicity/fetotoxicity was 1000 mg/kg body weight. Two branched-chain nonanols (perhaps incorrectly identified as isononanol) caused a marked degree of maternal and fetal toxicity in rats at daily doses of 7.5 and 10 mmol/kg per d and slight fetal effects at 5 mg/kg per d doses. Neopentyl glycol at oral doses up to 1000 mg/kg per d did not induce reproductive effects.

While 1 mammalian cell assay of pelargonic acid was positive with metabolic activation (doses up to 600 μg/mL), it was negative without metabolic activation. All other bacterial, mammalian cell, and in vivo assays for pelargonic acid (doses up to 5000 μg/plate or 5000 mg/kg) and the following pelargonic acid esters (doses up to 5000 μg/plate) were negative: Cetiol SN (cetearyl isononanoate, percentage not stated), cetearyl nonanoate, ethylhexyl isononanoate, isononyl isononanoate, neopentyl glycol diisononanoate, and PEG-5 isononanoate. Negative results were also reported for neopentyl glycol at doses up to 5000 μg/plate (bacterial cells) and up to 5 mg/mL (mammalian cells). There was no evidence of gross skin tumors in mice dosed with undiluted pelargonic acid in a dermal carcinogenicity study.

Pelargonic acid is a known skin irritant, based on the results of both predictive and provocative human skin irritation studies. In predictive tests, pelargonic acid induced skin irritation at concentrations ranging from 5% to 80%; ethyl pelargonate was a skin irritant at a concentration of 20% but not 12%. Predictive human skin irritation test results for undiluted cetearyl nonanoate, Cetiol SN (cetearyl isononanoate, percentage not stated) at a concentration of 20%, and undiluted neopentyl glycol diisononanoate were negative, and the same was true for predictive human skin irritation and sensitization studies on cetearyl nonanoate, ethylhexyl isononanoate, and neopentyl glycol diisononanoate, all undiluted, and product formulations containing isodecyl isononanoate (51.35%) and isononyl isononanoate (3.552%). Similarly, predictive human skin sensitization studies on 12% pelargonic acid, 12% ethyl pelargonate, and formulations containing the following pelargonic acid esters were negative: cetearyl isononanoate (1.5%), cholesteryl nonanoate (20.86%), isotridecyl isononanoate (4.3%), isodecyl isononanoate (2.6%), isononyl isononanoate (24.66%), and PEG-5 isononanoate (14.5%). Results were negative for undiluted Cetiol SN (cetearyl isononanoate, percenatge not stated) and 5% isotridecyl alcohol in provocative human skin sensitization studies.

In other human studies, pelargonic acid (80%) increased the density of proliferating keratinocytes and caused epidermal cell apoptosis and a transient decrease in keratinocyte proliferation.

In case reports, a moisturizing cream containing cetearyl isononanoate induced contact dermatitis and a lipstick containing 20% isononyl isononanoate induced contact cheilitis. Patch test results for 4% cetearyl isononanoate and 5% isononyl isononanoate were negative in healthy control participants in these reports.

Discussion

The CIR Expert Panel recognizes that the pelargonic acid branched esters included in this safety assessment are not pure substances but are always mixtures. The INCI name for each pelargonic acid branched ester actually refers to a mixture with general properties that, in many instances, cannot be fully characterized. Regardless, the material, as supplied to the industry for use in cosmetics, is the same material that is used in safety testing. While specific data on the metabolic fate of the branched esters included in this safety assessment were not found, data on phytanic acid, a 20-carbon branched fatty acid, indicate that the α-methylene group is oxidatively excised (α-oxidation) in mammalian microsomes, yielding pristanic acid. Pristanic acid is then metabolized via the β-oxidation pathway. These data were deemed representative of the metabolic pathways for branched fatty acids in general.

The Expert Panel noted the availability of acute inhalation toxicity data on pelargonic acid, isononanoic acid, and isononyl alcohol, but not on any other ingredients that are being reviewed in this safety assessment. However, in the absence of these data, the Panel determined that the ingredients included in this review can be used safely in hair sprays, because the product particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays (around 38 μm) and pump hair sprays (>80 μm) is large compared to respirable particle sizes (≤10 μm). The Panel expressed concern over the findings of liver steatosis and acidophilic globules in the renal cortical tubules of male rats in both short-term oral and dermal toxicity studies on isononyl isononanoate but also acknowledged industry comments on the effect that high-fat diets produce liver steatosis. This sex- and species-specific hyaline droplet nephropathy was not considered relevant to man because the alpha-2-microglobulin protein is absent from man as well as many species.

Because animal sources of cetearyl isononanoate, cetyl isononanoate, cholesteryl nonanoate, dihydrocholesteryl nonanoate, and isostearyl isononanoate have been reported, the Panel was also concerned with the dangers inherent in using animal-derived ingredients, namely the transmission of infectious agents. The CIR Expert Panel stressed that the preceding ingredients must be free of detectable pathogenic viruses or infectious agents. Suppliers and users of these ingredients must accept responsibility for assuring that these ingredients are risk free. Tests to assure the absence of a pathogenic agent in the ingredients, or controls to assure derivation from pathogen-free sources are two approaches that should be considered.

The Expert Panel also recognized that pelargonic acid and related ingredients, because of the skin penetration enhancement property of pelargonic acid in the presence of PABA, could enhance the penetration of similar chemicals, possibly cosmetic ingredients, through the skin. The Panel cautioned

that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

Panel deliberations on the safety of pelargonic acid esters focused on current ingredient use concentration data from industry in relation to human RIPT data on cosmetic products containing these ingredients. Current ingredient use concentrations ranged from 0.01% (cholesteryl nonanoate) to 74% (ethylhexyl isononanoate), and ethylhexyl isononanoate was a mild skin irritant, but a nonsensitizer, when tested undiluted. Similarly, cetearyl isononanoate, cetearyl nonanoate, and neopentyl glycol diisononanoate, each undiluted, did not induce sensitization in human RIPTs. Other data indicate that the highest ester concentration, undiluted excluded, evaluated in a human RIPT was 51.35% isodecyl isononanoate in a makeup product (nonirritant and nonsensitizer), which approaches the maximum use concentration of 59% for this ingredient. Results from a non-good laboratory practice (GLP) sensitization study on Cetiol SN (cetearyl isononanoate, percentage not stated) at a test concentration of 25% were also considered only because the skin reactions of test animals did not differ from those of controls. Based on negative results for sensitization at high ingredient test concentrations, the Expert Panel reasoned that is not likely that the pelargonic acid esters reviewed in this safety assessment would induce sensitization in the present practices of use.

Conclusion

The CIR Expert Panel concluded that butylene glycol diisononanoate, cetearyl isononanoate, cetearyl nonanoate, cetyl isononanoate, cholesteryl nonanoate, diethylene glycol diethyl-hexanoate/diisononanoate, dipentaerythrityl pentaisononanoate, ethylhexyl isononanoate, isodecyl isononanoate, isononyl isononanoate, isotridecyl isononanoate, neopentyl glycol diisononanoate, PEG-2 diisononanoate, PEG-5 isononanoate, pentaerythrityl tetraisononanaote, polyglyceryl-20 octaisononanoate, tridecyl isononanoate, ethylhexyl pelargonate, pentaerythrityl tetrapelargonate, cellobiose octanonanoate, diethylene glycol diisononanoate, dihydrocholesteryl nonanoate, glycereth-7 diisononanoate, isostearyl isononanoate, phytosteryl nonanoate, propylene glycol diisononanoate, ethyl pelargonate, isobutyl pelargonate, methyl pelargonate, neopentyl glycol dicaprylate/dipelargonate/dicaprate, and pelargonic acid are safe as cosmetic ingredients in the present practices of use and concentration described in this safety assessment (note 1).

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Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th St., Suite 412, Washington, DC 20036, USA.

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Note

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

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2016 VCRP Use Data – Monoalkylglycol Dialkyl Acid Esters

08A - Basecoats and Undercoats	TRIMETHYL PENTANYL DIISOBUTYRATE	35
08E - Nail Polish and Enamel	TRIMETHYL PENTANYL DIISOBUTYRATE	257
08G - Other Manicuring Preparations	TRIMETHYL PENTANYL DIISOBUTYRATE	23
		315

01B - Baby Lotions, Oils, Powders, and Creams	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	2
03D - Eye Lotion	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	1
04A - Cologne and Toilet waters	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	28
04B - Perfumes	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	22
04E - Other Fragrance Preparation	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	1
07C - Foundations	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	18
07E - Lipstick	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	1
07F - Makeup Bases	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	2
12C - Face and Neck (exc shave)	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	7
12D - Body and Hand (exc shave)	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	6
12F - Moisturizing	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	5
12J - Other Skin Care Preps	BUTYLENE GLYCOL DICAPRYLATE/DICAPRATE	1
		94

01A - Baby Shampoos	GLYCOL DISTEARATE	1
01C - Other Baby Products	GLYCOL DISTEARATE	16
02A - Bath Oils, Tablets, and Salts	GLYCOL DISTEARATE	7
02B - Bubble Baths	GLYCOL DISTEARATE	42
02D - Other Bath Preparations	GLYCOL DISTEARATE	20
03D - Eye Lotion	GLYCOL DISTEARATE	1
04E - Other Fragrance Preparation	GLYCOL DISTEARATE	1
05A - Hair Conditioner	GLYCOL DISTEARATE	13
05C - Hair Straighteners	GLYCOL DISTEARATE	1
05F - Shampoos (non-coloring)	GLYCOL DISTEARATE	516
05G - Tonics, Dressings, and Other Hair Grooming Aids	GLYCOL DISTEARATE	1

05I - Other Hair Preparations	GLYCOL DISTEARATE	3
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	GLYCOL DISTEARATE	455
06B - Hair Tints	GLYCOL DISTEARATE	22
06D - Hair Shampoos (coloring)	GLYCOL DISTEARATE	10
06G - Hair Bleaches	GLYCOL DISTEARATE	4
06H - Other Hair Coloring Preparation	GLYCOL DISTEARATE	3
07I - Other Makeup Preparations	GLYCOL DISTEARATE	1
10A - Bath Soaps and Detergents	GLYCOL DISTEARATE	210
10C - Douches	GLYCOL DISTEARATE	1
10E - Other Personal Cleanliness Products	GLYCOL DISTEARATE	129
11E - Shaving Cream	GLYCOL DISTEARATE	5
11F - Shaving Soap	GLYCOL DISTEARATE	1
11G - Other Shaving Preparation Products	GLYCOL DISTEARATE	1
12A - Cleansing	GLYCOL DISTEARATE	115
12C - Face and Neck (exc shave)	GLYCOL DISTEARATE	6
12D - Body and Hand (exc shave)	GLYCOL DISTEARATE	7
12F - Moisturizing	GLYCOL DISTEARATE	5
12G - Night	GLYCOL DISTEARATE	3
12H - Paste Masks (mud packs)	GLYCOL DISTEARATE	2
12I - Skin Fresheners	GLYCOL DISTEARATE	1
12J - Other Skin Care Preps	GLYCOL DISTEARATE	9
13A - Suntan Gels, Creams, and Liquids	GLYCOL DISTEARATE	1
		1613

03A - Eyebrow Pencil	NEOPENTYL GLYCOL DICAPRATE	1
03E - Eye Makeup Remover	NEOPENTYL GLYCOL DICAPRATE	3
03G - Other Eye Makeup Preparations	NEOPENTYL GLYCOL DICAPRATE	1
07A - Blushers (all types)	NEOPENTYL GLYCOL DICAPRATE	12
07C - Foundations	NEOPENTYL GLYCOL DICAPRATE	3
07E - Lipstick	NEOPENTYL GLYCOL DICAPRATE	18
07I - Other Makeup Preparations	NEOPENTYL GLYCOL DICAPRATE	1
11D - Preshave Lotions (all types)	NEOPENTYL GLYCOL DICAPRATE	2
12C - Face and Neck (exc shave)	NEOPENTYL GLYCOL DICAPRATE	6
12D - Body and Hand (exc shave)	NEOPENTYL GLYCOL DICAPRATE	1
12F - Moisturizing	NEOPENTYL GLYCOL DICAPRATE	3
12J - Other Skin Care Preps	NEOPENTYL GLYCOL DICAPRATE	6
		57

01B - Baby Lotions, Oils, Powders, and Creams	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
02A - Bath Oils, Tablets, and Salts	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
03C - Eye Shadow	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
03D - Eye Lotion	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
05A - Hair Conditioner	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	2
05I - Other Hair Preparations	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	3
07A - Blushers (all types)	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
07C - Foundations	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	7
07E - Lipstick	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	13
07F - Makeup Bases	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	2
07I - Other Makeup Preparations	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	3
11A - Aftershave Lotion	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	2
11E - Shaving Cream	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
12A - Cleansing	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	5
12C - Face and Neck (exc shave)	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	3
12D - Body and Hand (exc shave)	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	12
12F - Moisturizing	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	9
12G - Night	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	5
12J - Other Skin Care Preps	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	4
13B - Indoor Tanning Preparations	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
13C - Other Suntan Preparations	NEOPENTYL GLYCOL DICAPRYLATE/DICAPRATE	1
		82

03A - Eyebrow Pencil	NEOPENTYL GLYCOL DIETHYLHEXANOATE	4
03B - Eyeliner	NEOPENTYL GLYCOL DIETHYLHEXANOATE	3
03C - Eye Shadow	NEOPENTYL GLYCOL DIETHYLHEXANOATE	3

03D - Eye Lotion	NEOPENTYL GLYCOL DIETHYLHEXANOATE	3
03G - Other Eye Makeup Preparations	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
05A - Hair Conditioner	NEOPENTYL GLYCOL DIETHYLHEXANOATE	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	NEOPENTYL GLYCOL DIETHYLHEXANOATE	5
05I - Other Hair Preparations	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
07A - Blushers (all types)	NEOPENTYL GLYCOL DIETHYLHEXANOATE	2
07B - Face Powders	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
07C - Foundations	NEOPENTYL GLYCOL DIETHYLHEXANOATE	7
07E - Lipstick	NEOPENTYL GLYCOL DIETHYLHEXANOATE	11
07F - Makeup Bases	NEOPENTYL GLYCOL DIETHYLHEXANOATE	3
07I - Other Makeup Preparations	NEOPENTYL GLYCOL DIETHYLHEXANOATE	5
10E - Other Personal Cleanliness Products	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
12A - Cleansing	NEOPENTYL GLYCOL DIETHYLHEXANOATE	2
12C - Face and Neck (exc shave)	NEOPENTYL GLYCOL DIETHYLHEXANOATE	3
12D - Body and Hand (exc shave)	NEOPENTYL GLYCOL DIETHYLHEXANOATE	3
12F - Moisturizing	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
12G - Night	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
12H - Paste Masks (mud packs)	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
12J - Other Skin Care Preps	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
13B - Indoor Tanning Preparations	NEOPENTYL GLYCOL DIETHYLHEXANOATE	1
		65

03C - Eye Shadow	NEOPENTYL GLYCOL DIHEPTANOATE	6
03D - Eye Lotion	NEOPENTYL GLYCOL DIHEPTANOATE	9
03G - Other Eye Makeup Preparations	NEOPENTYL GLYCOL DIHEPTANOATE	6
04B - Perfumes	NEOPENTYL GLYCOL DIHEPTANOATE	1
04E - Other Fragrance Preparation	NEOPENTYL GLYCOL DIHEPTANOATE	5
05A - Hair Conditioner	NEOPENTYL GLYCOL DIHEPTANOATE	3

05E - Rinses (non-coloring)	NEOPENTYL GLYCOL DIHEPTANOATE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	NEOPENTYL GLYCOL DIHEPTANOATE	2
07C - Foundations	NEOPENTYL GLYCOL DIHEPTANOATE	9
07E - Lipstick	NEOPENTYL GLYCOL DIHEPTANOATE	5
07F - Makeup Bases	NEOPENTYL GLYCOL DIHEPTANOATE	4
07I - Other Makeup Preparations	NEOPENTYL GLYCOL DIHEPTANOATE	3
10A - Bath Soaps and Detergents	NEOPENTYL GLYCOL DIHEPTANOATE	1
10E - Other Personal Cleanliness Products	NEOPENTYL GLYCOL DIHEPTANOATE	1
12C - Face and Neck (exc shave)	NEOPENTYL GLYCOL DIHEPTANOATE	10
12D - Body and Hand (exc shave)	NEOPENTYL GLYCOL DIHEPTANOATE	27
12F - Moisturizing	NEOPENTYL GLYCOL DIHEPTANOATE	230
12G - Night	NEOPENTYL GLYCOL DIHEPTANOATE	5
12J - Other Skin Care Preps	NEOPENTYL GLYCOL DIHEPTANOATE	9
		337

07E - Lipstick	NEOPENTYL GLYCOL DIISOSTEARATE	1
07I - Other Makeup Preparations	NEOPENTYL GLYCOL DIISOSTEARATE	1
13B - Indoor Tanning Preparations	NEOPENTYL GLYCOL DIISOSTEARATE	1
		3

03D - Eye Lotion	PROPANEDIOL DICAPRYLATE	2
12C - Face and Neck (exc shave)	PROPANEDIOL DICAPRYLATE	1
12D - Body and Hand (exc shave)	PROPANEDIOL DICAPRYLATE	1
12F - Moisturizing	PROPANEDIOL DICAPRYLATE	2
12H - Paste Masks (mud packs)	PROPANEDIOL DICAPRYLATE	1
		7

12F - Moisturizing	PROPANEDIOL DICAPRYLATE/CAPRATE	2

There were no reported uses in the VCRP for:

1. 1,4-Butanediol Bisdecanoate
2. Butylene Glycol Diisononanoate
3. Butylethylpropanediol Dimer Dilinoleate
4. Diethylpentanediol Dineopentanoate
5. Dioctadecanyl Didecyltetradecanoate
6. Dioctadecanyl Ditetradecyloctadecanoate
7. Glycol Dibehenate
8. Glycol Diethylhexanoate
9. Glycol Dilaurate
10. Glycol Dioleate
11. Glycol Dipalmate/Palm Kernelate/Olivate/Macadamiate
12. Glycol Dipalmate/Rapeseedate/Soyate
13. Glycol Dipivalate
14. Glycol Ditallowate
15. Hexanediol Distearate
16. 1,2-Hexanediyl Dicaprate
17. Neopentyl Glycol Dicaprylate/Dipelargonate/Dicaprate
18. Neopentyl Glycol Diisononanoate
19. Neopentyl Glycol Dilaurate
20. Propanediol Diisostearate
21. Propanediol Dipelargonate

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 20, 2016

SUBJECT: Information Propanediol Dipelargonate, Propanediol Dicaprylate/Caprate and Neopentyl Glycol Diethylhexanoate

AMA Laboratories, Inc. 2011. 50 Human subject repeat insult patch test skin irritation/sensitization evaluation (occlusive patch) of Propanediol Dipelargonate.

AMA Laboratories, Inc. 2009. 50 Human subject repeat insult patch test skin irritation/sensitization evaluation (occlusive patch) of Propanediol Dicaprylate/Caprate.

Consumer Product Testing Co. 2010. The MatTek Corporation EpiOcular™ tissue model *in vitro* toxicity testing system - Propanediol Dicaprylate/Caprate.

Nelson Laboratories. 2013. The *Salmonella typhimurium* reverse mutation assay (Ames Test), liquids or soluble chemicals GLP report - Propanediol Dicaprylate/Caprate.

AMA Laboratories, Inc. 2006. 50 Human subject repeat insult patch test skin irritation/sensitization evaluation (occlusive patch) of Neopentyl Glycol Diethylhexanoate.

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50 HUMAN SUBJECT REPEAT INSULT PATCH TEST SKIN IRRITATION/SENSITIZATION EVALUATION (Occlusive Patch)

Propanediol Dipelargonate

AMA Ref. No.: MS11.RIPT.M1305O.50.PCI

Date: October 13, 2011

Sponsor: Phoenix Chemical, Inc.
60 Fourth Street
Somerville, New Jersey 08876

1.0 Objective:

Consumer products or raw materials designed for consistent reapplication to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/sensitization potential if such exists.

2.0 Test Material:

2.1 Test Material Description:

On July 29, 2011 one test sample labeled PELEMOL P-99, Lot # B07411 was received from Phoenix Chemical, Inc. and assigned AMA Lab No. M-1305.

2.2 Handling:

Upon arrival at AMA Laboratories, Inc., the test material is assigned a unique laboratory code number and entered into a daily log identifying the lot number, sample description, sponsor, date received and tests requested.

Samples are retained for a period of three months beyond submission of final report unless otherwise specified by the sponsor or, if sample is known to be in support of governmental applications, representative retained samples are kept two years beyond final report submission.

Sample disposition is conducted in compliance with appropriate federal, state and local ordinances.

2.3 Test Material Evaluation Prerequisite:

Prior to induction of a human test panel, toxicology, microbiology or in-vitro performance spectra may be required to assess the feasibility of commencement as dictated by an Institutional Review Board (IRB) described in Section 3.0.

Sponsor purports that prior to sample submission the following tests were conducted with no adverse results and that the test data are on file on their premises and have not been made available to AMA personnel:

- USP or CTFA Preservative Efficacy Test or equivalent
- 90 Day Accelerated Stability and Container Compatibility Study

3.0 Institutional Review Board:

Reference: CFR Title 21 Part 56, Subparts A, B, C, and D. The IRB of AMA Laboratories, Inc., consists of five or more individuals, chosen from within the company for technical expertise and from the local community for lay interaction. The list of IRB members is kept on file at AMA Laboratories, Inc. and is available for inspection during the hours of operation.

4.0 Panel Selection:

4.1 Standards for Inclusion in a Study:

- Individuals who are not currently under a doctor's care.
- Individuals free of any dermatological or systemic disorder which would interfere with the results, at the discretion of the Investigator.
- Individuals free of any acute or chronic disease that might interfere with or increase the risk of study participation.
- Individuals who will complete a preliminary medical history form mandated by AMA Laboratories, Inc. and are in general good health.
- Individuals, who will read, understand and sign an informed consent document relating to the specific type of study they are subscribing. Consent forms are kept on file and are available for examination on the premises of AMA Laboratories, Inc. only.
- Individuals able to cooperate with the Investigator and research staff, willing to have test materials applied according to the protocol, and complete the full course of the study.

4.2 Standards for Exclusion from a Study:

- Individuals under 18 years of age.
- Individuals who are currently under a doctor's care.
- Individuals who are currently taking any medication (topical or systemic) that may mask or interfere with the test results.
- Subjects with a history of any acute or chronic disease that might interfere with or increase the risk associated with study participation.
- Individuals diagnosed with chronic skin allergies.
- Female volunteers who indicate that they are pregnant or lactating.

4.3 Recruitment:

Panel selection is accomplished by advertisements in local periodicals, community bulletin boards, phone solicitation, electronic media or any combination thereof.

4.4 Informed Consent and Medical History Forms:

An informed consent was obtained from each volunteer prior to initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment and their limits of liability. Panelists signed and dated the informed consent document to indicate their authorization to proceed and acknowledge their understanding of the contents. Each subject was assigned a permanent identification number and completed an extensive medical history form. These forms along with the signed consent forms, are available for inspection on the premises of AMA Laboratories, Inc. only. Reference 21 CFR Ch. 1 Part 50, Subpart B.

The parties agree to comply with applicable state and federal privacy laws for the use and disclosure of a subject's personal health information by taking reasonable steps to protect the confidentiality of this information. This obligation shall survive the termination or expiration of this Agreement.

5.0 Population Demographics:

Number of subjects enrolled		52
Number of subjects completing study		50
Age Range		18-69
Sex	Male	9
	Female	43
Race	Caucasian	40
	Hispanic	12
	Asian	0

6.0 Equipment:

- Patch Description: Parke-Davis Hypoallergenic Readi Bandages or the equivalent.
- 1ml volumetric syringe without a needle.

7.0 Procedure:

- Subjects are requested to bathe or wash as usual before arrival at the facility.
- 0.2 ml or 0.2g of the test material is dispensed onto the occlusive, hypoallergenic patch.
- The patch is then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject is dismissed with instructions not to wet or expose the test area to direct sunlight.
- After 24 hours the patch is removed by the panelist at home.
- This procedure is repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday, and Friday for three consecutive weeks.
- In the event of an adverse reaction, the area of erythema and edema is measured. The edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions are scored just before applications two through nine and the next test date following application nine. In most instances this is approximately 24 hours after patch removal. Clients are notified immediately in the case of adverse reaction and determination is made as to treatment program if necessary.
- Subjects are then given a 10 - 14 day rest period after which a challenge or retest dose is applied once to a previously unexposed test site. The retest dose is equivalent to any one of the original nine exposures. Reactions are scored 24 and 48 hours after application.
- Comparison is made between the nine inductive responses and the retest dose.

8.0 Results:

Please refer to attached Table.

9.0 Observations:

No adverse reactions of any kind were noted during the course of this study.

10.0 Archiving:

All original samples, raw data sheets, technician's notebooks, correspondence files and copies of final reports and remaining specimens are maintained on premises of AMA Laboratories, Inc. in limited access storage files marked "Archive". A duplicate disk copy of final reports is separately archived in a bank safe deposit vault.

11.0 Reference:

Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, published by The Association of Food and Drug Officials of The United States, 1965 (modified).

12.0 Security Label Disclosure:

To prevent loss of and protect intellectual property, original, certified documents issued by AMA Laboratories Inc. can be identified by a proprietary, tamper evident security hologram affixed to all Conclusion/Signature pages on final reports. Any attempt to remove the hologram will irreversibly damage the label and leave an immediate trace, thus invalidating the document.

Only reports containing the AMA LABS, INC. hologram will be recognized by AMA Laboratories Inc. as a certified original.

13.0 Conclusions:

The test material (AMA Lab. No.: M-1305; Client No.: PELEMOL P-99, Lot # B07411) when tested under occlusion as described herein, may be considered:
a **NON-PRIMARY IRRITANT** and **NON-PRIMARY SENSITIZER** to the skin according to the reference.

Mayya Tafsene, M.D.
Study Director

Breanna Wanamaker, A.A. (Candidate)
Technician

David R. Winne, B.S.
Technical Director

10/13/11
Date

TABLE
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: M-1305
Client No.: PELEMOL P-99, Lot # B07411

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
1	34 1401	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
2	36 8618	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
3	36 9096	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
4	40 1274	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
5	40 2040	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
6	44 1289	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
7	44 9258	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
8	46 4172	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
9	46 8676	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
10	48 0946	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
11	48 3564	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
12	50 2448	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
13	50 7349	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
14	52 3942	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
15	54 1112	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
16	54 3415	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
17	54 4138	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
18	54 6537	C	M	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
19	54 7235	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
20	54 7647	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
21	54 7891	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
22	56 1816	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
23	56 3465	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
24	57 1504	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
25	60 1825	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
26	60 4534	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
27	62 0840	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
28	62 2960	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
29	62 9835	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

TABLE (CONT'D)
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: M-1305
Client No.: PELEMOL P-99, Lot # B07411

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
30	64 6740	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
31	66 1649	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
32	66 6606	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
33	72 3555	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
34	76 0532	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
35	76 0933	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
36	76 1298	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
37	76 2519	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
38	76 8279	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
39	76 8434	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
40	78 7400	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
41	78 8079	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
42	80 1611	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
43	80 4126	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
44	80 7273	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
45	80 8499	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
46	82 0569	H	F	0	0	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
47	82 0760	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
48	82 4417	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
49	82 6224	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
50	82 6807	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
51	82 7507	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
52	87 6602	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0

Evaluation Period:

This study was conducted from September 7, 2011 through October 12, 2011.

Scoring Scale and Definition of Symbols Shown in Table:

0 - No evidence of any effect

? - (Barely perceptible) minimal faint (light pink) uniform or spotty erythema

1 - (Mild) pink uniform erythema covering most of contact site

2 - (Moderate) pink\red erythema visibly uniform in entire contact area

3 - (Marked) bright red erythema with accompanying edema, petechiae or papules

4 - (Severe) deep red erythema with vesiculation or weeping with or without edema

D - Patch eliminated due to reaction

Dc - Discontinued due to absence of subject on application date

M - Patch applied to an adjacent site after strong test reaction

N/A - Score is not calculated for subjects discontinued before challenge

S - Skin stained from pigment in product

T - Tan

NOTE: All technical employees of AMA LABORATORIES, INC. are required to take and pass a visual discrimination examination conducted by a Board Certified Ophthalmologist using the Farnsworth-Munsell 100 Hue Test as published; which determines a person's ability to discern color against a black background. This test was additionally modified to include a flesh tone background more nearly approaching actual use conditions, wherein erythematous skin is graded according to intensity.

14.0 Quality Assurance Statement:

This study was inspected in accordance with the Standard Operating Procedures of AMA Laboratories, Inc. To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the study records and report.

Report reviewed by:

Tasmiya Masud, B.A.
Quality Assurance Supervisor

10/13/11
Date

AMA LABORATORIES, INC.
216 Congers Road, Bldg. 1
New City, NY 10956 USA
(845) 634-4330
FAX: (845) 634-5565
www.amalabs.com

50 HUMAN SUBJECT REPEAT INSULT PATCH TEST SKIN IRRITATION/SENSITIZATION EVALUATION (Occlusive Patch)

Propanediol Dicaprylate / Caprate

AMA Ref. No.: MS09.RIPT.L6034O.50.PCI

Date: November 30, 2009

Sponsor: Phoenix Chemical, Inc.
60 Fourth Street
Somerville, New Jersey 08876

1.0 Objective:

Consumer products or raw materials designed for consistent reapplication to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/sensitization potential if such exists.

2.0 Test Material:

2.1 Test Material Description:

On September 28, 2009 one test sample labeled PELEMOL P-810, Lot # LRL02-245 was received from Phoenix Chemical, Inc. and assigned AMA Lab No. L-6034.

2.2 Handling:

Upon arrival at AMA Laboratories, Inc., the test material is assigned a unique laboratory code number and entered into a daily log identifying the lot number, sample description, sponsor, date received and tests requested.

Samples are retained for a period of three months beyond submission of final report unless otherwise specified by the sponsor or, if sample is known to be in support of governmental applications, representative retained samples are kept two years beyond final report submission.

Sample disposition is conducted in compliance with appropriate federal, state and local ordinances.

2.3 Test Material Evaluation Prerequisite:

Prior to induction of a human test panel, toxicology, microbiology or in-vitro performance spectra may be required to assess the feasibility of commencement as dictated by an Institutional Review Board (IRB) described in Section 3.0.

Sponsor purports that prior to sample submission the following tests were conducted with no adverse results and that the test data are on file on their premises and have not been made available to AMA personnel:

- USP or CTFA Preservative Efficacy Test or equivalent
- 90 Day Accelerated Stability and Container Compatibility Study

3.0 Institutional Review Board:

Reference: CFR Title 21 Part 56, Subparts A, B, C, and D. The IRB of AMA Laboratories, Inc., consists of five or more individuals, chosen from within the company for technical expertise and from the local community for lay interaction. The list of IRB members is kept on file at AMA Laboratories, Inc. and is available for inspection during the hours of operation.

4.0 Panel Selection:

4.1 Standards for Inclusion in a Study:

- Individuals who are not currently under a doctor's care.
- Individuals free of any dermatological or systemic disorder which would interfere with the results, at the discretion of the Investigator.
- Individuals free of any acute or chronic disease that might interfere with or increase the risk of study participation.
- Individuals who will complete a preliminary medical history form mandated by AMA Laboratories, Inc. and are in general good health.
- Individuals, who will read, understand and sign an informed consent document relating to the specific type of study they are subscribing. Consent forms are kept on file and are available for examination on the premises of AMA Laboratories, Inc. only.
- Individuals able to cooperate with the Investigator and research staff, willing to have test materials applied according to the protocol, and complete the full course of the study.

4.2 Standards for Exclusion from a Study:

- Individuals under 18 years of age.
- Individuals who are currently under a doctor's care.
- Individuals who are currently taking any medication (topical or systemic) that may mask or interfere with the test results.
- Subjects with a history of any acute or chronic disease that might interfere with or increase the risk associated with study participation.
- Individuals diagnosed with chronic skin allergies.
- Female volunteers who indicate that they are pregnant or lactating.

4.3 Recruitment:

Panel selection is accomplished by advertisements in local periodicals, community bulletin boards, phone solicitation, electronic media or any combination thereof.

4.4 Informed Consent and Medical History Forms:

An informed consent was obtained from each volunteer prior to initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment and their limits of liability. Panelists signed and dated the informed consent document to indicate their authorization to proceed and acknowledge their understanding of the contents. Each subject was assigned a permanent identification number and completed an extensive medical history form. These forms along with the signed consent forms, are available for inspection on the premises of AMA Laboratories, Inc. only. Reference 21 CFR Ch. 1 Part 50, Subpart B.

The parties agree to comply with applicable state and federal privacy laws for the use and disclosure of a subject's personal health information by taking reasonable steps to protect the confidentiality of this information. This obligation shall survive the termination or expiration of this Agreement.

5.0 Population Demographics:

Number of subjects enrolled		52
Number of subjects completing study		50
Age Range		20-66
Sex	Male	7
	Female	45
Race	Caucasian	43
	Hispanic	8
	Asian	1

6.0 Equipment:

- Patch Description: Parke-Davis Hypoallergenic Readi Bandages or the equivalent.
- 1ml volumetric syringe without a needle.

7.0 Procedure:

- Subjects are requested to bathe or wash as usual before arrival at the facility.
- 0.2 ml or 0.2g of the test material is dispensed onto the occlusive, hypoallergenic patch.
- The patch is then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject is dismissed with instructions not to wet or expose the test area to direct sunlight.
- After 24 hours the patch is removed by the panelist at home.
- This procedure is repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday, and Friday for three consecutive weeks.
- In the event of an adverse reaction, the area of erythema and edema is measured. The edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions are scored just before applications two through nine and the next test date following application nine. In most instances this is approximately 24 hours after patch removal. Clients are notified immediately in the case of adverse reaction and determination is made as to treatment program if necessary.
- Subjects are then given a 10 - 14 day rest period after which a challenge or retest dose is applied once to a previously unexposed test site. The retest dose is equivalent to any one of the original nine exposures. Reactions are scored 24 and 48 hours after application.
- Comparison is made between the nine inductive responses and the retest dose.

8.0 Results:

Please refer to attached Table.

9.0 Observations:

No adverse reactions of any kind were noted during the course of this study.

10.0 Archiving:

All original samples, raw data sheets, technician's notebooks, correspondence files and copies of final reports and remaining specimens are maintained on premises of AMA Laboratories, Inc. in limited access storage files marked "Archive". A duplicate disk copy of final reports is separately archived in a bank safe deposit vault.

11.0 Reference:

Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, published by The Association of Food and Drug Officials of The United States, 1965 (modified).

12.0 Conclusions:

The test material (AMA Lab. No.: L-6034; Client No.: PELEMOL P-810, Lot # LRL02-245) when tested under occlusion as described herein, may be considered:
a **NON-PRIMARY IRRITANT** and **NON-PRIMARY SENSITIZER** to the skin according to the reference.

Mayya Tafsene, M.D.
Study Director

Patrycja Biehias, M.S.
Technician

David R. Winne, B.S.
Technical Director

11/30/09
Date

TABLE
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: L-6034
Client No.: PELEMOL P-810, Lot # LRL02-245

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
1	08 4686	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
2	11 5901	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
3	32 4178	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
4	36 4104	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
5	36 7304	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
6	38 7929	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
7	38 8908	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
8	40 5759	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
9	42 7264	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
10	46 4172	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
11	46 4290	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
12	46 6499	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
13	48 0738	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
14	50 0586	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
15	50 1729	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
16	50 3800	A	M	0	0	0	0	0	0	0	0	0	0	0	0.0
17	50 6005	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
18	52 2296	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
19	52 5000	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
20	52 5059	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
21	52 8736	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
22	54 0763	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
23	54 2951	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
24	54 3957	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
25	54 5333	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
26	56 0412	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
27	56 1615	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
28	56 9543	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
29	58 7412	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

TABLE (CONT'D)
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: L-6034
Client No.: PELEMOL P-810, Lot # LRL02-245

No.	Subject ID	RACE	SEX	Response 1	2	3	4	5	6	7	8	9	Chall. 24 HR	Chall. 48 HR	Score
30	58 8637	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
31	60 3018	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
32	60 4635	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
33	62 9252	C	F	0	0	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
34	62 9431	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
35	64 1949	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
36	64 5526	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
37	64 7220	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
38	64 7558	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
39	68 3625	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
40	70 4212	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
41	70 7314	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
42	71 3180	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
43	72 3637	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
44	72 6941	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
45	74 1855	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
46	74 4878	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
47	76 8113	H	F	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
48	76 8303	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
49	78 4237	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
50	82 6379	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
51	89 1884	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
52	90 6566	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0

Evaluation Period:

This study was conducted from October 21, 2009 through November 25, 2009.

Scoring Scale and Definition of Symbols Shown in Table:

0 - No evidence of any effect

? - (Barely perceptible) minimal faint (light pink) uniform or spotty erythema

1 - (Mild) pink uniform erythema covering most of contact site

2 - (Moderate) pink\red erythema visibly uniform in entire contact area

3 - (Marked) bright red erythema with accompanying edema, petechiae or papules

4 - (Severe) deep red erythema with vesiculation or weeping with or without edema

D - Patch eliminated due to reaction

Dc - Discontinued due to absence of subject on application date

M - Patch applied to an adjacent site after strong test reaction

N/A - Score is not calculated for subjects discontinued before challenge

S - Skin stained from pigment in product

T - Tan

NOTE: All technical employees of AMA LABORATORIES, INC. are required to take and pass a visual discrimination examination conducted by a Board Certified Ophthalmologist using the Farnsworth-Munsell 100 Hue Test as published; which determines a person's ability to discern color against a black background. This test was additionally modified to include a flesh tone background more nearly approaching actual use conditions, wherein erythematous skin is graded according to intensity.

13.0 Quality Assurance Statement:

This study was inspected in accordance with the Standard Operating Procedures of AMA Laboratories, Inc. To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the study records and report.

Report reviewed by:

Kamil Wojtowicz

Kamil Wojtowicz, M.S.
Quality Assurance Supervisor

11/30/09

Date

Consumer Product Testing Co.
EST. 1975

FINAL REPORT

CLIENT:	Phoenix Chemical, Inc. 60 Fourth Street Somerville, New Jersey 08876
ATTENTION:	Lidia Subotkowska
TEST:	The MatTek Corporation EpiOcular™ Tissue Model *In Vitro* Toxicity Testing System
TEST ARTICLE:	Pelemol P810 Propanediol Dicaprylate/Caprate
EXPERIMENT REFERENCE NO.:	V10-2770-2

2/7/10

Steven Nitka
Vice President
Laboratory Director

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

Consumer Product Testing Co.
EST. 1973

QUALITY ASSURANCE UNIT STATEMENT

Study No.: V10-2770-2

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practice principles (including government regulations to the extent applicable) and in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date listed below. The findings of this inspection may have been reported to management and the Study Director.

Date of data inspection: 7/7/10

Quality Assurance:

Signature/Date 7/7/10

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-723
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective:

To evaluate the test article for irritancy potential utilizing the MatTek Corporation EpiOcular *in vitro* toxicity testing system.

Introduction:

"MatTek's patented EpiOcular corneal Model consists of normal, human-derived epidermal keratinocytes which have been cultured to form a stratified, squamous epithelium similar to that found in the cornea. The epidermal cells, which are cultured on specially prepared cell culture inserts using serum free medium, differentiate to form a multilayered structure which closely parallels the corneal epithelium . . . " This system " . . . provides a predictive, morphologically relevant *in vitro* means to assess ocular irritancy."[1]

EpiOcular, when used with the recommended cell metabolism assay, can quickly provide toxicological profiles. The procedure utilizes a water-soluble, yellow, tetrazolium salt (MTT {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide}), which is reduced by succinate dehydrogenase in the mitochondria of viable cells to a purple, insoluble formazan derivative. Substances which damage this mitochondrial enzyme inhibit the reduction of the tetrazolium salt. The amount of MTT reduced by a culture is therefore proportional to the number of viable cells.

Test Article: Pelemol P810

Method:

According to the material receipt letter supplied by the Sponsor, the test article is not wate soluble. As per MatTek's protocol, the test article dosed as received. After the appropriate tissu preparation, 100 microliters of the test article and the negative control (distilled water) were added to the Millicells containing the EpiOcular samples. The six (6) well plates containing the dosed EpiOcular samples were then incubated at 37°C, five (5)% carbon dioxide and ≥ 90% humidity.

[1]MatTek Corporation, 200 Homer Avenue, Ashland, Massachusetts 01721

Method (continued):

After the appropriate exposure period, each insert was individually removed from its plate and rinsed with phosphate buffered saline (PBS) to remove any residual material. Each was then rinsed a second and third time. Following the 3 rinses, each Millicell was submerged in 5 milliliters of assay media for 10 minutes, at room temperature. This final soak removed any residual, absorbed article. After the 10 minutes, excess liquid was shaken off and each EpiOcular tissue was placed into 300 microliters of MTT solution. The EpiOcular samples were then returned to the incubator.

After the three (3) hour MTT exposure, each insert was removed and gently rinsed with PBS to remove any residual MTT solution. Excess PBS was shaken from each of the inserts, which were then blotted on the bottom using paper towels. The inserts were then each placed into one (1) well of a 24 well extraction plate. Each insert was then immersed in two (2) milliliters of extraction, at room temperature, overnight. After the extraction procedure, the liquid within each insert was decanted back into the well from which it was taken. The remaining extractant solution was then agitated and a 200 microliter aliquot of each extract was removed for evaluation. A Dynatech MR 4000 Automatic Microplate Reader was used to determine the absorbance of each extract at 570nm. With the absorbance of the negative control (distilled water) defined as 100%, the percent absorbencies of the articles were determined. The percentages listed below directly correlate with the cell metabolism in the EpiOcular samples.

Results:

Article (% & Exposure)	System	Percent Viability	Percent Inhibition
Pelemol P810			
(100% - 20 min.)	EpiOcular	102	-2
(100% - 1 hr.)	EpiOcular	101	-1
(100% - 4 hr.)	EpiOcular	100	0

When possible, using a semi-log scale, the percent viabilities for the articles were plotted on the linear y axis versus the dosing time on the log x axis. By interpolation, the time at which the percent viability would be 50% was determined (ET-50). As a general guideline (provided by MatTek) the following equation can be used to estimate the rabbit Draize eye score:

$$\text{Draize} = -4.74 + 101.7/(\text{ET-50})^{0.5}$$

Based on the literature (Kay, J.H. and Calandra, J.C., "Interpretation of eye irritation tests," *J. Soc. Cosmetic Chem.*, 13, 281-289 (1962)), the ocular irritancy estimated potential has been categorized by MatTek into the following groups, based on the Draize score:

Draize Score	Irritancy Classification	Example	EpiOcular ET-50 (min)
0-15	Non-irritating, Minimal	PEG-75 Lanolin, Tween 20	>256 – 26.5
15.1 – 25	Mild	3% Sodium Dodecyl Sulfate	<26.5 – 11.7
25.1 – 50	Moderate	5% Triton X-100	<11.7 – 3.45
50.1 – 110	Severe, Extreme	5% Benzalkonium Chloride	<3.45

Discussion:

Under the conditions of this test, the Pelemol P810 test article, at 100%, elicited *in vitro* results which indicate that its ET-50 is greater than 256 minutes. Therefore, the test article, at 100%, has an estimated Draize ocular irritation score of "0" with a "non-irritating" irritancy classification.

Conclusion:

Under the conditions of this test, the results indicate that the Pelemol P810 test article, at 100%, has a "non-irritating" irritancy classification.

Record Retention:

All records and documents pertaining to the conduct of this study shall be retained in the CPTC archives for a minimum of ten (10) years. At any time prior to the completion of the tenth archival year, a Sponsor may submit a written request to the CPTC QA Department to obtain custody of study records once the CPTC archive period has been completed. This transfer shall be performed at the Sponsor's expense. In the absence of a written request, study-related records shall be destroyed at the end of the CPTC archive period in a manner that renders them useless.

Professional personnel involved:

Steven Nitka, B.S.	-	Vice President Laboratory Director (Study Director)
Lillian Vazquez, B.S.	-	Laboratory Supervisor
Sarah A. Nahrebne	-	Quality Assurance Associate

NELSON LABORATORIES

Sponsor:
John Imperante
Phoenix Chemical, Inc.
60 Fourth St.
Somerville NJ 08876

The *Salmonella typhimurium* Reverse Mutation Assay (Ames Test), Liquids or Soluble Chemicals GLP Report

Propanediol Dicaprylate/Caprate

Test Article:	Pelemol P-810; Lot #02398	
Laboratory Number:	665434	
Study Received Date:	29 Nov 2012	
Test Procedure(s):	Standard Test Protocol (STP) Number:	STP0098 Rev 07
	Protocol Detail Sheet (PDS) Number:	201204927 Rev 01

Summary: The *Salmonella typhimurium* reverse mutation assay (Ames test) is used to determine the potential mutagenic activity of the test article by exposing a large number of the test organism to the test article in agar plates. The agar plates are monitored for growth of revertants (organisms mutating to the wild type) which are counted and used to estimate the mutagenic potential of the test article.

The Ames test employs several histidine dependent (His+) strains of *S. typhimurium* which require the amino acid histidine for growth. The test detects mutations which cause the bacterial strains to revert to histidine independent (His-) bacteria which are capable of synthesizing histidine and can grow in the absence of histidine. The assay uses tester strains TA97a, TA98, TA100, TA102 and TA1535 which were selected to detect various types of mutagens. The test is performed both with and without metabolic activation using an S-9 activation system. The S-9 activation system is designed to simulate mammalian liver enzyme systems and is used to detect substances which undergo metabolic activation from non-mutagenic forms.

All test method acceptance criteria were met.

Results: The results are calculated using a validated computer program. Manual calculations may differ slightly due to rounding. All results greater than 300 colony forming units (CFU) are considered estimates.

The test article concentration did not produce a two-fold or three-fold increase in the number of revertants. The spot tests showed no zone of increased reversion or of toxicity. In summary, the test article concentration tested against the five strains did not meet the criteria for a potential mutagen.

Brittany Scott
Study Director — Brittany Scott, M.S. RM(NRCM)

17 Jan 2013
Study Completion Date

TA97a (Number of Revertants): Percent of control results greater than (>) 200 qualify as positive according to the test acceptance criteria. The expected result for the chemical controls is included as ± in the parentheses ( ).

Results Without Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	74	95	102	90	N/A
Test Article 5 µL/plate	86	86	104	92	102
NPD	435	392	335	387	429 (+)
Results With S-9 Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	151	126	123	133	N/A
Test Article 5 µL/plate	95	130	113	113	85
2-AF	1,509	1,141	1,315	1,322	991 (+)

TA98 (Number of Revertants): Percent of control results greater than (>) 300 qualify as positive according to the test acceptance criteria. The expected result for the chemical controls is included as ± in the parentheses ( ).

Results Without Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	20	20	23	21	N/A
Test Article 5 µL/plate	22	28	25	25	119
NPD	692	691	630	671	3,195 (+)
Results With S-9 Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	29	32	30	30	N/A
Test Article 5 µL/plate	28	27	32	29	96
2-AF	2,863	2,864	2,848	2,858	9,423 (+)

TA100 (Number of Revertants): Percent of control results greater than (>) 200 qualify as positive according to the test acceptance criteria. The expected result for the chemical controls is included as ± in the parentheses ( ).

Results Without Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	74	90	61	75	N/A
Test Article 5 µL/plate	72	80	106	86	115
Sodium Azide	981	958	945	961	1,282 (+)
Results With S-9 Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	90	78	73	80	N/A
Test Article 5 µL/plate	65	79	80	75	93
2-AF	1,612	2,378	2,270	2,087	2,598 (+)

TA102 (Number of Revertants): Percent of control results greater than (>) 200 qualify as positive according to the test acceptance criteria. The expected result for the chemical controls is included as ± in the parentheses ( ).

Results Without Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	368	364	362	365	N/A
Test Article 5 µL/plate	373	368	379	373	102
Mitomycin-C	2,047	2,343	2,504	2,298	630 (+)
Results With S-9 Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	392	445	457	431	N/A
Test Article 5 µL/plate	401	401	438	413	96
2-AA	1,629	1,562	1,658	1,616	375 (+)

TA1535 (Number of Revertants): Percent of control results greater than (>) 300 qualify as positive according to the test acceptance criteria. The expected result for the chemical controls is included as ± in the parentheses ( ).

Results Without Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	16	23	19	19	N/A
Test Article 5 µL/plate	27	19	18	21	110
Sodium Azide	1,156	1,191	1,266	1,204	6,229 (+)
Results With S-9 Activation					
Identification	Plate Count Results			Average	Percent of Control
Solvent Control	9	10	16	12	N/A
Test Article 5 µL/plate	9	6	13	9	80
2-AA	182	176	210	189	1,623 (+)

Spot Test: Results for the spot tests recorded as + (positive) or - (negative). A positive result indicates that the material showed a zone of increased reversion at the inoculation site. A negative result indicates that the material did not show a zone of increased reversion or toxicity at the inoculation site.

Results Without Activation					
Identification	TA97A	TA98	TA100	TA102	TA1535
Test Article	-	-	-	-	-
Results With S-9 Activation					
Identification	TA97A	TA98	TA100	TA102	TA1535
Test Article	-	-	-	-	-

Acceptance Criteria: The criteria for acceptance of the test and criteria for determination of a mutagen are listed below.

1) Tested strains for genotype verification and achieved the appropriate responses.
2) All chemical controls included in the test gave the appropriate responses.
3) The reversion rates for each tester strain were within the historical ranges as outlined in the protocol. Historical data are constantly changing, as new data from acceptable tests are created. Therefore, reversion rates may differ slightly.

Criteria for a Mutagen:

1) A reversion rate greater than 200% of the solvent control in strains TA97a, TA100 and TA102. A reversion rate greater than 300% of the solvent control in strains TA98 and TA1535.

2) Demonstration of a clear dose related response when dilutions are tested.

Criteria for a Non-Mutagen:

1) A reversion rate less than or equal to 200% of the solvent control in strains TA97a, TA100 and TA102. A reversion rate less than or equal to 300% of the solvent control in strains TA98 and TA1535.

2) No dose related response when dilutions are tested.

Procedure:

Broth Culture Preparation: Commercial culture discs were used to inoculate nutrient broth for testing. The cultures were incubated at 37 ± 2°C for 10-14 hours on an orbital shaker or until when measured spectrophotometrically at 660 nm, an absorbance reading of approximately 1.0 to 2.0 was obtained. Validation data of the cultures showed absorbance readings in the above range resulted in concentrations of approximately 10^9 CFU/mL.

Strain Genotype Verification: The strains used for the test were checked for presence of appropriate strain genotype characteristics. These tests included verification of the following:

- Presence of uvrB mutation
- Presence or absence of R-factor plasmid
- Presence of rfa mutation
- Requirement for histidine

The uvrB mutation was verified by demonstrating UV sensitivity (lack of repair system). The R-factor was checked by determining sensitivity or resistance to ampicillin (0.08% in 0.02 NaOH). The presence of the rfa mutation was verified by demonstrating sensitivity to crystal violet (0.1% in water) on nutrient agar plates. The histidine requirement was assured by plating onto minimal glucose agar plates spread with 0.1 mL of 0.5 mM biotin and both with and without 0.1 mL of 0.1 M histidine.

Test Article Preparation: The test article was diluted in dimethyl sulfoxide (DMSO) and tested at the following concentration: 5 µL/plate. An aliquot of the solvent used was included and tested as the negative control.

Metabolic Activation System: The S-9 activation system was used to screen for the presence of mutagens from byproducts of the test article. Rat liver S-9 homogenate was obtained from Molecular Toxicology, Inc. The homogenate was kept frozen at ≤ -60°C upon receipt. Plates requiring activation contained approximately 20 µL S-9 per plate. When working with soft agar the plates did not exceed 47°C.

Top Agar Preparation: Aliquots of top agar were melted and maintained at 45 ± 2°C. Each 100 mL aliquot of top agar was fortified with 5-10 mL of 0.5 mM biotin and 0.5 mM histidine prior to use.

Plate Incorporation Tests: Each test article concentration and the solvent control were tested both with and without S-9 metabolic activation. The S-9 specific chemical controls (2-aminofluorene and 2-aminoanthracene) were tested with S-9 metabolic activation only. Strain specific non-metabolic chemical controls were also included (Sodium Azide, Mitomycin-C and 4-nitro-0-phenylene-diamine). The non-metabolic chemical controls were tested without S-9 activation only.

Sterile 13 x100 mm test tubes were transferred to a waterbath held at 45 ± 2°C. Two mL allquots of top agar were transferred to each test tube. Three replicates for each test article or control were prepared. The test organism and materials were added as specified in the table below:

Identification	Added/Replicate
Solvent Controls	2 mL top agar, 100 µL test organism and 100 µL of the solvent control.
Test Article	2 mL top agar, 100 µL test organism and 100 µL of each test article.
Chemical Controls	2 mL top agar, 100 µL test organism and 10 µL of the specified chemical.

Each replicate requiring S-9 metabolic activation had 0.5 mL of the prepared S-9 mix added.

The replicates were vortexed, poured onto MGPA plates, swirled to form an even layer and allowed to solidify. The plates were incubated for growth 37 ± 2°C for 48-72 hours.

Spot Tests: The test article was also analyzed using the spot method on plates with and without the S-9 activation system. Two mL aliquots of the top agar mixture and 100 µL of the appropriate test organism were added to minimal glucose agar plates. The plates were allowed to harden then 10 µL of the test article was added as a spot on the surface of the plate. The plates were incubated for growth of the organisms at 37 ± 2°C for 48-72 hours.

Chemical Control Materials: The following chemical controls were used. The concentrations listed are the amount added per plate: 1.5 µg Sodium Azide, 2.5 µg Mitomycin-C, 20 µg 4-nitro-0-phenylene-diamine (NPD), 20 µg 2-aminofluorene (2-AF) and 7 µg 2-aminoanthracene (2-AA). The chemical controls were tested using the plate incorporation method only.

Historical Data 2011							
Strain TA97a without S9 Activation				Strain TA97a with S9 Activation			
Saline or Water	DMSO	PEG 400	NPD	Saline or Water	DMSO	PEG 400	2-AF
Minimum							
81	90	96	251	103	113	114	392
Maximum							
160	135	165	641	185	159	203	1435
Mean							
116	112	122	434	136	131	145	854
Standard Deviation							
16	12	15	91	17	15	19	194

Historical Data 2011							
Strain TA98 without S9 Activation				Strain TA98 with S9 Activation			
Saline or Water	DMSO	PEG 400	NPD	Saline or Water	DMSO	PEG 400	2-AF
Minimum							
14	13	18	404	19	16	17	1027
Maximum							
84	46	82	792	91	53	92	2867
Mean							
32	27	31	562	39	33	39	2017
Standard Deviation							
15	10	13	94	16	10	15	307

Historical Data 2011							
Strain TA100 without S9 Activation				Strain TA100 with S9 Activation			
Saline or Water	DMSO	PEG 400	Sodium Azide	Saline or Water	DMSO	PEG 400	2-AF
Minimum							
99	101	102	794	102	98	105	867
Maximum							
250	154	249	1508	170	159	187	2200
Mean							
136	125	143	1169	132	128	138	1492
Standard Deviation							
29	18	35	178	19	17	22	280

Historical Data 2011							
Strain TA102 without S9 Activation				Strain TA102 with S9 Activation			
Saline or Water	DMSO	PEG 400	Mitomycin C	Saline or Water	DMSO	PEG 400	2-AA
Minimum							
278	306	284	332	350	382	362	880
Maximum							
543	553	519	1943	678	630	622	3889
Mean							
377	386	387	1264	470	477	475	2655
Standard Deviation							
57	62	54	350	71	64	67	541

Historical Data 2011							
Strain TA1535 without S9 Activation				Strain TA1535 with S9 Activation			
Saline or Water	DMSO	PEG 400	Sodium Azide	Saline or Water	DMSO	PEG 400	2-AA
Minimum							
11	12	8	675	8	10	9	46
Maximum							
73	49	81	1290	65	22	80	227
Mean							
21	20	20	931	15	14	15	119
Standard Deviation							
13	10	15	168	8	4	12	43

Quality Assurance Statement

Compliance Statement: The test was conducted in accordance with the USFDA (21 CFR Part 58) Regulations.

Activity	Date
Study Initiation	06 Dec 2012
Audit Performed by Quality Assurance	14 Jan 2013
Audit Results Reported to Study Director	15 Jan 2013
Audit Results Reported to Management	15 Jan 2013

Scientists	Title
Chad Summers	Supervisor
Brittany Scott	Study Director

Data Disposition: The raw data and final report from this study are archived at NLI or an approved off-site location.

Quality Assurance

18 Jan 2013
Date

AMA LABORATORIES, INC.
216 Congers Road, Bldg. 1
New City, NY 10956 USA
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FAX: (845) 634-5565
www.amalabs.com

50 HUMAN SUBJECT REPEAT INSULT PATCH TEST SKIN IRRITATION/SENSITIZATION EVALUATION (Occlusive Patch)

Neopentyl Glycol Diethylhexanoate

Date: October 13, 2006

AMA Ref. No.: MS06.RIPT.K9415O.50.PCI

Sponsor: Phoenix Chemical, Inc.
60 Fourth Street
Somerville, New Jersey 08876

1.0 Objective: Consumer products or raw materials designed for consistent reapplication to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certaln individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/ sensitization potential if such exists.

2.0 Test Material:

2.1 Test Material Description:

On August 28, 2006 one test sample labeled Pelemol NGDO, Lot # AE14AR1 was received from Phoenix Chemical, Inc. and assigned AMA Lab No. K-9415.

2.2 Handling:

Upon arrival at AMA Laboratories, Inc., the test material is assigned a unique laboratory code number and entered into a daily log identifying the lot number, sample description, sponsor, date received and tests requested.

Samples are retained for a period of three months beyond submission of final report unless otherwise specified by the sponsor or, if sample is known to be in support of governmental applications, representative retained samples are kept two years beyond final report submission. Sample disposition ls conducted in compliance with appropriate federal, state and local ordinances.

2.3 Test Material Evaluation Prerequisite:

Prior to induction of a human test panel, toxicology, microbiology or in-vitro performance spectra may be required to assess the feasibility of commencement as dictated by an Institutional Review Board (IRB) described in Section 4.0.

2.31 Sponsor purports that prior to sample submission the following tests were conducted with no adverse results and that the test data are on file on their premises and have not been made available to AMA personnel:

- USP or CTFA Preservative Efficacy Test or equivalent
- 90 Day Accelerated Stability and Container Compatibility Study

3.0 Institutional Review Board:

Reference: CFR Title 21 Part 56, Subparts A, B, C, and D. The IRB of AMA Laboratories, Inc., consists of five or more individuals, chosen from within the company for technical expertise and from the local community for lay interaction. The list of IRB members is kept on file at AMA Laboratories, Inc. and is available for inspection during the hours of operation.

4.0 Panel Selection:

4.1 Standards for Inclusion in a Study:

-Individuals who are not currently under a doctor's care.
-Individuals free of any dermatological or systemic disorder which would interfere with the results, at the discretion of the Investigator.
-Individuals free of any acute or chronic disease that might interfere with or increase the risk of study participation.
-Individuals who will complete a preliminary medical history form mandated by AMA Laboratories, Inc. and are in general good health.
-Individuals who will read, understand and sign an informed consent document relating to the specific type of study they are subscribing. Consent forms are kept on file and are available for examination on the premises of AMA Laboratories, Inc. only.
-Individuals able to cooperate with the Investigator and research staff, be willing to have test materials applied according to the protocol, and complete the full course of the study.

4.2 Standards for Exclusion from a Study:

-Individuals under 18 years of age.
-Individuals who are currently under a doctor's care.
-Individuals who are currently taking any medication (topical or systemic) that may mask or interfere with the test results.
-Subjects with a history of any acute or chronic disease that might interfere with or increase the risk associated with study participation.
-Individuals diagnosed with chronic skin allergies.
-Female volunteers who indicate that they are pregnant or lactating.

4.3 Recruitment:

Panel selection is accomplished by advertisements in local periodicals, community bulletin boards, phone solicitation, electronic media or any combination thereof.

4.4 Informed Consent and Medical History Forms:

An informed consent was obtained from each volunteer prior to initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment and their limits of liability. Panelists signed and dated the informed consent document to indicate their authorization to proceed and acknowledge their understanding of the contents. Each subject was assigned a permanent identification number and completed an extensive medical history form. These forms along with the signed consent forms, are available for inspection on the premises of AMA Laboratories, Inc. only. Reference 21 CFR Ch. 1 Part 50, Subpart B.

The parties agree to comply with applicable state and federal privacy laws for the use and disclosure of a subject's personal health information by taking reasonable steps to protect the confidentiality of this information. This obligation shall survive the termination or expiration of this Agreement.

5.0 Population Demographics:

Number of subjects enrolled		52
Number of subjects completing study		50
Age Range		18-65
Sex	Male	7
	Female	45
Race	Caucasian	45
	Hispanic	7
	Asian	0

6.0 Equipment:

-Patch Description: Parke-Davis Hypoallergenic Readi Bandages or the equivalent.
-1ml volumetric syringe without a needle.

7.0 Procedure:

-Subjects are requested to bathe or wash as usual before arrival at the facility.
-0.2 ml or 0.2g of the test material is dispensed onto the occlusive, hypoallergenic patch.
-The patch is then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject is dismissed with instructions not to wet or expose the test area to direct sunlight.
-After 24 hours the patch is removed by the panelist at home.
-This procedure is repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday, and Friday for three consecutive weeks.
-In the event of an adverse reaction, the area of erythema and edema is measured. The edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions are scored just before applications two through nine and the next test date following application nine. In most instances this is approximately 24 hours after patch removal. Clients are notified immediately in the case of adverse reaction and determination is made as to treatment program if necessary.
-Subjects are then given a 10 - 14 day rest period after which a challenge or retest dose is applied once to a previously unexposed test site. The retest dose is equivalent to any one of the original nine exposures. Reactions are scored 24 and 48 hours after application.
-Comparison is made between the nine inductive responses and the retest dose.

8.0 Results:

Please refer to attached Table.

9.0 Observations:

No adverse reactions of any kind were noted during the course of this study.

10.0 Archiving:

All original samples, raw data sheets, technician's notebooks, correspondence files and copies of final reports and remaining specimens are maintained on premises of AMA Laboratories, Inc. in limited access storage files marked "Archive". A duplicate disk copy of final reports is separately archived in a bank safe deposit vault.

11.0 Reference:

Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, published by The Association of Food and Drug Officials of The United States, 1965 (modified).

12.0 Conclusions:

The test material (AMA Lab. No.: K-9415; Client No.: Pelemol NGDO, Lot # AE14AR1) when tested under occlusion as described herein, may be considered as a **NON-PRIMARY IRRITANT** and **NON-PRIMARY SENSITIZER** to the skin according to the reference.

Mayya Tatsene

Mayya Tatsene, M.D.
Study Director

Ilona Lapkisa

Ilona Lapkisa, Pharm.D.
Technician

David R. Winne

David R. Winne, B.S.
Technical Director

10/13/06

Date

TABLE
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: K-9415
Client No.: Pelemol NGDO, Lot # AE14AR1

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
1	00 0002	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
2	25 0215	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
3	28 0971	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
4	32 3068	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
5	34 3421	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
6	34 8917	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
7	36 1827	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
8	36 3693	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
9	36 7970	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
10	38 0044	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
11	38 1583	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
12	40 2487	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
13	40 4371	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
14	42 0442	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
15	42 1837	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
16	44 6021	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
17	44 7823	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
18	44 8248	H	M	0	0	0	0	0	0	0	0	0	0	0	0.0
19	44 9258	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
20	46 4172	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
21	46 5776	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
22	46 8520	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
23	46 8676	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
24	48 1605	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
25	50 1729	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
26	50 6005	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
27	50 9982	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
28	52 2712	C	F	0	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
29	52 3942	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
30	52 4898	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
31	52 5549	C	F	0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	N/A
32	54 0763	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

TABLE (CONT'D)
SUMMARY OF RESULTS
(Occlusive Patch)

AMA Lab No.: K-9415
Client No.: Pelemol NGDO, Lot # AE14AR1

No.	Subject ID	RACE	SEX	Response 1	2	3	4	5	6	7	8	9	Chall. 24 HR	Chall. 48 HR	Score
33	54 9327	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
34	54 9626	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
35	56 3659	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
36	58 7412	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
37	58 9750	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
38	60 9426	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
39	62 4500	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
40	62 6182	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
41	62 7431	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
42	64 5370	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
43	64 6653	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
44	64 8003	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
45	66 4641	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
46	68 1557	H	F	0	0	0	0	0	0	0	0	0	0	0	0.0
47	68 4299	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
48	70 5391	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
49	70 6130	C	M	0	0	0	0	0	0	0	0	0	0	0	0.0
50	72 5343	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
51	76 2801	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0
52	88 4232	C	F	0	0	0	0	0	0	0	0	0	0	0	0.0

Evaluation Period:

This study was conducted from September 6, 2006 through October 12, 2006.

Scoring Scale and Definition of Symbols Shown in Table:

0 - No evidence of any effect

? - (Barely perceptible) minimal faint (light pink) uniform or spotty erythema

1 - (Mild) pink uniform erythema covering most of contact site

2 - (Moderate) pink\red erythema visibly uniform in entire contact area

3 - (Marked) bright red erythema with accompanying edema, petechiae or papules

4 - (Severe) deep red erythema with vesiculation or weeping with or without edema

D - Patch eliminated due to reaction

Dc - Discontinued due to absence of subject on application date

M - Patch applied to an adjacent site after strong test reaction

NA - Score is not calculated for subjects discontinued before challenge

S - Skin stained from pigment in product

T - Tan

NOTE: All technical employees of AMA LABORATORIES, INC. are required to take and pass a visual discrimination examination conducted by a Board Certified Ophthalmologist using the Farnsworth-Munsell 100 Hue Test as published; which determines a person's ability to discern color against a black background. This test was additionally modified to include a flesh tone background more nearly approaching actual use conditions, wherein erythematous skin is graded according to intensity.

13.0 Quality Assurance Statement:

This study was inspected in accordance with the Standard Operating Procedures of AMA Laboratories, Inc. To assure compliance with the study protocol, the Quality Assurance Unit completed an audit of the study records and report.

Report reviewed by:

P. Elistratova
Polina Elistratova, M.A.
Quality Assurance Supervisor

10/13/06
Date

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 20, 2016

SUBJECT: Information on Glycol Distearate

Jeen. 2016. Safety data sheet JEECHEM EGDS (Glycol Distearate).

Jeen. 2016. Product information sheet JEECHEM EGDS (Glycol Distearate).

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SAFTY DATA SHEET
According to Regulation (EC) No 1907/2006 (REACH)

Revision Date: October 1, 2016 **Version No.: 1**

SECTION 1 – IDENTIFICATION OF THE SUBSTANCE / MIXTURE AND OF THE COMPANY / UNDERTAKING

1.1 Product Identifier
Product Name: **JEECHEM EGDS** Glycol Distearate

1.2 Relevant Identified Uses of the Substance or Mixture and Uses Advised Against
Identified uses: Cosmetic raw material

1.3 Details of the Supplier of the Safety Data Sheet
Company:
JEEN International Corporation
24 Madison Road
Fairfield, New Jersey 07004
Tel: +1-973-439-1401
Fax: +1-973-439-1402
email: info@jeen.com
Website: www.jeen.com

1.4 Emergency telephone number: +1703-527-3887(Chemtrec Int'l Tel - Collect calls accepted)

SECTION 2 – HAZARDS IDENTIFICATION

2.1 Classification of the Substance or Mixture according to Regulation (EC) 1272/2008
None

2.2 Label Elements according to Regulation (EC) EU 1272/2008

Hazard pictogram	None
Signal words	None
Hazard statements	None
Precautionary statements	None

2.3 Other Hazards: None known

SECTION 3 – COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substances: -

3.2 Mixture

Chemical characterization	Cosmetic ingredients	
INCI	Glycol Distearate	Ethylene Glycol Monostearate
CAS	627-83-8	111-60-4
EC	211-014-3	203-886-9
Concentration	88-95%	5-15%

INCI	Ethylene Glycol
CAS	107-21-1
EC	203-473-3
Concentration	<4%

SECTION 4 – FIRST AID MEASURES

4.1 Description of First Aid Measures

If in Contact with Eyes	Wash out immediately with fresh running water. Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids. Seek medical attention without delay; if pain persists or recurs seek medical attention. Removal of contact lenses after an eye injury should only be undertaken by skilled personnel.
If on skin	Flush skin and hair with running water (and soap if available). Seek medical attention in event of irritation. If swallowed Rinse out mouth and drink 2-3 glasses of water. Seek medical attention if discomfort or other symptoms develop.
If inhaled	If fumes, aerosols or combustion products are inhaled remove from contaminated area. Other measures are usually unnecessary.
If Ingested	If swallowed do NOT induce vomiting. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration. Observe the patient carefully. Never give liquid to a person showing signs of being sleepy or with reduced awareness; i.e. becoming unconscious. Give water to rinse out mouth, then provide liquid slowly and as much as casualty can comfortably drink. Seek medical advice.

4.2 Indication of an Immediate Medical Attention and Special Treatment Needed

Treat symptomatically.

For acute or short term repeated exposures to ethylene glycol:

Early treatment of ingestion is important. Ensure emesis is satisfactory.
Test and correct for metabolic acidosis and hypocalcaemia.
Apply sustained diuresis when possible with hypertonic mannitol.
Evaluate renal status and begin haemodialysis if indicated. [I.L.O]
Rapid absorption is an indication that emesis or lavage is effective only in the first few hours. Cathartics and charcoal are generally not effective.
Correct acidosis, fluid/electrolyte balance and respiratory depression in the usual manner. Systemic acidosis (below 7.2) can be treated with intravenous sodium bicarbonate solution.
Ethanol therapy prolongs the half-life of ethylene glycol and reduces the formation of toxic metabolites.
Pyridoxine and thiamine are cofactors for ethylene glycol metabolism and should be given (50 to 100 mg respectively) intramuscularly, four times per day for 2 days.
Magnesium is also a cofactor and should be replenished. The status of 4-methylpyrazole, in the treatment regime, is still uncertain. For clearance of the material and its metabolites, haemodialysis is much superior to peritoneal dialysis.

SECTION 5 – FIRE FIGHTING MEASURES

5.1 Special Hazards arising from the Substance or Mixture

Fire Incompatibility	Avoid contamination with oxidizing agents i.e. nitrates, oxidizing

acids, chlorine bleaches, pool chlorine etc. as ignition may result

5.2 Extinguishing Media

Foam, Dry chemical powder, BCF (where regulations permit), Carbon dioxide. Water spray or fog - Large fires only.

5.3 Fire Fighting Procedures

Alert Fire Brigade and tell them location and nature of hazard. Wear breathing apparatus plus protective gloves. Prevent, by any means available, spillage from entering drains or water courses. Use water delivered as a fine spray to control fire and cool adjacent area. DO NOT approach containers suspected to be hot.

5.4 Fire/Explosion Hazards

Combustible solid which burns but propagates flame with difficulty; it is estimated that most organic dusts are combustible (circa 70%) – according to the circumstances under which the combustion process occurs, such materials may cause fires and / or dust explosions. Organic powders when finely divided over a range of concentrations regardless of particulate size or shape and suspended in air or some other oxidizing medium may form explosive dust-air mixtures and result in a fire or dust explosion (including secondary explosions). Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a particular hazard; accumulations of fine dust (420 micron or less) may burn rapidly and fiercely if ignited - particles exceeding this limit will generally not form flammable dust clouds; once initiated, however, larger particles up to 1400 microns diameter will contribute to the propagation of an explosion. In the same way as gases and vapors, dusts in the form of a cloud are only ignitable over a range of concentrations; in principle, the concepts of lower explosive limit (LEL) and upper explosive limit (UEL) are applicable to dust clouds but only the LEL is of practical use; - this is because of the inherent difficulty of achieving homogeneous dust clouds at high temperatures (for dusts the LEL is often called the "Minimum Explosible Concentration", MEC). Combustion products include:, carbon monoxide (CO), carbon dioxide (CO_2), other pyrolysis products typical of burning organic material May emit poisonous fumes. May emit corrosive fumes.

SECTION 6 – ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, Protective Equipment and Emergency Procedures

Caution! Floors may become slippery. Wear appropriate protective gear and respiratory protection where dusts or airborne Particulates of unknown concentrations may be generated (self-contained breathing apparatus preferred for large spills).

6.2 Methods and Material for Containment and Cleaning Up

Minor spills

Remove all ignition sources. Clean up all spills immediately. Avoid contact with skin and eyes. Control personal contact with the

	substance, by using protective equipment. Use dry clean up procedures and avoid generating dust.
Major spills	Moderate hazard. CAUTION: Advise personnel in area. Alert Emergency Services and tell them location and nature of hazard. Control personal contact by wearing protective clothing. Prevent, by any means available, spillage from entering drains or water courses.

SECTION 7 – HANDLING AND STORAGE

7.1 Precautions for Safe Handling

Avoid all personal contact, including inhalation. Wear protective clothing when risk of exposure occurs. Use in a well-ventilated area. Prevent concentration in hollows and sumps. DO NOT enter confined spaces until atmosphere has been checked. Organic powders when finely divided over a range of concentrations regardless of particulate size or shape and suspended in air or some other oxidizing medium may form explosive dust-air mixtures and result in a fire or dust explosion (including secondary explosions). Minimize airborne dust and eliminate all ignition sources. Keep away from heat, hot surfaces, sparks, and flame. Establish good housekeeping practices. Remove dust accumulations on a regular basis by vacuuming or gentle sweeping to avoid creating dust clouds. Use continuous suction at points of dust generation to capture and minimize the accumulation of dusts.

Other Information	Store in original containers. Keep containers securely sealed. Store in a cool, dry area protected from environmental extremes. Store away from incompatible materials and foodstuff containers. Protect containers against physical damage and check regularly for leaks.

7.2 Conditions for Safe Storage, including any Incompatibilities

Suitable container	Polyethylene or polypropylene container. Check all containers are clearly labelled and free from leaks.
Storage incompatibility	Avoid reaction with oxidizing agents

SECTION 8 – EXPOSURE CONTROLS / PERSONAL PROTECTION

8.1 Occupational Exposure Limits (OEL)

Source	US ACGIH Threshold Limit Values (TLV)
Ingredient	Ethylene Glycol
Material Name	Ethylene Glycol
TWA	Not available
STEL	Not available
Peak	100 mg/m3
Source	US NIOSH Recommended Exposure Limits (RELs)
Ingredient	Ethylene Glycol
Material Name	1,2-Dihydroxyethane; 1,2-Ethanediol; Glycol; Glycol alcohol; Monoethylene glycol
TWA	Not available

STEL	Not available
Peak	Not available

8.2 Emergency Limits

Ingredient	Ethylene Glycol
Material Name	Ethylene Glycol
TEEL-1	10 ppm
TEEL-2	40 ppm
TEEL-3	60 ppm

Material Data for Ethylene Glycol:

Odor Threshold: 25 ppm
NOTE: Detector tubes for ethylene glycol, measuring in excess of 10 mg/m3, are commercially available.
It appears impractical to establish separate TLVs for ethylene glycol vapor and mists. Atmospheric concentration that do not cause discomfort are unlikely to cause adverse effects. The TLV-C is thought to be protective against throat and respiratory irritation and headache reported in exposed humans. NIOSH has not established a limit for this substance due to the potential teratogenicity associated with exposure and because respiratory irritation reported at the TLV justified a lower value

8.2 Exposure Controls

Appropriate Engineering Controls:

Engineering controls are used to remove a hazard or place a barrier between the worker and the hazard. Well-designed engineering controls can be highly effective in protecting workers and will typically be independent of worker interactions to provide this high level of protection. The basic types of engineering controls are:
Process controls which involve changing the way a job activity or process is done to reduce the risk. Enclosure and/or isolation of emission source which keeps a selected hazard "physically" away from the worker and ventilation that strategically "adds" and "removes" air in the work environment. Ventilation can remove or dilute an air contaminant if designed properly.

Personal Protection:

Eye and face	Safety glasses with side shields. Chemical goggles.Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lenses or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience.
Skin	See Hand protection below.
Hands/feet	The selection of suitable gloves does not only depend on the material, but also on further marks of quality which vary from manufacturer to manufacturer. Where the chemical is a preparation of several substances, the resistance of the glove material cannot be calculated in advance and has therefore to be checked prior to the application.The exact break through time for substances has to be obtained from the manufacturer of the protective gloves and

	has to be observed when making a final choice. Personal hygiene is a key element of effective hand care. Gloves must only be worn on clean hands. Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present. - polychloroprene. - nitrile rubber. - butyl rubber. - fluorocaoutchouc.
Body	See other protection below
Other protection	Overalls, PVC apron, barrier cream, skin cleansing cream

SECTION 9 – PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic Physical and Chemical Properties

Appearance	White flake or beads
Odor	Not available
Vapor Density (Air=1)	Not available
Relative Density (Water =1)	0.93
Auto Ignition Temperature	Not available
pH (as supplied)	Not available
Melt Point, °C	60-67
Initial Boiling Point, °C	>150
Flash Point, °C	>198
Evaporation Rate	Not available
Upper/Lower Explosion Limit (%)	Not available
Vapor Pressure	Not available
Solubility in Water (g/L)	Immiscible
Acid Value	7 Maximum
Saponification Value	194.2
Iodine Value	2 Maximum
Molecular Weight	Not available
Viscosity (cST)	Not available
pH as a solution (5%)	5-7
VOC g/L	Not available

SECTION 10 – STABILITY AND REACTIVITY

10.1 Stability — Product is considered stable. Product is unstable in the presence of incompatible materials.

10.2 Conditions to Avoid — See section 7.

10.3 Incompatible Materials — See section 7.

10.4 Hazardous Decomposition Products — See section 5.

SECTION 11 - TOXICOLOGICAL INFORMATION

11.1 Information on Toxicological Effects

Inhaled	The material is not thought to produce either adverse health effects or irritation of the respiratory tract following inhalation (as classified by EC Directives using animal models). Nevertheless, adverse systemic effects have been produced following exposure of animals by at least one other route and good hygiene practice requires that exposure be kept to a minimum and that suitable control measures be used in an occupational setting.
Ingestion	Accidental ingestion of the material may be damaging to the health of the individual. Nonionic surfactants may produce localized irritation of the oral or gastrointestinal mucosa and induce vomiting and mild diarrhea.
Skin Contact	The material is not thought to produce adverse health effects or skin irritation following contact (as classified by EC Directives using animal models). Nevertheless, good hygiene practice requires that exposure be kept to a minimum and that suitable gloves be used in an occupational setting. Repeated exposure may cause skin cracking, flaking or drying following normal handling and use. One of the mechanisms of skin irritation caused by surfactants is considered to be denaturation of the proteins of skin. It has also been established that there is a connection between the potential of surfactants to denature protein in vitro and their effect on the skin. Nonionic surfactants do not carry any net charge and, therefore, they can only form hydrophobic bonds with proteins. For this reason, proteins are not deactivated by nonionic surfactants, and proteins with poor solubility are not solubilized by nonionic surfactants. Open cuts, abraded or irritated skin should not be exposed to this material Entry into the blood-stream through, for example, cuts, abrasions, puncture wounds or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.
Eye	Limited evidence exists, or practical experience suggests, that the material may cause eye irritation in a substantial number of individuals and/or is expected to produce significant ocular lesions which are present twenty-four hours or more after instillation into the eye(s) of experimental animals. Repeated or prolonged eye contact may cause inflammation characterized by temporary redness (similar to windburn) of the conjunctiva (conjunctivitis); temporary impairment of vision and/or other transient eye damage/ulceration may occur. Some nonionic surfactants may produce a localized anaesthetic effect on the cornea; this may effectively eliminate the warning discomfort produced by other substances and lead to corneal injury. Irritant effects range from minimal to severe dependent on the nature of the surfactant, its concentration and the duration of contact. Pain and corneal damage represent the most severe manifestation of irritation.
Chronic	Prolonged or repeated skin contact may cause drying with cracking, irritation and possible dermatitis following. Limited evidence suggests that repeated or long-term occupational exposure may produce cumulative health effects involving organs or biochemical

	systems. Prolonged or repeated skin contact may cause degreasing with drying, cracking and dermatitis following.
Ethylene Glycol	Ethylene glycol is quickly and extensively absorbed through the gastrointestinal tract. Limited information suggests that it is also absorbed through the respiratory tract; dermal absorption is apparently slow. Following absorption, ethylene glycol is distributed throughout the body according to total body water. In most mammalian species, including humans, ethylene glycol is initially metabolized by alcohol.
Acute Toxicity	Data Not Available to make classification
Skin Irriation/Corrosion	Data Not Available to make classification
Serious Eye Damage	Data Not Available to make classification
Respiratory or Skin Sensitization	Data Not Available to make classification
Mutagenicity	Data Not Available to make classification
Carcinogenicity	Data Not Available to make classification
Reproductivity	Data Not Available to make classification
STOT – Single Exposure	Data Not Available to make classification
STOT-Repeated Exposure	Data Not Available to make classification
Aspiration Hazard	Data Not Available to make classification

SECTION 12 - ECOLOGICAL INFORMATION

12.1 Persistence and Degradability

Ingredient	Ethylene Glycol
Persistence: Water/Soil	LOW (Half-life = 24 days)
Persistence: Air	LOW (Half-life = 3.46 days)

12.2 Bioaccumulative Potential

Ingredient	Ethylene Glycol
Bioaccumulation	LOW (BCF = 200)

12.3 Mobility in Soil

Ingredient	Ethylene Glycol
Mobility	HIGH (KOC =1)

SECTION 13 - DISPOSAL CONSIDERATIONS

13.1 Waste Treatment Methods

DO NOT allow wash water from cleaning or process equipment to enter drains. It may be necessary to collect all wash water for treatment before disposal. In all cases disposal to sewer may be subject to local laws and regulations and these should be considered first. Where in doubt contact the responsible authority.

SECTION 14 – TRANSPORTATION INFORMATION

14.1 AIR- ICAO/ IATA Not regulated for transport of dangerous goods

14.2 SEA-IMO/IMDG Not regulated for transport of dangerous goods

14.3 ADR/RID-ADNR Not regulated for transport of dangerous goods

14.4 Transport in Bulk according to Annex II of MARPOL and the IBC code Not applicable.

SECTION 15 – REGULATORY INFORMATION

15.1 Safety, health and environmental regulations / legislation specific for the substance or mixture
ETHYLENE GLYCOL(107-21-1) IS FOUND ON
THE FOLLOWING REGULATORY LISTS

US - Alaska Limits for Air Contaminants
US - California OEHHA/ARB - Chronic Reference Exposure Levels and Target Organs (CRELs)
US - California Permissible Exposure Limits for Chemical Contaminants
US - California Proposition 65 - Reproductive Toxicity
US - Hawaii Air Contaminant Limits
US - Michigan Exposure Limits for Air Contaminants
US - Minnesota Permissible Exposure Limits (PELs)
US - Oregon Permissible Exposure Limits (Z-1)
US - Tennessee Occupational Exposure Limits - Limits For Air Contaminants
US - Vermont Permissible Exposure Limits Table Z-1-A Final Rule Limits for Air Contaminants
US - Vermont Permissible Exposure Limits Table Z-1-A Transitional Limits for Air Contaminants
US - Washington Permissible exposure limits of air contaminants
US - Washington Toxic air pollutants and their ASIL, SQER and de minimis emission values
US ACGIH Threshold Limit Values (TLV)
US ACGIH Threshold Limit Values (TLV) - Carcinogens
US ACGIH Threshold Limit Values (TLV) - Notice of Intended Changes
US ATSDR Minimal Risk Levels for Hazardous Substances (MRLs)
US EPCRA Section 313 Chemical List
US NIOSH Recommended Exposure Limits (RELs)
US Spacecraft Maximum Allowable Concentrations (SMACs) for Airborne Contaminants
US Toxic Substances Control Act (TSCA) - Chemical Substance Inventory

15.2 US. EPA CERCLA HAZARDOUS SUBSTANCES AND REPORTABLE QUANTITIES (40 CFR 302.4)

Name	Ethylene Glycol
Reportable Quantity in Pounds (lb)	5000
Reportable Quantity in kg	2270

15.4 U.S. California Proposition 65 WARNING: This product contains a chemical known to the State of California to cause cancer and birth defects or other reproductive harm.

15.5 U.S. California Preposition 65 - Carcinogens & Reproductive Toxicity (CRT) Listed Substance Ethylene glycol (ingested) Listed

15.6 Inventory Listings
National Inventory Status

Australia - AICS Y
Canada - DSL Y
Canada - NDSL N (ethylene glycol)

China - IECSC Y
Europe - EINEC / ELINCS /
NLP
Y
Japan - ENCS Y
Korea - KECI Y
New Zealand - NZIoC Y
Philippines - PICCS Y
USA - TSCA Y
Legend:
Y = All ingredients are on the inventory
N = Not determined or one or more ingredients are not on the inventory and are not exempt from listing(see specific ingredients in brackets)

SECTION 16 – OTHER INFORMATION

Disclaimer: These data are offered in good faith as typical values and not as a Product Specifications. No warranty, either expressed or implied, is hereby made. The recommended industrial hygiene and safe handling procedures are believed to be generally applicable; however, each user should review these recommendations in the specific context of intended use and determine whether they are appropriate.

24 Madison Road, Fairfield, New Jersey 07004, USA
Tel: 800-771-JEEN (5336), Tel: 973-439-1401, Fax: 973-439-1402,
email: info@jeen.com , Website: www.jeen.com

October 21, 2016

PRODUCT INFORMATION SHEET

TRADE NAME: JEECHEM® EGDS - Glycol Distearate

Food Allergen *(circle all that apply)* *Milk Egg Fish Shellfish Tree Nuts Peanut Wheat Soybeans Sesame*	☐ YES ☒ NO ☐ UNKNOWN
Gluten	☐ YES ☒ NO ☐ UNKNOWN
Animal Testing	☐ YES ☒ NO ☐ UNKNOWN (*see notes 1)
Micro- test	☒ YES ☐ NO ☐ UNKNOWN
BSE/TSE	☐ YES ☒ NO ☐ UNKNOWN
EU Allergen	☐ YES ☒ NO ☐ UNKNOWN
Fragrances	☐ YES ☒ NO ☐ UNKNOWN
Phthalates	☐ YES ☒ NO ☐ UNKNOWN
Latex	☐ YES ☒ NO ☐ UNKNOWN
Sulfates	☐ YES ☒ NO ☐ UNKNOWN
Quaternium-15	☐ YES ☒ NO ☐ UNKNOWN
GMO	☐ YES ☒ NO ☐ UNKNOWN
Formaldehyde	☐ YES ☒ NO ☐ UNKNOWN
1.4-Dioxane:	☐ YE ☒ NO ☐ UNKNOWN
Ethylene oxide:	☐ YES ☒ NO ☐ UNKNOWN
Propylene oxide:	☐ YES ☒ NO ☐ UNKNOWN
Monomers:	☐ YES ☒ NO ☐ UNKNOWN

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email: info@jeen.com , Website: www.jeen.com

Residual Solvents	☒ YES ☐ NO ☐ UNKNOWN (*see notes)
Heavy metals (cadmium, mercury, antimony, arsenic, chromium, cobalt, nickel, lead, silver) concentration > 10 ppm:	☐ YES ☒ NO ☐ UNKNOWN
Pesticides (DDT, DDE, PCBs ect)	☐ YES ☒ NO ☐ UNKNOWN
Present preservatives If yes, list the names and content (%):	☐ YES ☒ NO ☐ UNKNOWN
Nano-technology process	☐ YES ☒ NO ☐ UNKNOWN
CLP (available upon request)	☒ YES ☐ NO ☐ UNKNOWN
GHS	☒ YES ☐ NO ☐ UNKNOWN
CMR substances	☐ YES ☒ NO ☐ UNKNOWN
SVHC free	☒ YES ☐ NO ☐ UNKNOWN

*Notes

California Prop 65:

May contain trace level of the following:

Toluene < 1 ppb

ISO 9001:2008 Certified

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 24, 2016

SUBJECT: Concentration of Use by FDA Product Category: Monalkylglycol dialkyl acid esters

Concentration of Use by FDA Product Category – Monoalkylglycol Dialkyl Acid Esters*

Trimethyl Pentanyl Diisobutyrate
1,4-Butanediol Bisdecanoate
Butylene Glycol Dicaprylate/Dicaprate
Butylene Glycol Diisononanoate
Butylethylpropanediol Dimer Dilinoleate
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
1,2-Hexanediyl Dicaprate
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

Ingredient	**Product Category**	**Maximum Concentration of Use**
Trimethyl Pentanyl Diisobutyrate	Basecoats and undercoats (manicuring preparations)	1-9.8%
Trimethyl Pentanyl Diisobutyrate	Nail creams and lotions	2%
Trimethyl Pentanyl Diisobutyrate	Nail polish and enamel	0.1-8.4%
Trimethyl Pentanyl Diisobutyrate	Nail polish and enamel removers	2%
Trimethyl Pentanyl Diisobutyrate	Other manicuring preparations	3.8-8.4%
Butylene Glycol Dicaprylate/Dicaprate	Eye shadows	1.3%
Butylene Glycol Dicaprylate/Dicaprate	Other eye makeup preparations	9%
Butylene Glycol Dicaprylate/Dicaprate	Blushers	10%
Butylene Glycol Dicaprylate/Dicaprate	Face powders	10%
Butylene Glycol Dicaprylate/Dicaprate	Foundations	2-10%
Butylene Glycol Dicaprylate/Dicaprate	Makeup bases	10%
Butylene Glycol Dicaprylate/Dicaprate	Other makeup preparations	9%
Butylene Glycol Dicaprylate/Dicaprate	Face and neck products Not spray	8%
Butylene Glycol Dicaprylate/Dicaprate	Body and hand products Spray	10%
Diethylpentanediol Dineopentanoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
Glycol Diethylhexanoate	Foundations	5%
Glycol Dilaurate	Body and hand products Not spray	1.3%

Glycol Distearate	Baby shampoos	0.4-0.6%
Glycol Distearate	Baby lotions, oils and creams Not powders	 0.6%
Glycol Distearate	Other baby products Rinse-off	 0.4%
Glycol Distearate	Bath oils, tablets and salts	2%
Glycol Distearate	Bubble baths	0.45-5%
Glycol Distearate	Other bath preparations	0.2-1.5%
Glycol Distearate	Eyeliners	13.1%
Glycol Distearate	Eye shadows	7.9%
Glycol Distearate	Eye lotions	0.2%
Glycol Distearate	Mascara	3%
Glycol Distearate	Hair conditioners	0.5-1.8%
Glycol Distearate	Hair straighteners	1.5%
Glycol Distearate	Shampoos (noncoloring)	0.39-10%
Glycol Distearate	Tonics, dressings and other hair grooming aids Not spray	1-2.5% 10%
Glycol Distearate	Hair dyes and colors	2-8%
Glycol Distearate	Hair tints	5%
Glycol Distearate	Hair rinses (coloring)	0.5%
Glycol Distearate	Hair shampoos (coloring)	0.5-1.2%
Glycol Distearate	Hair bleaches	2%
Glycol Distearate	Blushers (all types)	0.6%
Glycol Distearate	Face powders	2.5%
Glycol Distearate	Foundations	0.6%
Glycol Distearate	Cuticle softeners	2%
Glycol Distearate	Bath soaps and detergents	0.2-5%
Glycol Distearate	Other personal cleanliness products	0.29-1.3%
Glycol Distearate	Shaving cream	0.25-9.5%
Glycol Distearate	Other shaving preparations	0.05%
Glycol Distearate	Skin cleansing (cold creams cleansing lotions, liquids and pads)	0.36-7.3%
Glycol Distearate	Face and neck products Not spray	 2-5.4%
Glycol Distearate	Body and hand products Not spray	 2-3%
Glycol Distearate	Other skin care preparations Rinse-off	 1.5-2.5%
Neopentyl Glycol Dicaprate	Bath oils, tablets and salts	11%
Neopentyl Glycol Dicaprate	Eyebrow pencils	24%
Neopentyl Glycol Dicaprate	Eyeliners	3.5%
Neopentyl Glycol Dicaprate	Eye shadows	7.5-25%
Neopentyl Glycol Dicaprate	Eye makeup removers	50%
Neopentyl Glycol Dicaprate	Other eye makeup preparations	4%
Neopentyl Glycol Dicaprate	Hair conditioners	3.5%

Neopentyl Glycol Dicaprate	Hair sprays Aerosol	 6%
Neopentyl Glycol Dicaprate	Rinses (noncoloring)	1%
Neopentyl Glycol Dicaprate	Tonics, dressings and other hair grooming aids	3.5-6%
Neopentyl Glycol Dicaprate	Wave sets	3.5%
Neopentyl Glycol Dicaprate	Hair tints	3.5%
Neopentyl Glycol Dicaprate	Face powders	2.5-16.8%
Neopentyl Glycol Dicaprate	Foundations	3-14.5%
Neopentyl Glycol Dicaprate	Lipstick	5-40%
Neopentyl Glycol Dicaprate	Makeup bases	3.5%
Neopentyl Glycol Dicaprate	Rouges	39.3%
Neopentyl Glycol Dicaprate	Makeup fixatives	10%
Neopentyl Glycol Dicaprate	Other makeup preparations	10%
Neopentyl Glycol Dicaprate	Deodorants Not spray Aerosol	 0.1% 4%
Neopentyl Glycol Dicaprate	Aftershave lotions	1.5-2%
Neopentyl Glycol Dicaprate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.24-10%
Neopentyl Glycol Dicaprate	Face and neck products Not spray	 1-28.5%
Neopentyl Glycol Dicaprate	Body and hand products Not spray	 6-7%
Neopentyl Glycol Dicaprate	Moisturizing products Not spray	 5%
Neopentyl Glycol Dicaprate	Paste masks and mud packs	3%
Neopentyl Glycol Dicaprate	Other skin care preparations	0.3%
Neopentyl Glycol Dicaprylate/Dicaprate	Eyebrow pencils	18.9%
Neopentyl Glycol Dicaprylate/Dicaprate	Eyeliners	0.094%
Neopentyl Glycol Dicaprylate/Dicaprate	Eye lotions	1.1%
Neopentyl Glycol Dicaprylate/Dicaprate	Other eye makeup preparations	2.2-14%
Neopentyl Glycol Dicaprylate/Dicaprate	Hair conditioners	0.25%
Neopentyl Glycol Dicaprylate/Dicaprate	Tonics, dressings and other hair grooming aids	0.045-0.9%
Neopentyl Glycol Dicaprylate/Dicaprate	Blushers (all types)	19%
Neopentyl Glycol Dicaprylate/Dicaprate	Face powders	1%
Neopentyl Glycol Dicaprylate/Dicaprate	Foundations	0.35-5%
Neopentyl Glycol Dicaprylate/Dicaprate	Lipstick	1.9-22.7%
Neopentyl Glycol Dicaprylate/Dicaprate	Makeup bases	13.4%
Neopentyl Glycol Dicaprylate/Dicaprate	Makeup fixatives	8.3%
Neopentyl Glycol Dicaprylate/Dicaprate	Other makeup preparations	14%
Neopentyl Glycol Dicaprylate/Dicaprate	Other personal cleanliness products	0.017%
Neopentyl Glycol Dicaprylate/Dicaprate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.063-15%
Neopentyl Glycol Dicaprylate/Dicaprate	Face and neck products	

	Not spray	2.2%
Neopentyl Glycol Dicaprylate/Dicaprate	Moisturizing products Not spray	 0.88%
Neopentyl Glycol Diethylhexanoate	Eyebrow pencils	2.8-9.2%
Neopentyl Glycol Diethylhexanoate	Eyeliners	1-16.2%
Neopentyl Glycol Diethylhexanoate	Eye shadows	7.2-36.5%
Neopentyl Glycol Diethylhexanoate	Eye lotions	3%
Neopentyl Glycol Diethylhexanoate	Mascara	4.5%
Neopentyl Glycol Diethylhexanoate	Other eye makeup preparations	14%
Neopentyl Glycol Diethylhexanoate	Hair conditioners	3%
Neopentyl Glycol Diethylhexanoate	Hair sprays Aerosol Pump spray	 3.6% 9.3%
Neopentyl Glycol Diethylhexanoate	Rinses (noncoloring)	1.5%
Neopentyl Glycol Diethylhexanoate	Tonics, dressings and other hair grooming aids	7.5%
Neopentyl Glycol Diethylhexanoate	Hair tints	1.8%
Neopentyl Glycol Diethylhexanoate	Blushers	9-22.8%
Neopentyl Glycol Diethylhexanoate	Face powders	1.1-2%
Neopentyl Glycol Diethylhexanoate	Foundations	5-32.8%
Neopentyl Glycol Diethylhexanoate	Lipstick	3.1-11.3%
Neopentyl Glycol Diethylhexanoate	Other makeup preparations	14%
Neopentyl Glycol Diethylhexanoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	4-11%
Neopentyl Glycol Diethylhexanoate	Face and neck products Not spray or powder Not spray	 5.4% 3-57%
Neopentyl Glycol Diethylhexanoate	Body and hand products Not spray	 57%
Neopentyl Glycol Diethylhexanoate	Suntan products Not spray	 9.1%
Neopentyl Glycol Diethylhexanoate	Indoor tanning preparations	0.9%
Neopentyl Glycol Diheptanoate	Baby lotions, oils and creams Not powder	 1.2-2.2%
Neopentyl Glycol Diheptanoate	Eye shadows	2.8-14.4%
Neopentyl Glycol Diheptanoate	Eye lotions	3-4%
Neopentyl Glycol Diheptanoate	Eye makeup removers	6%
Neopentyl Glycol Diheptanoate	Other eye makeup preparations	18%
Neopentyl Glycol Diheptanoate	Colognes and toilet waters	5%
Neopentyl Glycol Diheptanoate	Hair conditioners	1.9-3%
Neopentyl Glycol Diheptanoate	Hair sprays Pump spray	 19.5%
Neopentyl Glycol Diheptanoate	Tonics, dressings and other hair grooming aids	3-19.5%
Neopentyl Glycol Diheptanoate	Blushers	2.4%
Neopentyl Glycol Diheptanoate	Face powders	2.4%

Neopentyl Glycol Diheptanoate	Foundations	7.1-25-6%
Neopentyl Glycol Diheptanoate	Lipstick	7%
Neopentyl Glycol Diheptanoate	Makeup bases	9-11%
Neopentyl Glycol Diheptanoate	Other makeup preparations	24%
Neopentyl Glycol Diheptanoate	Bath soaps and detergents	9%
Neopentyl Glycol Diheptanoate	Face and neck products Not spray	1-20%
Neopentyl Glycol Diheptanoate	Body and hand products Not spray	1.2-20.7%
Neopentyl Glycol Diheptanoate	Moisturizing products Not spray	3-9.3%
Neopentyl Glycol Diheptanoate	Other skin care preparations	3.5-15%
Neopentyl Glycol Diheptanoate	Suntan products Not spray	3.5-33%
Neopentyl Glycol Diisononanoate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2-5%
Neopentyl Glycol Diisononanoate	Body and hand creams, lotions and powders Not spray or powder	1.3%
Neopentyl Glycol Diisostearate	Hair tints	0.2%
Neopentyl Glycol Diisostearate	Face and neck products Not spray	0.9%
Neopentyl Glycol Diisostearate	Suntan products Not spray	1.1%
Propanediol Dicaprylate	Face and neck products Not spray	1%
Propanediol Dicaprylate/Dicaprate	Face and neck products Not spray	13.5%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2016

Table prepared October 24, 2016

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 24, 2016

SUBJECT: Comments on the Scientific Literature Review: Safety Assessment of Monoalkylglycol Dialkyl Acid Esters as Used in Cosmetics (release date: October 6, 2016)

The Council has no suppliers listed for the following ingredients:

Butylene Glycol Diisononanoate
Butylethylpropanediol Dimer Dilinoleate
Dioctadecanyl Didecyltetradecanoate
Dioctadecanyl Ditetradecyloctadecanoate
Glycol Dibehenate
Glycol Dilaurate
Glycol Dioleate
Glycol Dipalmitate/Palm Kernelate/Olivate/Macadamiate
Glycol Ditallowate
Hexandiol Distearate
Neopentyl Glycol
Dicaprylate/Dipelargonate/Dicaprate

Introduction, Summary - Among the ingredients in the report, only Trimethyl Pentanyl Diisobutyrate functions as a plasticizer and this function is consistent with its use only in nail products. In the Introduction and Summary, rather than listing all the functions of all of the ingredients, it would be helpful to be more specific and state that Trimethyl Pentanyl Diisobutyrate is the only ingredient included in the report reported to function as a plasticizer.

Introduction, Table 2 - The glycols previously reviewed by CIR, e.g., Butylene Glycol, and currently under review by CIR, e.g., Propanediol, should also be mentioned in the Introduction and Table 2.

Impurities/Constituents - The SIDS dossier on Trimethyl Pentanyl Diisobutyrate (reference 20) states: "Major Impurities: 2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate". Therefore, it is not correct to state: "The impurities were not reported."

A 1979 reference titled "Gas chromatographic determination of 1,4-dioxane in polysorbate 60 and polysorbate 80" does not seem to be an appropriate reference to

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support the suggestion that the ingredients in this report may have 1,4-dioxane as an impurity. Please delete this suggestion, or find a more appropriate reference to support it.

Cosmetic Use - The information about the NICNAS Tier I assessment does not belong in the Cosmetic Use section.

Acute Oral - As more than one compound is discussed in the summary paragraph, please state the compound to which the following sentence refers "In another study in rats, there were no mortalities...."

Short-Term, Dermal, Glycol Distearate - Please correct: "including hematologic, there..."

Short-Term - It should be mentioned that the 14-day study in Sprague-Dawley rats was a preliminary study for the gavage OECD 422 study (combined repeat dose/reproductive and development toxicity study). This study is mentioned in the ECHA dossier (reference 22) but it is not mentioned in reference 34.

Subchronic Toxicity - In the description of the 102-day rat feeding study, please correct "autopsy" to "necropsy". Autopsy is only used for post-mortem examination of humans.

Irritation, Table 10 - The dermal irritation studies in the ECHA dossier (reference 38) on Neopentyl Glycol Diethylhexanoate says: "Analytical purity: not stated". The dossier also indicates that the information for these studies was obtained from an abstract. The observation period lasted for 7 days for one of these studies. Rather than stating that the concentration was "not specified, assumed 100%", it would be more appropriate to state that a commercial product, analytical purity not stated was tested undiluted.

Sensitization, Glycol Distearate, 1982 - Please correct: "sensitization were 2 observed..."

Sensitization, Neopentyl Glycol - Please indicate the species (guinea pig or human) in which the maximization test was completed.

Sensitization, Glycol Distearate - Regarding the Buehler test of Glycol Distearate, it is not correct to state "No further details were provided." If the study is expanded, there are more details in the ECHA dossier (reference 38). For example, there was a preliminary study that showed that a 6 hour exposure to Glycol Distearate under occlusion was not irritating. A few drops of water were added to the Glycol Distearate before the 6 hour occlusive applications, and there was also a 72 hour observation (no effects) after the challenge exposure.

Summary - It is misleading to state that the VCRP and Council survey provide information on "actual use conditions". The VCRP reports frequency of use, the Council survey reports maximum use concentrations in FDA product categories. It would be helpful to be specific on what information is available.

Table 2 - As more than one ingredient is in each report, please indicate the ingredient for which the maximum use concentrations were reported.

Table 7 - It is not clear why 2 rows are needed for Trimethyl Pentanyl Diisobutyrate.

Table 8, Inhalation, Trimethyl Pentanyl Diisobutyrate - The second study on Trimethyl Pentanyl Diisobutyrate indicates that the exposure concentration was 5300 mg/L and the LC_{50} was >5.3 mg/L - this does not make sense. If no rats died at 5300 mg/L the LC_{50} should be >5300 mg/L.

Table 11 - In the first row, please correct "3 where washed"