

**Pentaerythrityl Tetraesters
as Used in Cosmetics**

August 23, 2012

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

© Cosmetic Ingredient Review

1101 17th Street, NW, Suite 412 ♦ Washington, DC 20036-4702 ♦ ph 202.331.0651 ♦ fax 202.331.0088 ♦ cirinfo@cir-safety.org

TABLE OF CONTENTS

TABLE OF CONTENTS.....	i
ABSTRACT.....	1
INTRODUCTION.....	1
CHEMISTRY.....	1
Definition and Structure.....	1
Physical and Chemical Properties.....	1
Method of Manufacture.....	1
Impurities.....	2
UV Absorption.....	2
USE.....	2
Cosmetic.....	2
Non-Cosmetic.....	3
TOXICOKINETICS.....	3
Absorption, Distribution, Metabolism, and Excretion.....	3
TOXICOLOGICAL STUDIES.....	3
Acute Toxicity.....	3
Dermal.....	3
Oral – Non-Human.....	3
Inhalation.....	3
Repeated Dose Toxicity.....	3
Dermal – Non-Human.....	3
Oral.....	4
Inhalation.....	4
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY.....	4
GENOTOXICITY.....	4
In Vitro.....	4
In Vivo.....	4
CARCINOGENICITY.....	4
IRRITATION AND SENSITIZATION.....	4
Irritation.....	4
Dermal – Non-Human.....	4
Dermal and Mucosal -Human.....	5
Ocular.....	5
Sensitization.....	5
Dermal – Non-Human.....	5
Dermal – Human.....	5
Phototoxicity.....	5
SUMMARY.....	5
DISCUSSION.....	6
CONCLUSION.....	7
TABLES.....	8
REFERENCES.....	14

ABSTRACT

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

INTRODUCTION

This safety assessment summarizes published and unpublished data relevant to the safety of pentaerythrityl tetraisostearate and other pentaerythrityl tetraester compounds used in cosmetics. These 16 ingredients are:

- Pentaerythrityl tetraisostearate
- Pentaerythrityl tetra C5-9 acid esters
- Pentaerythrityl tetra C5-10 acid esters
- Pentaerythrityl tetracaprylate/tetracaprate
- Pentaerythrityl tetralaurate
- Pentaerythrityl tetramyristate
- Pentaerythrityl tetrastearate
- Pentaerythrityl tetrabenenate
- Pentaerythrityl tetracocoate
- Pentaerythrityl tetraoleate
- Pentaerythrityl tetraethylhexanoate
- Pentaerythrityl tetraethylhexanoate/ benzoate
- Pentaerythrityl tetrabenenate/ benzoate/ethylhexanoate
- Pentaerythrityl tetrabenzoate
- Pentaerythrityl tetraisononanoate
- Pentaerythrityl tetrapelargonate

The functions of these ingredients include: hair conditioning agents; skin-conditioning agents – miscellaneous; binders; skin-conditioning agents - occlusive; viscosity increasing agents - nonaqueous; and skin-conditioning agents – emollient.

Two of these ingredients previously were reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in another safety assessment. Pentaerythrityl tetraisononanoate and pentaerythrityl tetrapelargonate, were determined to be safe in the present practices of use and concentration.¹ These 2 ingredients were added to this report to 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.²⁻⁴ Benzoic acid (a metabolite of pentaerythrityl tetrabenzoate, pentaerythrityl tetraethylhexanoate/benzoate, and pentaerythrityl tetrabenenate/benzoate/ethylhexanoate) was determined by the Panel to be safe for use in cosmetic formulations in the present practices of use and concentration at their meeting on September 26-27, 2011. This revised the earlier safety assessment of Benzoic Acid.⁵

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 CAS Nos., 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 has an estimated Log P_{ow} of 16.7.

Method of Manufacture

Pentaerythrityl tetraesters can be prepared from pentaerythritol by alcohol esterification methods (e.g., by reaction with acids, acid chlorides, or acid anhydrides).⁶ For example, pentaerythritol tetrastearate can be manufactured by heating stearoyl chloride and pentaerythritol (4:1 ratio) at 100°C, under 2 mmHg.⁷ 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 (i.e., for producing cosmetic grade esters), also is a potential process for the manufacture of these ingredients.⁸

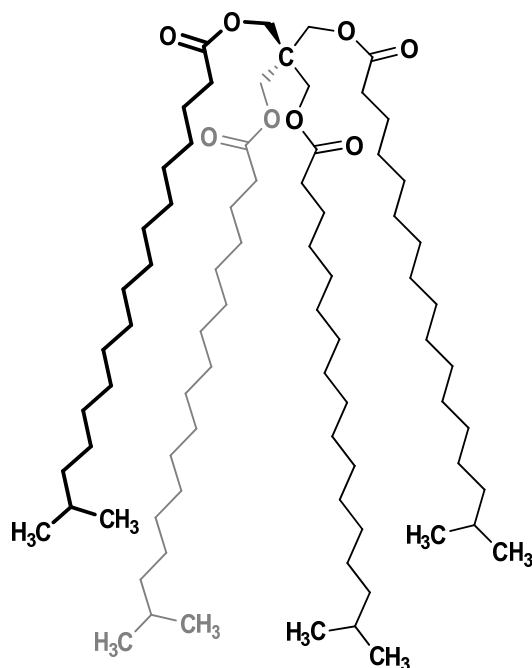


Figure 1. Pentaerythrityl tetraisostearate

Impurities

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

UV Absorption

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 ultraviolet (UV) absorption (i.e. no detectable absorption in the UVA and UVB bands). The alkyl carboxyl groups found in most of these ingredients would be expected to absorb in the UVC range, as would the non-conjugated alkenyl groups of pentaerythrityl tetraoleate. However, the aromatic, conjugated carboxyl groups present in pentaerythrityl tetrabenzoate, pentaerythrityl tetraethylhexanoate/benzoate, and pentaerythrityl tetrabeheenate/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 (FDA) Voluntary Cosmetic Registration Program (VCRP) and a survey conducted by the Personal Care Products Council (Council) collected use concentrations for ingredients in this group.¹²⁻¹⁷ 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% - 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.

Pentaerythrityl tetraethylhexanoate/benzoate was reported to be used in 4 leave-on products up to 40%. Pentaerythrityl tetrabeheenate was reported to be used up to 2% - 3% in 8 leave-on products. Pentaerythrityl tetrabeheenate/benzoate/ethylhexanoate was reported to be used in 7 leave-on products up to 2% - 16% and in rinse-off products up to 0.5%.

Pentaerythrityl tetracaprylate/tetracaprate was reported to be used in 26 leave-on products at 0.07% - 5%; up to 1% in hair sprays. Pentaerythrityl tetraethylhexanoate was reported to be used in 224 leave-on products up to 0.06% - 50% and 17 rinse-off products up to 1% - 20%. This includes suntan gels, creams, and liquids up to 16 % and other suntan products up to 21%, which may or not be spray products.

Pentaerythrityl tetrapelargonate was reported to be used in 1 hair product and pentaerythrityl tetralaurate in 1 eye product by the VCRP. The Council has no reported use concentrations for these ingredients. Pentaerythrityl tetrastearate was reported to be used up to 7% in leave-on products. The VCRP has no uses reported for this ingredient.

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, pentaerythrityl tetraisononanoate, and pentaerythrityl tetrapelargonate.

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 $>10 \mu\text{m}$.^{18,19} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal region and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.²⁰⁻²² 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.²¹ 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.

Non-Cosmetic

Pentaerythrityl tetraesters are used in lubricating oils of jet engines, low-temperature use grease, heat-resistant engine oil, and refrigerator oil.²³

Pentaerythrityl tetrastearate is an indirect food additive that may be used to make food packaging.²⁴ It may also be used in cellophane that comes in contact with food with a limit of 0.1%.²⁵ Pentaerythrityl fatty acids may be used as defoaming agents in paper and paperboard intended for food use.¹⁷

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

There were no experimental data discovered on the toxicokinetics of pentaerythrityl 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 the test article was 2% to 6%.²⁶

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal

There were no dermal studies discovered for pentaerythrityl tetraesters.

Oral – Non-Human

PENTAERYTHRITYL TETRA C5-9 ACID ESTERS

Sprague-Dawley rats (n = 5/sex) were orally administered pentaerythrityl tetra C5-9 acid esters (1940 mg/kg).^{9,10} There were no deaths. One male had unformed stool at 4 h 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).²⁷ 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).^{9,10} There were no deaths or clinical signs. Necropsy was unremarkable at 14 days.

PENTAERYTHRITYL TETRABENZOATE

The oral LD_{50} for pentaerythrityl tetrabenzoate was reported to be 1158 mg/kg in rats.²⁸

Inhalation

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

Repeated Dose Toxicity

Dermal – Non-Human

PENTAERYTHRITYL TETRA C5-9 ACID ESTERS

Pentaerythrityl tetra C5-9 acid esters (0, 800, 2000 mg/kg, neat) were dermally administered to clipped backs of Sprague-Dawley rats (n = 10/sex) for 5 days/week for 13 weeks.²⁶ 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; 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 NOAEL was 2000 mg/kg/day.

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.²⁹ 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, 2000 mg/kg) were dermally administered to clipped backs of Sprague-Dawley rats (n = 10/sex) for 5 days/week for 13 weeks.²⁶ 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 – 19 of gestation.³⁰ Neither maternal parameters (food consumption, 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 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, 5000 µg/plate) using *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *Escherichia coli* (WP2uvrA) with and without metabolic activation, the results were negative.³¹ 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.

In a reverse mutation assay using *E. coli* (WP2uvrA), pentaerythrityl tetra C5-9 acid esters (33.3, 100, 333, 1000, 3330, 5000 µg/plate) with and without metabolic activation, were not cytotoxic or mutagenic.³² The positive controls (2-aminoanthracene and 4-nitroquinoline-N-oxide) and negative vehicle controls (ethanol) had the expected results.

In a microsome reverse mutations assay using *S. typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP2uvrA), pentaerythrityl tetra C5-9 acid esters (33.3, 100, 333, 1000, 3330, 5000 µg/plate) was not mutagenic with or without metabolic activation.¹¹

PENTAERYTHRITYL TETRABENZOATE

A mutagenicity assay of pentaerythrityl tetrabenzoate (0.05 ml/plate) using *S. typhimurium* strains (TA97, TA98, TA100, TA1535, and TA1537) was negative.³³

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.²⁹ The test material was not cytotoxic to red blood cell formation nor did it induce increased micronucleated polychromatic erythrocytes (PCE) or normochromatic erythrocytes (NCE) in the bone marrow.

CARCINOGENICITY

There were no carcinogenicity studies discovered for pentaerythrityl tetraesters.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

PENTAERYTHRITYL TETRA C5-9 ACID ESTERS

Pentaerythrityl tetra C5-9 acid esters (0, 800, 2000 mg/kg) were dermally administered to clipped backs of Sprague-Dawley rats (n = 10/sex) for 5 days/week for 13 weeks.²⁶ 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 – 19 of gestation.³⁰ 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 tetrabenhenate (1.705%) daily for 4 weeks.³⁴ Trace increases in redness of the palpebral conjunctivae was 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 conjunctival irritation and no changes in visual acuity, corneal tissue integrity or contact lenses were observed.

Sensitization

Dermal – Non-Human

PENTAERYTHRITYL TETRABEHENATE/BENZOATE/ETHYLHEXANOATE

In a skin contact allergenicity test of pentaerythrityl tetrabenhenate/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%).^{34,35} The acetone control had the expected results.

PENTAERYTHRITYL TETRAETHYLHEXANOATE/BENZOATE

In a contact allergenicity test of pentaerythrityl tetraethylhexanoate/benzoate (100%) using female albino Harley guinea pigs (n = 10, 5 control), no signs of irritation or sensitization were observed when challenged (1.8%-100%).^{35,36} 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.³⁶

PENTAERYTHRITYL TETRABEHENATE

In a HRIPT (n = 107), an eyeliner containing pentaerythrityl tetrabenhenate (1.705%) was tested.³⁷ No irritation or sensitization was observed.

PENTAERYTHRITYL TETRAISOSTEARATE

In a HRIPT (n = 107) of a lip gloss containing pentaerythrityl tetraisostearate (55%), no irritation or sensitization was observed.³⁸

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% - 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 tetrabenhenate was reported to be used up to 2% – 3% in 8 leave-on products. Pentaerythrityl tetrabenhenate/benzoate/ethylhexanoate was reported to be used in 7 leave-on products up to 2% 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 0.07% - 5%; up to 1% in hair sprays. Pentaerythrityl tetraethylhexanoate was reported to be used in 224 leave-on products up to 0.06% - 50% and 17 rinse-off products up to 1% - 20%. Pentaerythrityl tetraethylhexanoate 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 not used in spray products at concentrations of 45%-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, penthrityl tetraisnononanoate, and pentaerythrityl tetrapelargonate.

There were no mortalities in rats orally administered 1943 mg/kg pentaerythrityl tetra C5-9 acid esters. There was no mortality to 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 LD₅₀ 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 micronucleated 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 tetrabenhenate at 1.705% for 4 weeks did not cause irritation.

Pentaerythrityl tetrabenhenate/benzoate/ethylhexanoate at 16.6% and pentaerythrityl tetraethylhexanoate/benzoate at 100% were not sensitizing to guinea pigs.

Pentaerythrityl tetrabenhenate 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.

Safety assessments have been completed that 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 tetrabenhenate/benzoate/ethylhexanoate) was determined by the Panel to be safe for use in cosmetic formulations in the present practices of use and concentration.

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 indicate 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 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% - 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
- 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.

TABLES

Table 1. Definitions, functions, and structures of pentaerythrityl ester ingredients in this safety assessment.³⁹

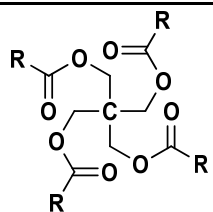
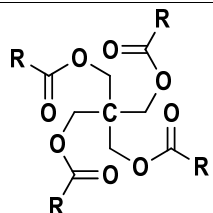
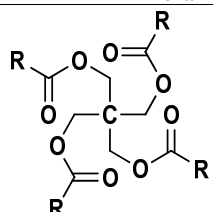
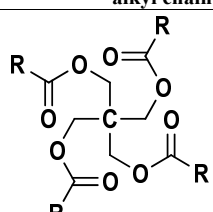
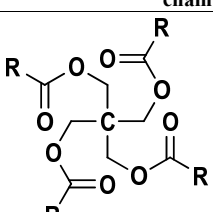
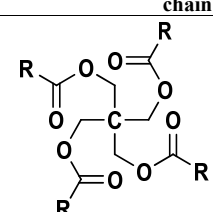
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Pentaerythrityl Tetra C5-9 Acid Esters 67762-53-2	The tetraester of branched and linear C5-9 acids with pentaerythritol.	Hair conditioning agent; plasticizer; skin-conditioning agent - miscellaneous	 <p style="text-align: center;">wherein R represents a 4-8 carbon alkyl chain</p>
Pentaerythrityl Tetra C5-10 Acid Esters 68424-31-7	The tetraester of C5-10 acids with pentaerythritol.	Plasticizer	 <p style="text-align: center;">wherein R represents a 4-9 carbon alkyl chain</p>
Pentaerythrityl Tetracaprylate/ Tetracaprate 68441-68-9	The tetraester of pentaerythritol and a blend of caprylic and capric acids.	Skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p style="text-align: center;">wherein R represents a 7 or 9 carbon alkyl chain</p>
Pentaerythrityl Tetralaurate 13057-50-6	The tetraester of pentaerythritol and lauric acid.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p style="text-align: center;">wherein R represents an 11 carbon alkyl chain</p>
Pentaerythrityl Tetramyristate 18641-59-3	The tetraester of pentaerythritol and myristic acid.	Skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p style="text-align: center;">wherein R represents an 13 carbon alkyl chain</p>
Pentaerythrityl Tetrastearate 115-83-3	The tetraester of pentaerythritol and stearic acid.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p style="text-align: center;">wherein R represents an 17 carbon alkyl chain</p>

Table 1. Definitions, functions, and structures of pentaerythrityl ester ingredients in this safety assessment.³⁹

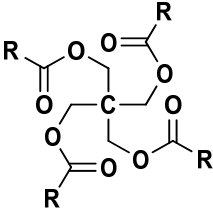
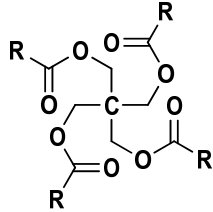

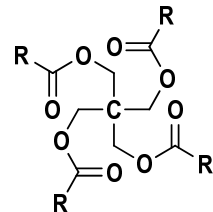

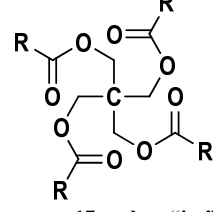
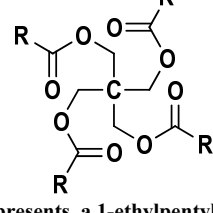
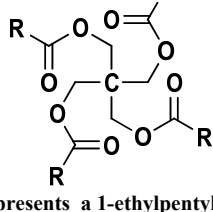
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Pentaerythrityl Tetrabenenate 61682-73-3	The tetraester of pentaerythritol and behenic acid.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p>wherein R represents a 21 carbon alkyl chain</p>
Pentaerythrityl Tetracocoate 92201-72-4	The tetraester of pentaerythritol and coconut fatty acid.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p>wherein  represents coconut fatty acid residues</p>
Pentaerythrityl Tetraoleate 19321-40-5	The tetraester of pentaerythritol and oleic acid.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p>wherein  represents an oleic acid (an Ω-9 unsaturated, 18 carbon fatty acid) residue</p>
Pentaerythrityl Tetraisostearate 62125-22-8	The tetraester of isostearic acid and pentaerythritol.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p>wherein R represents a 17 carbon "iso" alkyl chain</p>
Pentaerythrityl Tetraethylhexanoate 7299-99-2	The tetraester of pentaerythritol and 2-ethylhexanoic acid.	Binder; skin-conditioning agent - occlusive; viscosity increasing agent - nonaqueous	 <p>wherein R represents a 1-ethylpentyl chain</p>
Pentaerythrityl Tetraethylhexanoate/ Benzoate	The tetraester of pentaerythritol and a blend of ethylhexanoic and benzoic acids.	Hair conditioning agent; skin-conditioning agent - emollient	 <p>wherein R represents a 1-ethylpentyl chain or benzene</p>

Table 1. Definitions, functions, and structures of pentaerythrityl ester ingredients in this safety assessment.³⁹

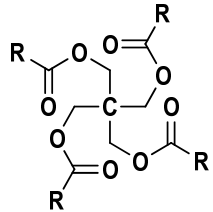
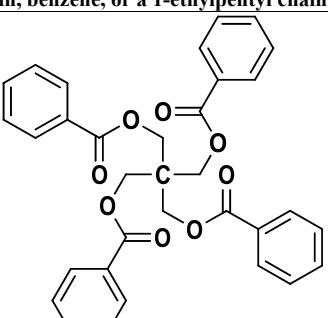
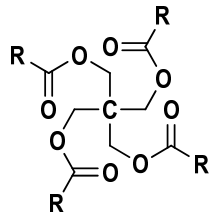
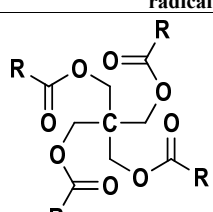
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Pentaerythrityl Tetrabenhenate/ Benzoate/ Ethylhexanoate	The tetraester of Pentaerythritol with a blend of behenic, benzoic and ethylhexanoic acids.	Hair conditioning agent; skin-conditioning agent - emollient	 <p>wherein R represents a 21 carbon alkyl chain, benzene, or a 1-ethylpentyl chain</p>
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	 <p>RCO- represents the isononanoic acid radical</p>
Pentaerythrityl Tetrapelargonate 14450-05-6	Tetraester of pentaerythritol and pelargonic acid	Fragrance ingredient; skin – conditioning agent – emollient	 <p>RCO- represents the pelargonic acid radical</p>

Table 2. Physical and chemical properties.

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 mmHg @ 25°C	1.6×10^{-21}	Estimated ⁴⁰
Log P _{ow}	16.7	Estimated ⁴⁰
Water Solubility g/L @ 25 °C (pH not provided)	3.4×10^{-15}	Estimated ⁴⁰
Pentaerythrityl Tetra C5-10 Acid Esters		
Molecular Weight g/mol	613	⁴⁰
Vapor pressure mmHg @ 25°C	7.03×10^{-21}	Estimated ⁴⁰
Water Solubility g/L @ 25 °C (pH not provided)	3.6×10^{-14}	Estimated ⁴⁰
Boiling Point °C	835	Estimated ⁴⁰
Melting Point °C	150	⁴¹
Pentaerythrityl Tetracaprylate/ Tetracaprate		

Table 2. Physical and chemical properties.

Property	Value	Reference
No data found		
Pentaerythrityl Tetralaurate		
Molecular Weight g/mol	865.36	Estimated ⁴²
Density/Specific Gravity @ 20°C	0.943 ± 0.06	Estimated ⁴²
Vapor pressure mmHg @ 25°C	3.28 x 10 ⁻²⁶	Estimated ⁴²
Melting Point °C	48.8-9	⁴³
Boiling Point °C	808.8 ± 60.0	Estimated ⁴²
Water Solubility g/L @ 25 °C & pH 1 – 10	4 x 10 ⁻⁹	Estimated ⁴²
Pentaerythrityl Tetramyristate		
Molecular Weight g/mol	977.58	⁴³
Density/Specific Gravity g/cm ³ @ 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 @ 25 °C & pH 1-10	4.7 x 10 ⁻¹⁰	Estimated ⁴²
Pentaerythrityl Tetrastearate		
Molecular Weight g/mol	1201.99	Estimated ⁴²
Density/Specific Gravity @ 20 °C	0.915 ± 0.06	Estimated ⁴²
Vapor pressure mmHg @ 25°C	1.5 x 10 ⁻²⁷	Estimated ⁴⁰
Boiling Point °C	998.5 ± 60.0	Estimated ⁴²
Melting Point °C	66-77	⁴⁰
Water Solubility g/L @ 25 °C & pH 1-10	6.3 x 10 ⁻¹¹	Estimated ⁴²
Pentaerythrityl Tetrabeheenate		
Molecular Weight g/mol	1426.42	Estimated ⁴²
Density/Specific Gravity @ 20°C	0.904 ± 0.06	Estimated ⁴²
Boiling Point °C	1109.5 ± 60.0	Estimated ⁴²
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 x 10 ⁻¹⁰	Estimated ⁴²
Pentaerythrityl Tetrakisostearate		
No data found		
Pentaerythrityl Tetraethylhexanoate		
Molecular Weight g/mol	640.93	Estimated ⁴²
Density/Specific Gravity @ 20°C	0.978 ± 0.06	Estimated ⁴²
Boiling Point °C	647.7 ± 50.0	Estimated ⁴²
Water Solubility g/L @ 25°C & pH 1-10	4 x 10 ⁻⁶	Estimated ⁴²
Pentaerythrityl Tetraethylhexanoate/Benzoate		
No data found		
Pentaerythrityl Tetrabeheenate/ Benzoate/ Ethylhexanoate		
No data found		
Pentaerythrityl tetrabenzoate		
Molecular Weight g/mol	552.57	Estimated ⁴²
Density/Specific Gravity @ 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 @ 25°C & pH 1-10	9.4 x 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 @ 20°C	0.969	⁴⁵
Melting Point °C	12	⁴⁵
Boiling Point °C	699.1± 50	⁴⁵
Water Solubility g/L @ 25°C & pH 1-10	7.7 x 10 ⁻⁷	⁴⁵
Vapor pressure mmHg@ 25°C	2.16E-19Torr	⁴⁵

Table 3. Frequency of use according to duration and maximum exposure range.¹²⁻¹⁷

Use type	Concentration		Concentration		Concentration		Concentration	
	Uses	(%)	Uses	(%)	Uses	(%)	Uses	(%)
	Pentaerythrityl tetracaprylate/tetracaprate		Pentaerythrityl tetralaurate		Pentaerythrityl tetrastearate		Pentaerythrityl tetrabenenate	
Total/range	26	0.07-5	1	NR	NR	7	8	2-3
<i>Duration of use</i>								
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
<i>Exposure type</i>								
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-non-coloring	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 tetrakisostearate		Pentaerythrityl tetraethylhexanoate		Pentaerythrityl tetraethylhexanoate/benzoate		Pentaerythrityl tetrabenenate/benzoate/ethylhexanoate	
	Uses	(%)	Uses	(%)	Uses	(%)	Uses	(%)
Total/range	541	0.1-55	241	0.06-50	4	40	7	0.5-16
<i>Duration of use</i>								
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
<i>Exposure type</i>								
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 ¹	NR	NR	2	0.5-2
Deodorant (underarm)	NR	NR	NR	0.1	NR	NR	NR	NR
Hair-non-coloring	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

Table 3. Frequency of use according to duration and maximum exposure range.¹²⁻¹⁷

Use type	Concentration		Concentration		Concentration		Concentration	
	Uses	(%)	Uses	(%)	Uses	(%)	Uses	(%)
	Pentaerythrityl tetrapelargonate							
Total/range	1	NR						
<i>Duration of use</i>								
Leave-on	1	NR						
Rinse-off	NR	NR						
Diluted for (bath) use	NR	NR						
<i>Exposure type</i>								
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-non-coloring	1	NR						
Hair-coloring	NR	NR						
Nail	NR	NR						
Mucous Membrane	NR	NR						
Baby	NR	NR						

NR – None reported

¹ Fragrance preparations (used up to 45% and 50%) are light gels that are applied with a small spatula-like applicator, not aerosols.

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

REFERENCES

1. Johnson Jr.WJ, Bergfeld, WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks Jr.J, Shank RC, Slaga TJ, and Snyder PW. Final report of the Cosmetic Ingredient Review Expert Panel n the safety assessment of pelargonic acid (aka nonanoic acid) and nonanoate esters. Washington, DC, Cosmetic Ingredient Review. 6-29-2010. pp. 1-77.
2. Andersen FA. Final report on the safety assessment of coconut oil, coconut acid, hydrogenated coconut acid, and hydrogenated coconut oil. *Journal of the American College of Toxicology*. 1986;8(3):103-121.
3. Andersen FA. Final report on the safety assessment of isostearic acid. *Journal of the American College of Toxicology*. 1983;2(7):61-74.
4. Andersen FA. Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. *International Journal of Toxicology*. 1987;6(3):321-401.
5. Andersen FA. Final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate. *International Journal of Toxicology*. 2001;20(Suppl 3):23-50.
6. Marrian SF. The chemicalreactions of pentaerythritol and its derivatives. *Chemical Reviews*. 1947;42(1):149-202.
7. Youngs CG. Preparation of esters and anhydrides from long chain fatty acid chlorides. *Journal of the American Oil Chemists' Society*. 1958;35:416-417.
8. Thum O and Oxenbøll M. Biocatalysis - A sustainable method for the production of emollient esters. *SÖFW Journal*. 2008;134(1-2):44-47.
9. Environmental Protection Agency (EPA). Test results - acute toxicity, pentaerythrityl tetra C5-10 acid esters, study 1. 1987. http://iaspub.epa.gov/opptpv/Public_Search.PublicTabs?SECTION=1&epcount=2&v_rs_list=25025425,25014754. Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
10. Environmental Protection Agency (EPA). Test results - acute toxicity, pentaerythrityl tetra C5-10 acid esters, study 2. 1. http://iaspub.epa.gov/opptpv/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; Date accessed 2/2011.
11. Environmental Protection Agency (EPA). Genetic toxicity in vitro: (6772-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 3. 1000. <http://iaspub.epa.gov/opptpv/quicksearch/display?pChem=101091>. Unreferenced study submitted to the High Production volume Information System (HPVIS); NO DATE PROVIDED; Date accessed 2/2011.
12. Personal Care Products Council. 11-7-2011. Concentration of Use Pentaerythrityl Tetraisnonanoate and Pentaerythrityl Tetrapelargonate. Unpublished data submitted by Personal Care Products Council. 1 pages.
13. Personal Care Products Council. 11-16-2011. Updated Concentration of Use by FDA Product Category: Pentaerythrityl Tetraesters. Unpublished data submitted by Personal Care Products Council. 4 pages.
14. Personal Care Products Council. Updated Concentration of Use by FDA Product Category Pentaerythrityl Tetraisostearate, Pentaerythrityl Tetraabietate, Pentaerythrityl Tetraacetate, Pentaerythrityl Tetrabeheenate, Pentaerythrityl Tetrabeheenate/Benzoate/Ethylhexanoate, Pentaery thrityl Tetrabenzoate, Pentaerythrityl Tetra C5-9 Acid Esters, Pentaerythrityl Tetra CS-b Acid Esters, Pentaerythrityl Tetraprylate/Tetracprate, Pentaerythrityl Tetracocoate, Pentaerythrityl Tetraethylhexanoate, Pentaerythrityl Tetraethylhexanoate/Benzoate, Pentaerythrityl Tetralaurate, Pentaerythrityl Tetramyristate, Pentaerythrityl Tetraoleate, Pentaerythrityl Tetrapelargonate and Pentaerythrityl Tetrastearate. 2011. pp. 1-3. Unpublished data submitted by the Personal Care Products Council.
15. Personal Care Products Council. Concentration of use by FDA product category pentaerythrityl tetraisostearate, pentaerythrityl tetraabietate, pentaerythrityl tetraacetate, pentaerythrityl tetrabeheenate, pentaerythrityl tetrabeheenate/benzoate/ethylhexanoate, pentaery thrityl tetrabenzoate, pentaerythrityl tetra C5-9 acid esters, pentaerythrityl tetra C5-10 acid esters, pentaerythrityl tetraprylate/tetracprate, pentaerythrityl tetracocoate, pentaerythrityl tetraethylhexanoate, pentaerythrityl tetraethylhexanoate/benzoate, pentaerythrityl tetralaurate, pentaerythrityl tetramyristate, pentaerythrityl tetraoleate, pentaerythrityl tetrapelargonate and pentaerythrityl tetrastearate. 2011. pp. 1-3. Unpublished data submitted by the Personal Care Products Council.
16. Personal Care Products Council (Council). 2008. Concentration of use - Additional coconut oil-derived ingredients. Unpublished data submitted by Personal Care Products Council. 7 pages.
17. U.S.Food and Drug Administration. Defoaming agents used in the manufacture of paper and paperboard. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=176.210>.
18. Johnson, M. A. The Influence of Particle Size. *Spray Technology and Marketing*. 2004;November:24-27.
19. Rothe H. Special aspects of cosmetic spray evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.
20. Bower, D. 1999. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting.
21. 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. <http://www.rivm.nl/bibliotheek/rapporten/320104002.pdf>. Date Accessed 8-24-2011. Report No. RIVM 320104002/2006. pp. 1-31.

22. 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.* 8-28-2011;205(2):97-104.
23. Shiokawa Y, Matsumoto S, Sato Y, Kato K, and Kitamura M; inventor. Process for the production of polyol ester and ester-containing lubricating oil. 5,705,459. 1-6-1998.
24. U.S. Food and Drug Administration. Indirect food additives: Paper and paperboard components. 2009. 21CFR176.170: http://edocket.access.gpo.gov/cfr_2009/aprqrtr/21cfr176.170.htm
25. 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. http://edocket.access.gpo.gov/cfr_2009/aprqrtr/21cfr177.1590.htm.
26. Environmental Protection Agency (EPA). Repeated-dose toxicity: (67762-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1. 1985. <http://iaspub.epa.gov/oppphpv/quicksearch/display?pChem=101091>. pp. 1- Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
27. Environmental Protection Agency (EPA). Acute toxicity: (67762-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1. 1999. http://iaspub.epa.gov/oppphpv/Public_Search/PublicTabs?SECTION=1&epcount=2&v_rs_list=25014643,25025073. pp. 1- Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
28. Nihon Iyaku Joho Senta. Pentaerythritol tetranitrate. In: *Nihon Iyakuin Shu [Drugs in Japan]*. Tokyo, Japan: Nippon Iyaku Joho Senta; 1974:1105-1106.
29. Environmental Protection Agency (EPA). Genetic toxicity in vivo: (67662-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1. 1991. <http://iaspub.epa.gov/oppphpv/quicksearch/display?pChem=101091>. Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
30. Environmental Protection Agency (EPA). Reproductive toxicity: (67762-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1. 1986. <http://iaspub.epa.gov/oppphpv/quicksearch/display?pChem=101091>. Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
31. Environmental Protection Agency (EPA). Genetic Toxicity in vitro: (6772-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 1. 1999. <http://iaspub.epa.gov/oppphpv/quicksearch/display?pChem=101091>. Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
32. Environmental Protection Agency (EPA). Genetic Toxicity in vitro: (6772-53-2) Carboxylic acids, C5-9, tetraesters with pentaerythritol, Study 2. 1999. <http://iaspub.epa.gov/oppphpv/quicksearch/display?pChem=101091>. Unpublished data submitted to the High Production Volume Information System (HPVIS); Date accessed 2/2011.
33. Zeiger E, Anderson B, Haworth S, Lawlor T, and Mortelmans K. Salmonella mutagenicity test V. Results from the testing of 311 chemicals. *Environmental and Molecular Mutagenesis.* 1992;19(21):2-141.
34. Clinical Research Laboratories. 2008. An in-use safety evaluation to determine the ocular irritation potential of a cosmetic product (eyeliner containing 1.705% Pentaerythrityl Tetrabenenate). CRL Study Number: CRL169007. Unpublished data submitted by the Personal Care Products Council.
35. Anonymous. 2011. Safety data (contact allergenicity in guinea pigs) of Pentaerythrityl Tetrabenzoate/Benzoate/Ethylhexanoate and Pentaerythrityl Tetraethylhexanoate/Benzoate. Unpublished data submitted by Personal Care Products Council. 10 pages.
36. Clinical Research Laboratories Inc. 2006. 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.
37. Consumer Product Testing Co. 2008. Repeated insult patch test of an eyeliner containing 1.705% Pentaerythrityl Tetrabenenate. Experiment Reference Number: C08—1387.02. Unpublished data submitted by the Personal Care Products Council.
38. TKL Research. 2010. Repeated insult patch test of a lip product containing 55% Pentaerythrityl Tetraisoostearate. TKL Study No.: DS110110-3. Unpublished data submitted by the Personal Care Products Council.
39. Gottschalck TE and Bailey JE eds. International Cosmetic Ingredient Dictionary and Handbook. 13th ed. Washington, D.C.: Personal Care Products Council; 2010.
40. American Chemistry Council's Aliphatic Esters Polyol Esters Task Force. High Production Volume (HPV) Chemical Challenge Program; Test plan for the polyol esters category of the aliphatic esters chemicals. 2010. Report No. 201-16833B. pp. 1-41.
41. Estimation Programs Interface Suite™ for Microsoft® Windows. Washington, DC, USA: United States Environmental Protection Agency, Washington, DC, USA.; 2011.
42. Advanced Chemistry Development (ACD/Labs) Software V11.02. Toronto, ON; 2010.
43. Margailan L and Savary P. Sur les esters de la pentaérythrite et des acides gras. *Bulletin de la Société Chimique de France.* 1947;188.

44. Cambridge, MA:Cambridge Soft Corporation;2002.
45. Scientific and Technical Information Network (STN). Pentaerythrityl tetrapelargonate. Registry file. <http://stnweb.cas.org>. Date Accessed 9-7-2009.