Article

International Journal of Toxicology
2015, Vol. 34(Supplement 2) 99S-112S

DOI: 10.1177/1091581815596731
ijt.sagepub.com
SAGE

Safety Assessment of Pentaerythrityl Tetraesters as Used in Cosmetics

Lillian C. Becker[1], Wilma F. Bergfeld[2], Donald V. Belsito[2], Ronald A. Hill[2], Curtis D. Klaassen[2], Daniel C. Liebler[2], James G. Marks Jr[2], Ronald C. Shank[2], Thomas J. Slaga[2], Paul W. Snyder[2], and F. Alan Andersen[3]

Abstract

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 16 pentaerythrityl tetraester compounds as used in cosmetics. These ingredients mostly function as hair-conditioning agents, skin-conditioning agents—miscellaneous and binders, skin-conditioning agents–occlusive, viscosity-increasing agents–nonaqueous, and skin-conditioning agents—emollient. The Panel reviewed the available animal and human data related to these ingredients and previous safety assessments of the fatty acid moieties. The Panel concluded that pentaerythrityl tetraisostearate and the other pentaerythrityl tetraester compounds were safe in the practices of use and concentration as given in this safety assessment.

Keywords

pentaerythrityl tetraesters, safety, cosmetics

Introduction

This safety assessment summarizes published and unpublished data relevant to the safety of pentaerythrityl tetraisostearate and other pentaerythrityl tetraester compounds used in cosmetics. As given in the *International Cosmetic Ingredient Dictionary and Handbook*,[1] these ingredients function mostly as hair-conditioning agents, skin-conditioning agents–miscellaneous, binders, skin-conditioning agents—occlusive, viscosity-increasing agents—nonaqueous, and skin-conditioning agents—emollient. The 17 ingredients included in this report are as follows:

- pentaerythrityl tetraisostearate,
- pentaerythrityl tetra C5-9 acid esters,
- pentaerythrityl tetra C5-10 acid esters,
- pentaerythrityl tetracaprylate/tetracaprate,
- pentaerythrityl tetralaurate,
- pentaerythrityl tetramyristate,
- pentaerythrityl tetrastearate,
- pentaerythrityl tetrabehenate,
- pentaerythrityl tetracocoate,
- pentaerythrityl tetraoleate,
- pentaerythrityl tetraethylhexanoate,
- pentaerythrityl tetraethylhexanoate/benzoate,
- pentaerythrityl tetrabehenate/ benzoate/ethylhexanoate,
- pentaerythrityl tetrabenzoate,
- pentaerythrityl tetraisononanoate, and
- pentaerythrityl tetrapelargonate.

In a previous review by CIR Expert Panel (Panel), pentaerythrityl tetraisononanoate and pentaerythrityl tetrapelargonate were determined to be safe in the present practices of use and concentration.[2] These 2 ingredients were added to this report so that all of the reviewed pentaerythrityl tetraesters would be in one report. In addition, the Panel issued safety assessments of most of the fatty acid component of these ingredients, including coconut, isostearic, oleic, lauric, myristic, and stearic acids. These are the esterase metabolites that would result from pentaerythrityl tetracocoate, pentaerythrityl tetraisostearate, pentaerythrityl tetraoleate, pentaerythrityl tetralaurate, pentaerythrityl tetramyristate, and pentaerythrityl tetrastearate, respectively. In previous safety assessments, CIR determined that these fatty acids are safe in the present practices of cosmetic use.[3-5] Benzoic acid (a metabolite of pentaerythrityl tetrabenzoate, pentaerythrityl tetraethylhexanoate/benzoate, and pentaerythrityl tetrabehenate/benzoate/ethylhexanoate) was determined by the Panel to be safe for use in cosmetic formulations in the present practices of use and concentration

[1] Cosmetic Ingredient Review Scientific Analyst/Writer, Washington, DC, USA
[2] Cosmetic Ingredient Review Expert Panel Member, Washington, DC, USA
[3] Former Director, Cosmetic Ingredient Review, Washington, DC, USA

Corresponding Author:
Lillian J. Gill, Cosmetic Ingredient Review, 1620L Street, NW, Suite 1200, Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

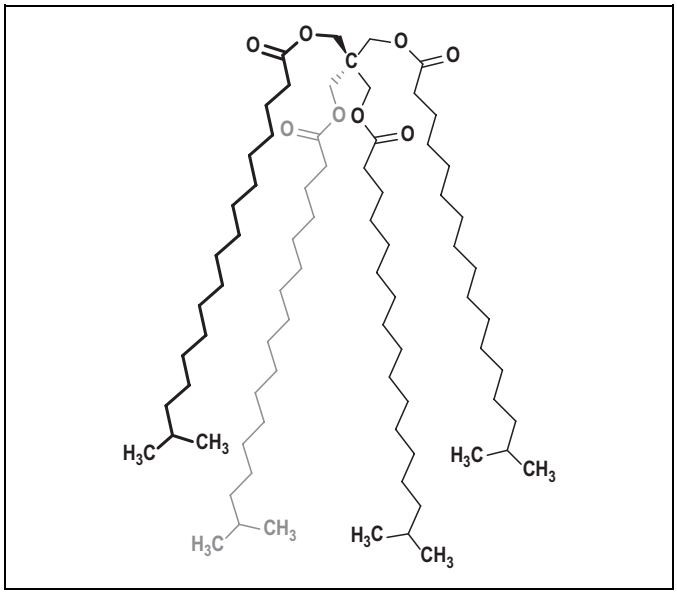


Figure 1. Pentaerythrityl tetraisostearate.

at their meeting on September 26 to 27, 2011. This revised the earlier safety assessment of benzoic acid.[6]

Chemistry

Definition and Structure

The pentaerythrityl tetraesters have a core pentaerythritol moiety that is esterified with 4 monobasic fatty acids. For example, pentaerythrityl tetraisostearate consists of a pentaerythritol core, esterified with 4 stoichiometric equivalents of isostearic acid (Figure 1). The Chemical Abstracts Service numbers, definitions, functions, and structures of these ingredients are provided in Table 1.

Physical and Chemical Properties

The physical and chemical properties of the pentaerythrityl tetraester ingredients in this safety assessment are provided in Table 2. The pentaerythrityl tetraesters, as a group, are solid crystalline materials. These ingredients have very poor solubility in water and have large molecular weights (too large to pass through the dermal layer). Pentaerythrityl tetra C5-9 acid esters have an estimated $\log P_{ow}$ of 16.7.

Method of Manufacture

Pentaerythrityl tetraesters can be prepared from pentaerythritol by alcohol esterification methods (eg, by reaction with acids, acid chlorides, or acid anhydrides).[7] For example, pentaerythritol tetrastearate can be manufactured by heating stearoyl chloride and pentaerythritol (4:1 ratio) at 100°C under 2 mm Hg.[8] The resulting product can then be recrystallized from chloroform to form a pure product. A greener, biocatalytic process developed specifically for the manufacture of esters for use in the formulation of cosmetic ingredients (ie, for producing cosmetic grade esters) also is a potential process for the manufacture of these ingredients.[9]

Impurities

Pentaerythrityl tetra C5-9 acid esters were reported by one source to be 100% pure.[10,11] Another source, however, reported 81% purity with the other 19% comprised of carboxylic acids and dipentaerythritol C5-9 hexaesters.[12]

Absorption of UV

While no UV absorption data on the ingredients in this safety assessment were available, most of the ingredients included in this review would not be expected to have any meaningful UV absorption (ie, no detectable absorption in the UV-A and UV-B bands). The alkyl carboxyl groups and the nonconjugated alkenyl groups of pentaerythrityl tetraoleate found in most of these ingredients would be expected to absorb in the UVC range. For the majority of these ingredients, there simply are no chemical functional groups present that have any possibility of UV-A or UV-B absorption. However, the aromatic, conjugated carboxyl groups present in pentaerythrityl tetrabenzoate, pentaerythrityl tetraethylhexanoate/benzoate, and pentaerythrityl tetrabehenate/benzoate/ethylhexanoate would be expected to have some meaningful UV absorption.

Use

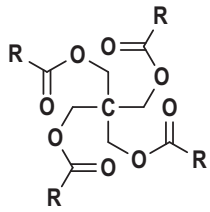
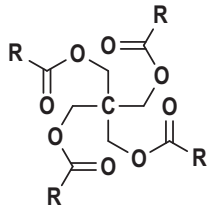
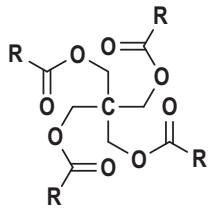
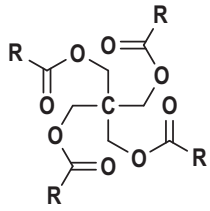
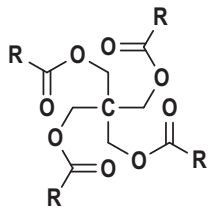
Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration Voluntary Cosmetic Registration Program (VCRP), and a survey conducted by the Personal Care Products Council (Council) collected use concentrations for ingredients in this group.[13-18] The total number of VCRP reported uses of pentaerythrityl tetraisostearate was 532 for leave-on and 9 for rinse-off products, and the Council survey found that pentaerythrityl tetraisostearate was used up to 0.1% to 55% (highest concentration in lipstick) in leave-on products and up to 0.1% in paste masks (mud packs), a rinse-off product. Table 3 summarizes the VCRP and Council survey data for all ingredients in this group.

There were no reports to the VCRP or the Council survey of use for pentaerythrityl tetra C5-9 acid esters, pentaerythrityl C5-10 acid esters, pentaerythrityl tetramyristate, pentaerythrityl tetracocoate, pentaerythrityl tetraoleate, pentaerythrityl tetrabenzoate, pentthrityl tetraisononononanoate, and penaerythirtyl tetrapleargonate.

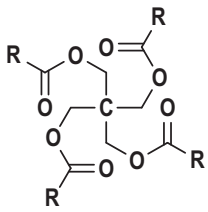
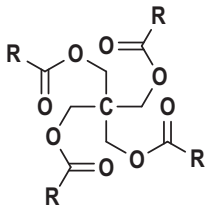
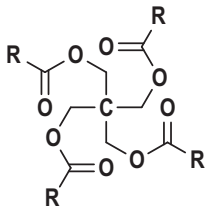
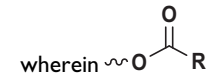
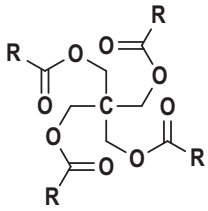
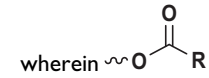
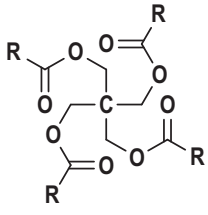
Pentaerythrityl tetracaprylate/tetracaprate is used in hair sprays, and pentaerythrityl tetraethylhexanolate is used in deodorants and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[19,20] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region and

Table 1. Definitions, Functions, and Structures of Pentaerythrityl Ester Ingredients in this Safety Assessment.[1]

Ingredient CAS No.	Definition	Functions	Formula/structure
Pentaerythrityl tetra C5-9 acid esters 67762-53-2	The tetraester of branched and linear C5-9 acids with pentaerythritol.	Hai-conditioning agent, plasticizer, skin-conditioning agent—miscellaneous	 wherein R represents a 4 to 8 carbon alkyl chain
Pentaerythrityl tetra C5-10 acid esters 68424-31-7	The tetraester of C5-10 acids with pentaerythritol.	Plasticizer	 wherein R represents a 4 to 9 carbon alkyl chain
Pentaerythrityl tetracaprylate/ tetracaprate 68441-68-9	The tetraester of pentaerythritol and a blend of caprylic and capric acids.	Skin-conditioning agent—occlusive, and viscosity-increasing agent—nonaqueous	 wherein R represents a 7 or 9 carbon alkyl chain
Pentaerythrityl tetralaurate 13057-50-6	The tetraester of pentaerythritol and lauric acid.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	 wherein R represents an 11 carbon alkyl chain
Pentaerythrityl tetramyristate 18641-59-3	The tetraester of pentaerythritol and myristic acid.	Skin-conditioning agent—occlusive, and viscosity-increasing agent—nonaqueous	 wherein R represents an 13 carbon alkyl chain

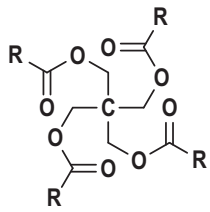
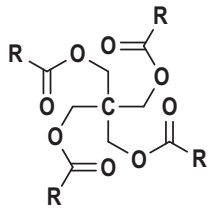
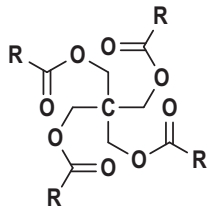
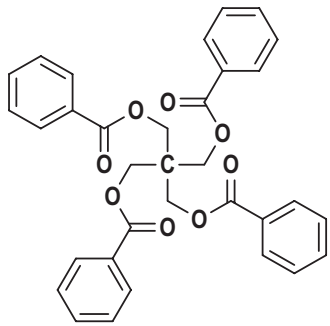
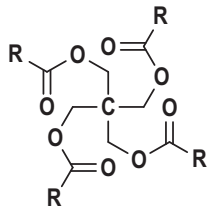
(continued)

Table 1. (continued)

Ingredient CAS No.	Definition	Functions	Formula/structure
Pentaerythrityl tetrastearate 115-83-3	The tetraester of pentaerythritol and stearic acid.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	 wherein R represents an 17 carbon alkyl chain
Pentaerythrityl tetrabehenate 61682-73-3	The tetraester of pentaerythritol and behenic acid.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	 wherein R represents a 21 carbon alkyl chain
Pentaerythrityl tetracocoate 92201-72-4	The tetraester of pentaerythritol and coconut fatty acid.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	  wherein represents coconut fatty acid residues
Pentaerythrityl tetraoleate 19321-40-5	The tetraester of pentaerythritol and oleic acid.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	  wherein represents an oleic acid (an Ω-9 unsaturated, 18 carbon fatty acid) residue
Pentaerythrityl tetraisostearate 62125-22-8	The tetraester of isostearic acid and pentaerythritol.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	 wherein R represents a 17 carbon "iso" alkyl chain

(continued)

Table 1. (continued)

Ingredient CAS No.	Definition	Functions	Formula/structure
Pentaerythrityl tetraethylhexanoate 7299-99-2	The tetraester of pentaerythritol and 2-ethylhexanoic acid.	Binder, skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	 wherein R represents a 1 ethylpentyl chain
Pentaerythrityl tetraethylhexanoate/ benzoate	The tetraester of pentaerythritol and a blend of ethylhexanoic and benzoic acids.	Hair-conditioning agent, skin-conditioning agent—emollient	 wherein R represents a 1 ethylpentyl chain or benzene
Pentaerythrityl tetrabehenate/ benzoate/ ethylhexanoate	The tetraester of Pentaerythritol with a blend of behenic, benzoic and ethylhexanoic acids.	Hair-conditioning agent, skin-conditioning agent—emollient	 wherein R represents a 21 carbon alkyl chain, benzene, or a 1 ethylpentyl chain
Pentaerythrityl tetrabenzoate 4196-86-5	The tetraester of pentaerythritol and benzoic acid.	Binder, skin-conditioning agent–emollient, viscosity-increasing agent—nonaqueous	
Pentaerythrityl tetraisononanoate 137636-04-5	The tetraester of pentaerythritol and a branched chain nonanoic acid	Skin-conditioning agent—occlusive, viscosity-increasing agent—nonaqueous	 RCO- represents the isononanoic acid radical

(continued)

Table 1. (continued)

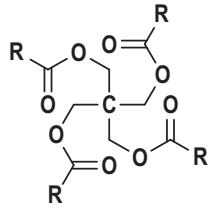
Ingredient CAS No.	Definition	Functions	Formula/structure
Pentaerythrityl tetrapelargonate 14450-05-6	Tetraester of pentaerythritol and pelargonic acid	Fragrance ingredient, skin-conditioning agent–emollient	 RCO- represents the pelargonic acid radical

Table 2. Physical and Chemical Properties of Pentaerythrityl Tetraesters in This Safety Assessment.

Property	Value	Reference
Pentaerythrityl tetra C5-9 acid esters		
Molecular weight, g/mol	529	[40]
Boiling point, °C	858	Estimated[40]
Melting point °C	150	[41]
Vapor pressure, mm Hg at 25°C	1.6×10^{-21}	Estimated[40]
log P_{ow}	16.7	Estimated[40]
Water solubility, g/L at 25°C (pH not provided)	$3.4\ 10^{-15}$	Estimated[40]
Pentaerythrityl tetra C5-C10 acid esters		
Molecular weight, g/mol	613	[40]
Vapor pressure, mm Hg at 25°C	7.03×10^{-21}	Estimated[40]
Water solubility, g/L at25°C (pH not provided)	3.6×10^{-14}	Estimated[40]
Boiling point, °C	835	Estimated[40]
Melting point, °C	150	[41]
Pentaerythrityl tetracaprylate/tetracaprate	No data found	
Pentaerythrityl tetralaurate		
Molecular weight, g/mol	865.36	Estimated[42]
Density/specific gravity at 20°C	0.943 ± 0.06	Estimated[42]
Vapor pressure, mm Hg at 25°C	3.28×10^{-26}	Estimated[42]
Melting point, °C	48.8-9	[43]
Boiling point, °C	808.8 ± 60.0	Estimated[42]
Water solubility, g/L at 25°C and pH 1-10	4×10^{-9}	Estimated[42]
Pentaerythrityl tetramyristate		
Molecular weight, g/mol	977.58	[43]
Density/specific gravity, g/cm^3 at 20°C	0.931 ± 0.06	Estimated[42]
Melting point, °C	62	[43]
Boiling point, °C	875.8 ± 60.0	Estimated[42]
Water solubility, g/L at 25°C and pH 1-10	4.7×10^{-10}	Estimated[42]
Pentaerythrityl tetrastearate		
Molecular weight, g/mol	1201.99	Estimated[42]
Density/specific gravity at 20 °C	0.915 ± 0.06	Estimated[42]
Vapor pressure, mm Hg at 25°C	1.5×10^{-27}	Estimated[40]
Boiling point, °C	998.5 ± 60.0	Estimated[42]
Melting point, °C	66-77	[40]
Water solubility, g/L at 25°C and pH 1-10	6.3×10^{-11}	Estimated[42]
Pentaerythrityl tetrabehenate		
Molecular weight, g/mol	1426.42	Estimated[42]
Density/specific gravity at 20°C	0.904 ± 0.06	Estimated[42]
Boiling point, °C	1109.5 ± 60.0	Estimated[42]

(continued)

Table 2. (continued)

Property	Value	Reference
Pentaerythrityl tetracocoate		
	No data found	
Pentaerythrityl tetraoleate		
Molecular weight, g/mol	1193.93	Estimated[42]
Density/specific gravity (temperature not provided)	0.926 ± 0.06	Estimated[42]
Boiling point, °C	996.0 ± 65.0	Estimated[42]
Water solubility, g/L (temperature and pH not provided)	2.5×10^{-10}	Estimated[42]
Pentaerythrityl tetraisostearate		
	No data found	
Pentaerythrityl tetraethylhexanoate		
Molecular weight, g/mol	640.93	Estimated[42]
Density/specific gravity at 20°C	0.978 ± 0.06	Estimated[42]
Boiling point, °C	647.7 ± 50.0	Estimated[42]
Water solubility, g/L at 25°C and pH 1-10	4×10^{-6}	Estimated[42]
Pentaerythrityl tetraethylhexanoate/benzoate		
	No data found	
Pentaerythrityl tetrabehenate/ benzoate/ethylhexanoate		
	No data found	
Pentaerythrityl tetrabenzoate		
Molecular weight, g/mol	552.57	Estimated[42]
Density/specific gravity at 20°C	1.255 ± 0.06	Estimated[42]
Melting point, °C	105	[43]
Boiling point, °C	684.3 ± 55.0	Estimated[42]
Water solubility, g/L at 25°C and pH 1-10	9.4×10^{-6}	Estimated[42]
Pentaerythrityl tetraisononanoate		
Molecular weight, g/mol	697.04	[44]
Pentaerythrityl tetrapelargonate		
Molecular weight, g/mol	697.04	[45]
Density/specific gravity at 20°C	0.969	[45]
Melting point, °C	12	[45]
Boiling point, °C	699.1 ± 50	[45]
Water solubility, g/L at 25°C and pH 1-10	7.7×10^{-7}	[45]
Vapor pressure at 25°C	2.16E-19 torr	[45]

would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[21-23] However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. 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.[22] 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.

Noncosmetic

Pentaerythrityl tetraesters are used in lubricating oils of jet engines, low-temperature use grease, heat-resistant engine oil, and refrigerator oil.[24] Pentaerythrityl tetrastearate is an indirect food additive that may be used to make food packaging.[25] It may also be used in cellophane that comes in contact with food with a limit of 0.1%.[26] Pentaerythrityl fatty acids may be used as defoaming agents in paper and paperboard intended for food use.[18]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

There were no experimental data discovered on the toxicokinetics of pentaerythritol tetraesters. However, due to the large size of the molecules and the high P_{ow} of pentaerythrityl tetra C5-9 acid esters, it is not expected that these ingredients would penetrate the skin. For example, pentaerythrityl tetrapelargonate has a log P >16.7, a molecular weight >500, and low solubility, so it is not likely to penetrate the skin. The dermal bioavailability of pentaerythrityl tetra C5-9 acid esters was 2% to 6%.[27]

Toxicological Studies

Acute Toxicity

Dermal. There were no dermal studies discovered for pentaerythrityl tetraesters.

Oral—nonhuman

Pentaerythrityl tetra C5-9 acid esters. Sprague-Dawley rats (n = 5/sex) were orally administered pentaerythrityl tetra C5-9

Table 3. Frequency of Use According to Duration and Maximum Exposure Range.[13-18,a]

Use type	Uses	Concentration, %	Uses	Concentration, %	Uses	Concentration, %	Uses	Concentration, %
	Pentaerythrityl tetracaprylate/ tetracaprate		Pentaerythrityl tetralaurate		Pentaerythrityl tetrastearate		Pentaerythrityl tetrabehenate	
Total/range	26	0.07-5	1	NR	NR	7	8	2-3
Duration of use								
Leave-on	26	0.07-5	1	NR	NR	7	8	2-3
Rinse-off	NR	NR	NR	NR	NR	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	1	3	1	NR	NR	7	4	2
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	3
Incidental inhalation—sprays	9	0.07-1	NR	NR	NR	NR	1	NR
Incidental inhalation—powders	1	NR	NR	NR	NR	NR	NR	NR
Dermal contact	17	2-5	1	NR	NR	NR	8	2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair noncoloring	9	0.07-1	NR	NR	NR	NR	NR	NR
Hair coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR	NR	3
Baby	1	NR	NR	NR	NR	NR	NR	NR
	Pentaerythrityl tetraisostearate		Pentaerythrityl tetraethylhexanoate		Pentaerythrityl tetraethylhexanoate/ benzoate		Pentaerythrityl tetrabehenate/ benzoate/ ethylhexanoate	
Total/range	541	0.1-55	241	0.06-50	4	40	7	0.5-16
Duration of use								
Leave-on	532	0.1-55	224	0.06-50	4	40	7	2-16
Rinse-off	9	0.1-0.8	17	1-20	NR	NR	NR	0.5
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	104	0.2-36	41	3-15	NR	NR	NR	NR
Incidental ingestion	227	0.8-55	10	2-49	NR	NR	5	16
Incidental inhalation—sprays	5	NR	4	0.1-21	NR	NR	NR	NR
Incidental inhalation—powders	47	1-4	17	0.1-2	NR	NR	NR	NR
Dermal contact	306	0.1-36	230	0.06-50[b]	NR	NR	2	0.5-2
Deodorant (underarm)	NR	NR	NR	0.1	NR	NR	NR	NR
Hair noncoloring	NR	NR	1	2-20	NR	NR	NR	NR
Hair coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	0.1	NR	5	NR	NR	NR	NR
Mucous membrane	227	0.8-55	10	2-49	4	40	5	16
Baby	NR	NR	NR	NR	NR	NR	NR	NR
	Pentaerythrityl tetrapelargonate							
Total/range	1	NR						
Duration of use								
Leave-on	1	NR						
Rinse-off	NR	NR						
Diluted for (bath) use	NR	NR						
Exposure type								
Eye area	NR	NR						
Incidental ingestion	NR	NR						
Incidental inhalation—sprays	NR	NR						
Incidental inhalation—powders	NR	NR						
Dermal contact	NR	NR						
Deodorant (underarm)	NR	NR						
Hair noncoloring	1	NR						
Hair coloring	NR	NR						
Nail	NR	NR						
Mucous membrane	NR	NR						
Baby	NR	NR						

Abbreviations: NR, none reported.

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

[b] Fragrance preparations (used up to 45% and 50%) are light gels that are applied with a small spatula-like applicator, not aerosols.

acid esters (1940 mg/kg).[10,11] There were no deaths. One male had unformed stool at 4 hours after administration. Necropsy was unremarkable at 15 days. Sprague-Dawley rats (n = 5/sex) had no deaths or clinical signs after oral gavage of pentaerythrityl tetra C5-9 acid esters (1940 mg/kg; 2.0 mL/kg).[28] Necropsy was unremarkable at 15 days.

Pentaerythrityl tetra C5-10 acid esters. Wistar rats (n = 5/sex) were orally administered pentaerythrityl tetra C5-10 acid esters (5000 mg/kg).[10,11] There were no deaths or clinical signs. Necropsy was unremarkable at 14 days.

Pentaerythrityl tetrabenzoate. The oral median lethal dose (LD_{50}) for pentaerythrityl tetrabenzoate was reported to be 1158 mg/kg in rats.[29]

Inhalation. There were no acute inhalation toxicological studies discovered for pentaerythrityl tetraesters.

Repeated Dose Toxicity

Dermal—nonhuman

Pentaerythrityl tetra C5-9 acid esters. Pentaerythrityl tetra C5-9 acid esters (0, 800, or 2000 mg/kg, neat) were dermally administered to clipped backs of Sprague-Dawley rats (n = 10/sex) for 5 days/week for 13 weeks.[27] The test material was not covered but collars were used to prevent grooming of the area. Males in the high-dose group weighed 10% less than the control group and 7% less than those in the low-dose group after 13 weeks. No effect on body weights occurred in females. There were no other signs of systemic toxicity. There was minimal skin irritation, and flaking with slight erythema was observed in both treatment groups. Microscopic examination of the skin revealed very minor epidermal hyperplasia and chronic inflammation of the dermis. No differences were seen in sperm morphology at necropsy. Ovaries, testes, epididymides, uterus, and vagina showed no adverse effects. The no observed adverse effect level (NOAEL) was 2000 mg/kg/d.

Oral. There were no oral repeated dose studies discovered for pentaerythrityl tetraesters.

Inhalation. A micronucleus assay was performed on male Sprague-Dawley rats (n = 10) that were exposed to aerosolized pentaerythrityl tetra C5-9 acid esters (0.5 mg/L) for 6 h/d, 5 d/week, for 2 weeks.[30] There were no reported mortalities or adverse effects reported.

Reproductive and Developmental Toxicity

Pentaerythrityl Tetra C5-9 Acid Esters

Pentaerythrityl tetra C5-9 acid esters (0, 800, or 2000 mg/kg) were dermally administered to clipped backs of Sprague-Dawley rats (n = 10/sex) for 5 d/week for 13 weeks.[27] There were no effects noted in sperm morphology. Gross necropsy and histopathology of the ovaries, testis, epididymides, uteruses, and vaginas were unremarkable.

Pentaerythrityl tetra C5-9 acid esters (0, 800, or 2000 mg/kg/d) were applied to the clipped backs of Sprague-Dawley rats (n = 20) on days 0 to 19 of gestation.[31] Neither maternal parameters (food consumption and body weight gains) monitored throughout gestation (days 0-19) nor reproductive parameters (number of implants, resorptions, or viable fetuses) were adversely affected by the test substance. No evidence of teratogenicity was observed by external examination of fetuses. Mean fetal body weights and crown-rump distances were similar in all the groups.

Genotoxicity

In Vitro

Pentaerythrityl tetra C5-9 acid esters. In a reverse mutation assay of pentaerythrityl tetra C5-9 acid esters (33.3, 100, 333, 1000, 3330, or 5000 μg/plate) using *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *Escherichia coli* (WP2uvrA) with and without metabolic activation, the results were negative.[32] Positive controls were 2-aminoanthracene and benzo[a]prene with metabolic activation. Positive controls, without metabolic activation, were sodium azide, 2-nitrofluorene, and ICR-191. The controls had the expected results.

Pentaerythrityl tetra C5-9 acid esters (33.3, 100, 333, 1000, 3330, or 5000 μg/plate) with and without metabolic activation were not cytotoxic or mutagenic in a reverse mutation assay using *E coli* (WP2uvrA).[33] The positive controls (2-aminoanthracen and 4-nitroquinoline-N-oxide) and negative vehicle controls (ethanol) had the expected results.

In a microsome reverse mutation assay using *S typhimurium* (TA98, TA100, TA1535, and TA1537) and *E coli* (WP2uvrA), pentaerythrityl tetra C5-9 acid esters (33.3, 100, 333, 1000, 3330, or 5000 μg/plate) were not mutagenic with or without metabolic activation.[12]

Pentaerythrityl tetrabenzoate. A mutagenicity assay of pentaerythrityl tetrabenzoate (0.05 mL/plate) using *S typhimurium* (TA97, TA98, TAl00, TAl535, and TA1537) was negative.[34]

In Vivo

Pentaerythrityl tetra C5-9 acid esters. A micronucleus assay was performed on male Sprague-Dawley rats (n = 10) that were exposed to aerosolized pentaerythrityl tetra C5-9 acid esters (0.5 mg/L) for 6 h/d, 5 d/week, for 2 weeks.[30] The test material was not cytotoxic to red blood cell formation nor did it induce increased micronucleated polychromatic erythrocytes (PCEs) or normochormatic erythrocytes (NCEs) in the bone marrow.

Carcinogenicity

There were no carcinogenicity studies discovered for pentaerythrityl tetraesters.

Irritation and Sensitization

Irritation

Dermal—nonhuman

Pentaerythrityl tetra C5-9 acid esters. Pentaerythrityl tetra C5-9 acid esters (0, 800, or 2000 mg/kg) were dermally administered to clipped backs of Sprague-Dawley rats (n = 10/sex) for 5 days/week for 13 weeks.[27] Minimal skin irritation, mostly flaking with slight erythema, was observed in both treatment groups. Microscopic examination of the skin revealed very minor epidermal hyperplasia and chronic inflammation of the dermis.

Pentaerythrityl tetra C5-9 acid esters (0, 800, or 2000 mg/kg/d) were applied to the clipped back of Sprague-Dawley rats (n = 20) on days 0 to 19 of gestation.[31] The test substances at both doses produced slight skin irritation (erythema and flaking) at the application site.

Dermal and mucosal—human. There were no human dermal or mucosal irritation studies discovered for pentaerythrityl tetraesters.

Ocular

Pentaerythrityl tetrabehenate. Subjects (n = 30) used an eyeliner containing pentaerythrityl tetrabehenate (1.705%) daily for 4 weeks.[35] Trace increases in redness of the palpebral conjunctivae were observed in 2 subjects at week 4. The authors decided that this was unrelated to the test substance. The subjects did not report any irritation. There were no increases in lacrimation, eye lid inflammation, or bulbar conjunctova1 irritation and no changes in visual acuity, corneal tissue integrity, or contact lenses were observed.

Sensitization

Dermal—nonhuman

Pentaerythrityl tetrabehenate/benzoate/ethylhexanoate. In a skin contact allergenicity test of pentaerythrityl tetrabehenate/benzoate/ethylhexanoate (16.6%) using female albino guinea pigs (n = 10 test, 5 control), no signs of irritation or sensitization were observed when challenged (16.6% and 50%).[35,36] The acetone control had the expected results.

Pentaerythrityl tetraethylhexanoate/benzoate. In a contact allergenicity test of pentaerythrityl tetraethylhexanoate/benzoate (100%) using female albino Hartley guinea pigs (n = 10, 5 control), no signs of irritation or sensitization were observed when challenged (1.8%-100%).[36,37] The acetone control had the expected results.

Dermal—human

Pentaerythrityl tetracaprylate/tetracaprate. In a human repeated insult patch test (HRIPT; n = 115) of a cream blush containing pentaerythrityl tetracaprylate/tetracaprate (5%), no irritation or sensitization was observed.[37]

Pentaerythrityl tetrabehenate. In an HRIPT (n = 107), an eyeliner containing pentaerythrityl tetrabehenate (1.705%), no irritation or sensitization was observed.[38]

Pentaerythrityl tetraisostearate. In an HRIPT (n = 107) of a lip gloss containing pentaerythrityl tetraisostearate (55%), no irritation or sensitization was observed.[39]

Phototoxicity

There were no phototoxicity studies discovered for the pentaerythrityl tetraesters.

Summary

This is a safety assessment of pentaerythrityl tetraisostearate and other pentaerythrityl tetraester compounds used as cosmetic ingredients. The functions of these ingredients include hair-conditioning agents, plasticizers, skin-conditioning agents—miscellaneous, binders, skin-conditioning agents—occlusive, viscosity-increasing agents—nonaqueous, and skin-conditioning agents—emollient.

Pentaerythrityl tetraisostearate was reported to be used in 532 leave-on and 9 rinse-off products up to 0.1% to 55% in leave-on products and up to 0.1% in a rinse-off product. Pentaerythrityl tetraethylhexanoate/benzoate was reported to be used in 4 leave-on products up to 40%. Pentaerythrityl tetrabehenate was reported to be used up to 3% in 8 leave-on products. Pentaerythrityl tetrabehenate/benzoate/ethylhexanoate was reported to be used in 7 leave-on products up to 16% and in rinse-off products up to 0.5%. Pentaerythrityl tetracaprylate/tetracaprate was reported to be used in 26 leave-on products at 5%, up to 1% in hair sprays. Pentaerythrityl tetraethylhexanoate was reported to be used in 224 leave-on products up to 50% and 17 rinse-off products up to 20%. Pentaerythrityl tetraethylhexonate is reported to be used in suntan gels, creams, and liquids up to 16% and other suntan products up to 21%, which may or not be spray products, but this ingredient is used in nonspray products at concentrations of 45% to 50%. Pentaerythrityl tetrapelargonate was reported to be used in 1 hair product and pentaerythrityl tetralaurate in 1 eye product. Pentaerythrityl tetrastearate was reported to be used up to 7% in leave-on products. There were no reports to the VCRP or the Council survey of use for pentaerythrityl tetra C5-9 acid esters, pentaerythrityl C5-10 acid esters, pentaerythrityl tetramyristate, pentaerythrityl tetracocoate, pentaerythrityl tetraoleate, pentaerythrityl tetrabenzoate, pentthrityl tetraisononononanoate, and penaerythirtyl tetrapleargonate.

There were no mortalities in rats orally administered 1943 mg/kg pentaerythrityl tetra C5-9 acid esters. There was no mortality in rats orally administered pentaerythrityl tetra C5-9 acid esters at 1940 mg/kg and pentaerythrityl tetra C5-10 acid esters at 5000 mg/kg. The oral LD_{50} for pentaerythrityl tetrabenzoate was reported to be 1158 mg/kg in rats. The dermal NOAEL was 2000 mg/kg/d for female rats and >2000 mg/kg/d over 13 weeks for pentaerythrityl tetra C5-9 acid esters.

Dermally applied pentaerythrityl tetra C5-9 acid esters at 2000 mg/kg had no effects on male or female reproductive organs in rats. There were no teratogenic effects up to 2000 mg/kg. Pentaerythrityl tetra C5-9 acid esters and pentaerythrityl tetrabenzoate were not genotoxic in reverse mutation assays. Aerosolized pentaerythrityl tetra C5-9 acid was neither cytotoxic to red blood cell formation nor did it induce increased micronulceated PCEs or NCEs in the bone marrow of rats.

Pentaerythrityl tetra C5-9 acid esters were mildly irritating in rats at 800 mg/kg when administered dermally for 13 weeks. Using an eyeliner containing pentaerythrityl tetrabehenate at 1.705% for 4 weeks did not cause irritation. Pentaerythrityl tetrabehenate/benzoate/ethylhexanoate at 16.6% and pentaerythrityl tetraethylhexanoate/benzoate at 100% were not sensitizing to guinea pigs. Pentaerythrityl tetrabehenate in an eyeliner, pentaerythrityl tetraisostearate in a lip gloss, and pentaerythrityl tetracaprylate/tetracaprate in a cream blush were not sensitizing at 1.705%, 55%, and 5%, respectively.

Discussion

The Expert Panel noted gaps in the available safety data for the pentaerythrityl tetraester compounds in this safety assessment. The available data on many of the ingredients are sufficient, however, and similarity between structures suggested that the available data may be read across to address the entire group. In addition, these ingredients have similar functions in cosmetics.

Previous safety assessments support the safety for most of the fatty acid components of these ingredients, including coconut, isostearic, oleic, lauric, myristic, and stearic acids. These may be esterase metabolites that could result from the cleavage of pentaerythrityl tetracocoate, pentaerythrityl tetraisostearate, pentaerythrityl tetraoleate, pentaerythrityl tetralaurate, pentaerythrityl tetramyristate, and pentaerythrityl tetrastearate, respectively. Likewise, benzoic acid (a potential metabolite of pentaerythrityl tetrabenzoate, pentaerythrityl tetraethylhexanoate/benzoate, and pentaerythrityl tetrabehenate/benzoate/ethylhexanoate) was determined by the Panel to be safe for use in cosmetic formulations in the present practices of use and concentration.

The Panel stressed that the cosmetics industry continue to use current good manufacturing practices to limit impurities. Because these ingredients were reported to be used in products that may be aerosolized, including hair sprays and deodorants, the Panel discussed the issue of incidental inhalation exposure. The Panel considered that the preponderance of the data indicates that incidental inhalation exposures to these ingredients in aerosolized cosmetic products would not cause adverse health effects. The limited data available from one repeated dose inhalation study suggest little potential for respiratory effects at relevant doses. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than those in the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics. The Panel considered other data available to characterize the potential for pentaerythrityl tetraesters to cause reproductive toxicity, genotoxicity, irritation and sensitization, or other toxic effects. They noted the lack of systemic toxicity at high doses in acute and subchronic exposure studies, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, and the absence of genotoxicity in Ames tests and a micronucleus test. In addition, these ingredients are large molecules with a low dermal bioavailability (2%-6%), which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. Further, these ingredients are reportedly used at concentrations of 21% or less in cosmetic products that may be aerosolized. The Panel noted that 95% to 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Furthermore, several of these ingredients are used for viscosity-increasing functions, indicating that they tend to swell and aggregate in water and other solvents and would, thus, be too large to be inhaled or respired. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products that may be aerosolized is available at http://www.cir-safety.org/cir-findings.

Conclusion

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

- pentaerythrityl tetraisostearate,
- pentaerythrityl tetra C5-9 acid esters*,
- pentaerythrityl tetra C5-10 acid esters*,
- pentaerythrityl tetracaprylate/tetracaprate,
- pentaerythrityl tetralaurate,
- pentaerythrityl tetramyristate*,
- pentaerythrityl tetrastearate,
- pentaerythrityl tetrabehenate,
- pentaerythrityl tetracocoate*,
- pentaerythrityl tetraoleate*,
- pentaerythrityl tetraethylhexanoate,
- pentaerythrityl tetraethylhexanoate/benzoate,
- pentaerythrityl tetrabehenate/ benzoate/ethylhexanoate,
- pentaerythrityl tetrabenzoate*,
- pentaerythrityl tetraisononanoate, and
- pentaerythrityl tetrapelargonate.

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

Authors' Contributions

Becker contributed to conception and design; contributed to acquisition, analysis, and interpretation; and drafted the manuscript; Gill contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Bergfeld contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Belsito contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Hill contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Klaassen contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Liebler contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Marks contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Shank contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Slaga contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript; Snyder contributed to conception and design; contributed to analysis and interpretation; and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Author's Note

Unpublished sources cited in this report are available from the director, Cosmetic Ingredient Review, 1620L Street, NW, Suite 1200, Washington, DC 20036, USA.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The articles in this supplement were sponsored by the Cosmetic Ingredient Review.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review is financially supported by the Personal Care Products Council.

References

1. Gottschalck TE, Bailey JE, eds. *International Cosmetic Ingredient Dictionary and Handbook*. 13th ed. Washington, DC: Personal Care Products Council; 2010.
2. Johnson WJ Jr, Bergfeld WF, Belsito DV, Hill RA, et al. *Final Report of the Cosmetic Ingredient Review Expert Panel on the Safety Assessment of Pelargonic Acid (Aka Nonanoic Acid) and Nonanoate Esters*. Washington, DC: Cosmetic Ingredient Review; 2010:1-77.
3. Andersen FA. Final report on the safety assessment of coconut oil, coconut acid, hydorgenated coconut acid, and hydrogenated coconut oil. *J Am Coll Toxicol*. 1986;8(3):103-121.
4. Andersen FA. Final report on the safety assessment of isostearic acid. *J Am Coll Toxicol*. 1983;2(7):61-74.
5. Andersen FA. Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. *Int J Toxicol*. 1987;6(3):321-401.
6. Andersen FA. Final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate. *Int J Toxicol*. 2001;20(suppl 3):23-50.
7. Marrian SF. The chemicalreactions of pentaerythritol and its derivatives. *Chem Rev*. 1947;42(1):149-202.
8. Youngs CG. Preparation of esters and anhydrides from long chain fatty acid chlorides. *J Am Oil Chem Soc*. 1958;35(8):416-417.
9. Thum O, Oxenbøll M. Biocatalysis - a sustainable method for the production of emollient esters. *SÖFW J*. 2008;134(1-2):44-47.
10. Environmental Protection Agency. Test results—acute toxicity, pentaerythrityl tetra C5-10 acid esters, study 1; 1987. Web site. http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=2&v_rs_list=25025425,25014754. Unpublished data submited to the High Production Volume Information System (HPVIS). Accessed February 2011.
11. Environmental Protection Agency. Test results—acute toxicity, pentaerythrityl tetra C5-10 acid esters, study 2. 1. Web site. http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=2&v_rs_list=25025425,25014754. Report No. Study 2. Unpublished data submitted to the High Production Volume Information System (HPVIS). No Date Provided. Accessed February 2011.
12. Environmental Protection Agency. Genetic toxicity in vitro: (6772-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 3. 1000. Web site. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101091. Unreferenced study submitted to the High Production volume Information System (HPVIS). No Date Provided. Accessed February 2011.
13. Personal Care Products Council. Concentration of Use Pentaerythrityl Tetraisononanoate and Pentaerythrityl Tetrapelargonate. Unpublished data submitted by Personal Care Products Council; 2011:1.
14. Personal Care Products Council. Updated Concentration of Use by FDA Product Category: Pentaerythrityl Tetraesters. Unpublished data submitted by Personal Care Products Council; 2011:4.
15. Personal Care Products Council. Updated Concentration of Use by FDA Product Category Pentaerythrityl Tetraisostearate, Pentaerythrityl Tetraabietate, Pentaerythrityl Tetraacetate, Pentaerythrityl Tetrabehenate, Pentaerythrityl TetrabehenatefBenzoate/Ethylhexanoate, Pentaery thrityl Tetrabenzoate, Pentaerythrityl Tetra C5-9 Acid Esters, Pentaerythrityl Tetra CS-b Acid Esters, Pentaerythrityl Tetracaprylate/Tetracaprate, Pentaerythrityl Tetracocoate, Pentaerythrityl Tetraethylhexanoate, Pentaerythrityl TetraethylhexanoatefBenzoate, Pentaerythrityl Tetralaurate, Pentaerythrityl Tetramyristate, Pentaerythrityl Tetraoleate, Pentaerythrityl Tetrapelargonate and Pentaerythrityl Tetrastearate. Unpublished data submitted by the Personal Care Products Council; 2011:1-3.
16. Personal Care Products Council. Concentration of use by FDA product category pentaerythrityl tetraisostearate, pentaerythrityl tetraabietate, pentaerythrityl tetraacetate, pentaerythrityl tetrabehenate, pentaerythrityl tetrabehenate/benzoate/ethylhexanoate, pentaery thrityl tetrabenzoate, pentaerythrityl tetra C5-9 acid

esters, pentaerythrityl tetra C5-10 acid esters, pentaerythrityl tetracaprylate/tetracaprate, pentaerythrityl tetracocoate, pentaerythrityl tetraethylhexanoate, pentaerythrityl tetraethylhexanoate/benzoate, pentaerythrityl tetralaurate, pentaerythrityl tetramyristate, pentaerythrityl tetraoleate, pentaerythrityl tetrapelargonate and pentaerythrityl tetrastearate. Unpublished data submitted by the Personal Care Products Council; 2011:1-3.

17. Personal Care Products Council (Council). Concentration of use—additional coconut oil-derived ingredients. Unpublished data submitted by Personal Care Products Council; 2008:7.
18. US Food and Drug Administration. Defoaming agents used in the manufacture of paper and paperboard; 2010. Web site. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=176.210. Accessed April 2011.
19. Johnson MA. The influence of particle size. *Spray Technol Mark*. 2004;14(11):24-27.
20. Rothe H. Special aspects of cosmetic spray evaluation. Unpublished information presented to the 26 September CIR Expert Panel. Washington, DC; 2011.
21. Bower D. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting; 1999.
22. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. General Fact Sheet: limiting conditions and reliability, ventilation, room size, body surface area; Updated version for ConsExpo 4; 2006:1-31. Web site. http://www.rivm.nl/bibliotheek/rapporten/320104002.pdf. Accessed August 24, 2011. Report No. RIVM 320104002/2006.
23. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
24. Shiokawa Y, Matsumoto S, Sato Y, Kato K, Kitamura M. Process for the production of polyol ester and ester-containing lubricating oil. US patent 5,705,459. January 6, 1998.
25. U.S.Food and Drug Administration. Indirect food additives: Paper and paperboard components; 2009. 21CFR176.170. Web site. http://edocket.access.gpo.gov/cfr_2009/aprqtr/21cfr176.170.htm. Accessed April 15, 2011.
26. U.S.Food and Drug Administration. Indirect food additives: Polymers-Subpart B Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces Sec. 177. 1590 Polyester elastomers. Web site. http://edocket.access.gpo.gov/cfr_2009/aprqtr/21cfr177.1590.htm. Published 2009. Accessed April 15, 2011.
27. Environmental Protection Agency (EPA). Repeated-dose toxicity: (67762-53-2) carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1; 1985. Web site. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101091. pp. 1- Unpublished data submitted to the High Production Volume Information System (HPVIS). Accessed February 2011.
28. Environmental Protection Agency. Acute toxicity: (67762-53-2) carboxilyic acids, C5-9, tetraesters with pentaerythritol, Study 1; 1999:1. Web site. http://iaspub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=2&v_rs_list=25014643,25025073. Unpublished data submitted to the High Production Volume Information System (HPVIS). Accessed February 2011.
29. Nihon Iyaku Joho Senta. Pentaerythritol tetranitrate. In: *Nihon Iyakuhin Shu [Drugs in Japan]*. Tokyo, Japan: Nippon Iyaku Joho Senta; 1974:1105-1106.
30. Environmental Protection Agency. Genetic toxicity in vivo: (67662-53-2) carboxilic acids, C5-9, tetraesters with pentaerythritol, Study 1; 1991. Web site. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101091. Unpublished data submitted to the High Production Volume Information System (HPVIS). Accessed February 2011.
31. Environmental Protection Agency. Reproductive toxicity: (67762-53-2) carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1; 1986. Web site. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101091. Unpublished data submitted to the High Production Volume Information System (HPVIS). Accessed February 2011.
32. Environmental Protection Agency. Genetic Toxicity in vitro: (6772-53-2) carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1; 1999. Web site. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101091. Unpublished data submitted to the High Production Volume Information System (HPVIS). Accessed February 2011.
33. Environmental Protection Agency. Genetic Toxicity in vitro: (6772-53-2) carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 2; 1999. Web site. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101091. Unpublished data submitted to the High Production Volume Information System (HPVIS). Accessed February 2011.
34. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity test V. Results from the testing of 311 chemicals. *Environ Mol Mutagen*. 1992;19(21):2-141.
35. Clinical Research Laboratories. An in-use safety evaluation to determine the ocular irritation potential of a cosmetic product (eyeliner containing 1.705% Pentaerythrityl Tetrabehenate). CRL Study Number: CRL169007. Unpublished data submitted by the Personal Care Products Council; 2008.
36. Anonymous. Safety data (contact allergenicity in guinea pigs) of Pentaerythrityl Tetrabenzoate/Benzoate/Ethylhexanoate and Pentaerythrityl Tetraethylhexanoate/Benzoate. Unpublished data submitted by Personal Care Products Council; 2011:10.
37. Clinical Research Laboratories Inc. Repeated insult patch test of a blush product containing 5% Pentaerythrityl Tetracaprylate/Tetracaprate. CRL Study Number: CRL85006-1. Unpublished data submitted by the Personal Care Products Council; 2006.
38. Consumer Product Testing Co. Repeated insult patch test of an eyeliner containing 1.705% Pentaerythrityl Tetrabehenate. Experiment Reference Number: C08—1387.02. Unpublished data submitted by the Personal Care Products Council; 2008.
39. TKL Research. Repeated insult patch test of a lip product containing 55% Pentaerythrityl Tetraisostearate. TKL Study No.: DS11O11O-3. Unpublished data submitted by the Personal Care Products Council; 2010.
40. American Chemistry Council's Aliphatic Esters Poyol Esters Task Force. High Production Volume (HPV) Chemical Challenge Program; Test plan for the polyol esters category of the aliphatic esters chemicals. Report No. 201-16833B; 2010:1-41.

41. *Estimation Programs Interface Suite™ for Microsoft® Windows*. Washington, DC: United States Environmental Protection Agency;2011.
42. *Advanced Chemistry Development (ACD/Labs) Software*. Version 11.02. Toronto, ON: ACD/Labs; 2010.
43. Margaillan L and Savary P. Sur les esters de la pentaérythritite et des acides gras. *Bulletin de la Société Chimique de France*. 1947;188.
44. MOSES is a C++ chemoinformatics software library that is developed and maintained by Molecular Networks GmbH, Erlangen, Germany; 2013. Web site. http://www.molecular-networks.com/software/moses/.
45. Scientific and Technical Information Network. Pentaerythrityl tetrapelargonate. Registry file. Web site. http://stnweb.cas.org. Accessed September 7, 2009.