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Safety Assessment of Trialkyl Trimellitates as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 5 trialkyl trimellitates. These ingredients, which are all structurally related as alkyl esters of trimellitic acid, are reported to function in cosmetics as skin conditioning agents; 2 of the ingredients are also reported to function in cosmetics as plasticizers. The Panel reviewed the available data to determine the safety of these ingredients, and concluded that the trialkyl trimellitates are safe in the current practices of use and concentration when formulated to be non-irritating.

Keywords

Safety, Cosmetics, Tridecyl Trimellitate, Tricaprylyl/Capryl Trimellitate, Triethylhexyl Trimellitate, Triisodecyl Trimellitate, Triisotridecyl Trimellitate

Introduction

This is a safety assessment of the following 5 trialkyl trimellitates as used in cosmetic formulations:

Tridecyl Trimellitate
Tricaprylyl/Capryl Trimellitate
Triethylhexyl Trimellitate
Triisodecyl Trimellitate
Triisotridecyl Trimellitate

As given in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients are reported to function in cosmetics as skin conditioning agents (Table 1).[1] Tricaprylyl/capryl trimellitate and triethylhexyl trimellitate are also reported to function in cosmetics as plasticizers.

These trialkyl trimellitates form a family of cosmetic ingredients because they are all structurally related as alkyl esters of the aromatic triprotic acid, trimellitic acid. The only structural difference between these ingredients is the length/branching of the alkyl chains. Additionally, since arylesterases are known to be present in the skin, initial metabolic products of this family are also likely to be structurally related as (1) simple alkyl alcohols, (2) mono-esters of trimellitic acid, (3) di-esters of trimellitic acid, and (4) trimellitic acid. Indeed, the likely breakdown of these ingredients was demonstrated in an oral study in rats that examined the metabolic fate of triethylhexyl trimellitate; the products were the simple alcohol 2-ethylhexanol, the mono-ester ethylhexyl trimellitate, and the di-ester diethylhexyl trimellitate.[2]

Trialkyl trimellitates can be metabolized via hydrolysis back to the parent alcohol and acid, and therefore the parent alcohol and acid could be present as residual materials. Therefore, brief summaries of data on trimellitic acid, trimellitic anhydride (although this reactive starting material is unlikely to survive in the product),[3] and the alcohols[4-8] are provided (Table 2). This information is not intended to be exhaustive, but is included for support in reviewing the safety of the trialkyl trimellitates.

Limited published data were available for tridecyl trimellitate. However, according to Australia's National Industrial Chemicals Notification and Assessment Scheme

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Table 1. Definitions, Structures, and Reported Cosmetic Functions.

Ingredient (CAS No.)	Definition[1, CIR staff]	Cosmetic Function(s)[1]
Tridecyl Trimellitate (94109-09-8)	The triester of tridecyl alcohol and trimellitic acid; it conforms to the formula *in* Figure 2, *wherein R is a 10- carbon alkyl chain*	Skin conditioning agent - occlusive
Tricaprylyl/Capryl Trimellitate (90218-76-1)	The triester of a mixture of caprylyl and capryl alcohols with trimellitic acid; it conforms generally to the formula *in* Figure 2, *wherein R is an 8- or 10- carbon alkyl chain*	Plasticizer; skin conditioning agent - emollient
Triethylhexyl Trimellitate (3319-31-1)	The triester of 2-ethylhexanol and trimellitic acid; it conforms to the formula *in* Figure 2, *wherein R is the 2-ethylhexyl group*	Plasticizer; skin conditioning agent - emollient
Triisodecyl Trimellitate (36631-30-8)	The triester of isodecyl alcohol and trimellitic acid; it conforms generally to the formula *in* Figure 2, *wherein R is a branched, 10-carbon alkyl chain*	Skin conditioning agent – emollient; skin conditioning agent - miscellaneous
Triisotridecyl Trimellitate (72361-35-4)	The organic compound that conforms to the formula *in* Figure 2, *wherein R is a branched, 13- carbon alkyl chain*	Skin conditioning agent - miscellaneous

(NICNAS) public report of tridecyl trimellitate, triethylhexyl trimellitate should be considered as an acceptable analogue for read-across based on structure and properties.[9] Triethylhexyl trimellitate is structurally similar to tridecyl trimellitate, with the exception of the alkyl chains. The alkyl chains of triethylhexyl trimellitate are relatively short and branched, whereas those of tridecyl trimellitate are longer and linear. Because of this similarity, the data on triethylhexyl can be extrapolated to address the safety of tridecyl trimellitate, as well as all of the trialkyl trimellitates included in this report.

Many of the data included in this safety assessment are from dossiers available from the European Chemicals Agency (ECHA),[10] the Environmental Protection Agency (EPA) High Production Volume (HPV) challenge testing system,[11] the Organisation for Economic Development (OECD),[12] and from National Industrial Chemicals Notification and Assessment Scheme (NICNAS).[9] These sources provide summaries of information generated by industry, and it is those summary data that are included in this safety assessment when information from the mentioned sources is referenced. Also, because the same studies are often repeated in the dossiers available from each of these organizations, only one source is being cited when describing a study (although the same information may be found in several of the dossiers). Several of the original reports summarized in these dossiers were available through the National Technical Information Service,[13] and those were obtained when available.

Chemistry

Definition and Structure

The ingredients in this safety assessment are each a triester of trimellitic acid (i.e., 1,2,4-benzenetricarboxylic acid with alkyl side chain ester groups; Figure 1, Figure 2).

The definition and structure of each ingredient is provided in Table 1.

Physical and Chemical Properties

Trialkyl trimellitates are colorless to slightly yellow liquids, with molecular weights ranging from approximately 545 to 760 Da, and with low volatility (Table 3). Although they are generally insoluble or only slightly soluble in water, these ingredients are readily soluble in most organic solvents and oils.[14]

Method of Manufacture

The trialkyl trimellitates can be synthesized under traditional esterification conditions from trimellitic acid, the acid chloride, or the anhydride[15] with the corresponding alcohol (e.g., trimellitic anhydride with 2-ethylhexanol to synthesize triethylhexyl trimellitate).[16] Most commonly, these trialkyl trimellitates are manufactured by reacting the appropriate alcohol with trimellitic anhydride.[14,17]

There is also literature on the regioselective synthesis of these types of chemicals by the transition metal-catalyzed, cotrimerization of acetylynic compounds via a [2+2+2] cyclization (e.g., the trimerization of isopropyl 2-propynoate can be selectively directed to the production of "triisopropyl trimellitate" (not an ingredient)). However, there were no published examples of this method for the ingredients included in this safety assessment.

Impurities/Constituents

Tridecyl Trimellitate. From one source, tridecyl trimellitate is reportedly 99.97% pure and contains <.03% isodecanol and <.03% tridecanol.[9]

Triethylhexyl Trimellitate. Triethylhexyl trimellitate from one source was reportedly >99.9% pure,[18] and another supplier indicates that industrial triethylhexyl trimellitate is available with .1% by weight 1,1,3-tris(2-methyl-4-hydroxy-5-*t*-butylphenyl) butane.[19] In a study that used 97.1% pure triethylhexyl trimellitate, the major impurity was

Table 2. Data on Trimellitic Acid, Trimellitic Anhydride, and Constituent Alcohols.

Test Substance	Summary Data	Reference
Trimellitic Acid	single dose (acute) toxicity-inhalation: LC_{50} >3750 mg/m^3 (4-h exposure), with necropsy findings considered within normal limits repeated dose toxicity-oral: in rats dosed by gavage with 0-1000 mg/kg/day for 5 days/wk for 4 wks, GI effects were observed with 1000 mg/kg/day, but not with doses ≤300 mg/kg/day repeated dose inhalation toxicity: rats were exposed to 50 μg/m^3 for 6 h/day for 5 days, and then challenged after a 3 wk non-treatment period with a single exposure of trimellitic acid, trimellitic anhydride, or unfiltered air – there were no signs of respiratory sensitization or cross-reactivity with the anhydride; in a 13-wk study in rats, no lung lesions or increased antibody levels were observed with exposure to .05, .1, or .3 mg/m^3 for 6 h/day, 5days/wk for 13 wks genotoxicity: because trimellitic anhydride is rapidly hydrolyzed to the acid in aqueous solutions, the acid is expected to have similar genotoxic effects (negative, see below) dermal irritation and sensitization: mild irritation in rabbits (score=1.7/8.0) following a 500 mg dermal dose applied to a 240 cm^2 patch of pre-moistened skin for 4 hours ocular irritation: severe eye irritation potential trimellitic anhydride is rapidly converted to trimellitic acid in the body, so the toxicity of trimellitic acid is expected to be similar to that of trimellitic anhydride (below), with the exceptions that the allergic symptoms with the anhydride are attributable to its reaction with amino acids to form haptens, and the acid does not react this way, and there may be differences in the magnitude of the response at the reaction sites	[3]
Trimellitic Anhydride	single dose (acute) toxicity-dermal: LD_{50} = 5600 mg/kg single dose (acute) toxicity-oral: oral LD_{50} in rats of 2030 mg/kg (females) to 3340 mg/kg (males); stomach lesions appearing as the most consistent lesion upon necropsy single dose (acute) toxicity-inhalation: the inhalation LC_{50} value in rats was >2330 mg/m^3 (4-h exposure), with lung lesions appearing as the most consistent lesion upon necropsy repeated dose toxicity-oral: in rats fed 50-500 mg/kg/day for 90-days, a dose-dependent increase in leukocyte count was observed in one study but not another, and may have been due to respiratory infection in control and treated animals; in 2 dogs/sex/group fed 25-500 mg/kg/day for 13 wks, no microscopic lesions were observed repeated dose toxicity-inhalation: – in mice, exposure to .010, .070, or .150 mg/m^3 for 30 min/day for 5 days produced altered breathing patterns (decreased time of inspiration and expiration, increased length of apneic periods), but no microscopic changes; no adverse effects were observed in rats exposed to .3 mg/m^3 for 6 h/day, 5 days/wk for 2 wk; in rats exposed to .1 mg/m^3 for 6 h/day, minimal and marked lung injury was observed after 6 and 10 days of exposure, respectively; a dose-dependent increase in antibody levels and lung foci was observed in rats exposed to .010, .030, .10 or .30 mg/m^3 for 6 h/day, 5 days/wk for 1-2 wk, and the lung foci completely resolved within 12 days after the last exposure, but reappeared following exposure to a single challenge concentration; exposure to .5 mg/m^3 produced hemorrhagic foci of the lung and increased antibody levels in rats treated for 6 hours/day, 5 days/week for 2 wk – estrogen treatment reduced the number of lung foci in both male and female rats, while testosterone treatment had no effect; a dose-dependent increase in lung lesions (hemorrhagic foci, inflammatory cell infiltration, bronchoalveolar pneumonia) and antibody levels was observed; in rats exposed to .002, .015, or .054 mg/m^3 for 6 h/day, 5 days/wk for up to 13 wk, and these effects were more pronounced in rats following 6.5 wk of exposure than observed in animals following 13 wk of exposure, suggesting some degree of adaptation; mechanistic studies demonstrate that when the immune system of rats is suppressed, exposure to trimellitic anhydride does not produce lung lesions reproductive and developmental toxicity: in gravid rats exposed to .5 mg/m^3 on days 6-15 of gestation, lung foci and increased antibody levels were observed, and while there were no fetotoxic or teratogenic effects, increased antibody levels were reported in neonates; no reproductive, fetotoxic, or teratogenic effects were observed in an inhalation study in which guinea pigs were exposed to .5 mg/m^3 on days 6-15 of gestation genotoxicity: negative in Ames test in *S. typhimurium* and in chromosomal aberration assay and assay for HGPRT mutations (≤2000 mg/L in CHO cells), with and without metabolic activation dermal irritation and sensitization: irritation score of .7/8.0 following a 500 mg dermal application to rabbits, and irritation was greatest during the first 60 min and generally reversible by 48-72 h; dermal sensitization in guinea pigs with 30% in DMSO induction and 5% in acetone challenge (but not with 300 mg powder); in mice with 10-50% (in acetone/olive oil); in rats with 25-50% in acetone/corn oil ocular irritation: severe eye irritation potential effects on the respiratory tract: may be a respiratory sensory irritant; in repeated dose inhalation studies, the principal effects were on the immune system and the lung; elevated antibody levels, asthma, allergic rhinitis, and a late respiratory systemic syndrome were associated with occupational exposures in some workers	[3]
Caprylic Alcohol	dermal irritation – non-human: produced a mild irritation when applied undiluted to intact or abraded rabbit skin irritation – human: produced no irritation in a 48 h closed-patch test in 25 human subjects when tested at 2% in petrolatum	[4]

(continued)

Table 2. (continued)

Test Substance	Summary Data	Reference
Caprylyl Alcohol (1-octanol)	single dose (acute) toxicity-dermal: 2-4 g/kg in rabbits with 24-h occlusive patches of 1, 2, and 4 g/kg; >5 g/kg in NZW rabbits; >.5 g/animal in guinea pigs single dose (acute) toxicity-oral: >5 g/kg in male and female Wistar rats; 18.24 g/kg in male and female Holtzman albino rats reproductive and developmental toxicity: in Wistar rats dosed by gavage with 130-1300 mg/kg bw/day on days 6-15 of gestation, the LOAEL was 130 mg/kg bw/day for maternal toxicity and the NOAEL was 1300 mg/kg bw/day for teratogenicity and fetotoxicity; in 15 female Sprague-Dawley rats dosed 7 h/day on days 1-19 of gestation by whole body exposure to 400 mg/m^3, the NOAEC was >400 mg/m^3 for maternal toxicity, fetotoxicity, and teratogenicity genotoxicity: not mutagenic in an Ames test (≤5000 μg/plate) with and without metabolic activation carcinogenicity: no carcinogenicity was seen in male and female mice injected intraperitoneally 3x/wk with ≤500 mg/kg bw for 8 wks and observed for a further 16 weeks dermal irritation – non-human: slightly irritating when applied undiluted to 3 female NZW rabbits using 4-h semi-occlusive patches dermal irritation and sensitization – human: non-irritating; 2%in petrolatum was not a sensitizer in a maximization study in 25 subjects ocular irritation: irritating to the eyes of NZW rabbits (n=3) when instilled undiluted	[5,64]
Decyl Alcohol	single dose (acute) toxicity–dermal: LD_{50} in rabbits, 3.5 mL/kg single dose (acute) toxicity-oral: LD_{50} in rats, 9800 mg/kg single dose (acute) toxicity-inhalation: no deaths with exposure to concentrated vapors for 8 h irritation – human: produced no irritation in a 48 h closed-patch test in 25 human subjects when tested at 3% in petrolatum	[4]
Ethylhexyl Alcohol	absorption, distribution, metabolism, and excretion: in vitro dermal absorption rates were .22 mg/cm^2/h for rats and .038 mg/cm^2/h for humans, indicating the rate of absorption in humans was 5.78 times slower than in the rate in the rat; efficiently absorbed following oral administration to rats, rapidly excreted in respiratory CO_2 (6-7%), feces (8-9%) and urine (80-82%), with essentially complete elimination by 28 h after administration, only 3% was excreted unchanged, and the major metabolite, 2-ethylhexanoic acid, appeared in the urine; in perfused livers of female Sprague-Dawley rats, 2-ethylhexyl alcohol inhibited mitochondrial beta-oxidation of fatty acids in-vitro and in-vivo, resulting in decreased levels of plasma ketones, and increased levels of hepatic total lipids and triglycerides, but peroxisomal oxidation pathways were not inhibited single-dose (acute) toxicity-dermal: in several studies, LD_{50} values ranged from 1980- 5000 mg/kg bw; LD_{50} >3000 mg/kg in rats; LD_{50} of 1980-2600 mg/kg in rabbits single dose (acute) toxicity-oral: numerous LD_{50} values have be reported for several species; mice: 2500-4460 mg/kg; rats: 2047-7000 mg/kg; guinea pigs: 600-2820 mg/kg; rabbits: 1180-1470 mg/kg single dose (acute) toxicity-inhalation: LC_{50} (4 h) in rats was >.89 mg/L but <5.3 mg/L; LC_{50} > 227 ppm (6 h) in mice and guinea pigs repeated dose toxicity-dermal: groups of 10 rats/sex were dosed dermally with 0, 500, or 1000 mg/kg bw/day (5 days occlusive, 2 days untreated, 4 days treated); females of the 500 and 1000 mg/kg groups exhibited minimal exfoliation, decreased spleen weight and increased serum triglycerides repeated dose toxicity-oral: NOEL of 125 mg/kg bw/day and estimated NOAEL of 250 mg/kg bw/day in a 90-day gavage study in both mice and rats dosed with 0-500 mg/kg bw/day repeated dose toxicity-inhalation: NOAEC was 120 ppm (ie, 638.4 mg/m³) in male and female Wistar rats in a 90-day whole-body exposure study with exposure to 0-120 ppm 6h/day, 5 days/wk reproductive and developmental toxicity: exposure of female rats for 7 h per day to 850 mg/m^3 on gestation days 1-19 reduced maternal feed intake, but did not produce any malformations estrogenic activity: in an E-SCREEN assay using T47D human breast cancer cells, weak estrogenic activity was observed (additional details were not provided) genotoxicity: in vitro, negative in numerous Ames assays, a liquid suspension assay, mouse lymphoma assay, and unscheduled DNA synthesis assay; in a 3H-thymidine assay, there was a dose-dependent inhibition of 3H-thymidine into replicating DNA, with a dose-dependent increase in the ratio of thymidine incorporated into acid-soluble DNA; the urine of rats dosed orally with 1000 mg/kg bw was not mutagenic; in vivo, not genotoxic in a mouse micronucleus test or a transformation assay carcinogenicity: in B6C3F1 mice (50/sex/group) dosed 5 days/wk with 0, 50, 200, or 750 mg/kg bw/day by gavage for 18 mos, an adverse trend in increased liver carcinoma observed in females of the 750 mg dose group was attributed to toxicity at this dose, body wt gain decreased and mortality increased, and mortality was 52% in females of the 750 mg/kg dose group; in a 24-mos study, F344 rats (50/sex/group) were dosed 5 days/wk with 0, 50, 150, or 500 mg/kg bw/day by gavage, and animals dosed with ≥150 mg had decreased body weight gains, lethargy and unkemptness dermal irritation – non-human: 4-h occlusive patches of undiluted test material were irritating to rabbit skin (n= 3 males); application of .5 mL under occlusion on intact rabbit skin for 1, 2, 4, and 24 hours resulted in high irritation, and the effects seen after 7 days were not reversible clinical irritation and sensitization - human: in a 48-h occlusive patch test in 29 male volunteers, 4% in petrolatum was not irritating; not a sensitizer in a maximization study ocular irritation: instillation of 20 μg into the conjunctival sac of rabbit eyes caused moderately severe irritation of the cornea	[4,6]

(continued)

Table 2. (continued)

Test Substance	Summary Data	Reference
Isodecyl Alcohol	single dose (acute) toxicity-dermal: LD_{50} of a mixture of C9-11 branched alkyl alcohols in rats, >2600 mg/kg single dose (acute) toxicity-oral: LD_{50} of a mixture of C9-11 branched alkyl alcohols in rats, 4600 mg/kg reproductive and developmental toxicity: a mixture of C9-11, branched alkyl alcohols had a maternal NOAEL of 158 mg/kg bw and a fetal NOAEL of 790 mg/kg bw in an oral (gavage) developmental toxicity study in rats	4
Isotridecan-1-ol	single dose (acute) toxicity –dermal: LD_{50} in rabbits, >2600 mg/kg bw (24-h occlusive patch) single dose (acute) toxicity – oral: oral (gavage) LD_{50} >2000 mg/kg in male and female Wistar rats and >17.2 mL/kg bw in male Carworth Wistar rats single dose (acute) inhalation toxicity: LC_0 >.3 mg/L (8 h) in male and female rats genotoxicity: not genotoxic in an Ames test (20-5000 μg/plate, with or without metabolic activation) dermal irritation – non-human: 4-h semi-occlusive patches and occlusive patches with undiluted test material applied for 1-15 min or 20 h were irritating to rabbit skin sensitization – non-human: not a sensitizer in guinea pigs(n=20), with 1% and 5% for intradermal and topical induction, respectively, and .1% used at challenge ocular irritation: instillation of .05 mL (n=2) or .1 mL (n=3) undiluted test material into rabbit eyes for 24 h was classified as not irritating	8
Tridecyl Alcohol	single dose (acute) toxicity-dermal: dermal LD_{50} in rabbits, 5600 mg/kg single dose (acute) toxicity-oral: oral LD_{50} in rats, 17,200 mg/kg	7

Abbreviations: CHO, Chinese hamster ovary; GI, gastrointestinal; LOAEL, lowest observable adverse effect level; NOAEC, no-observable adverse effect concentration; NOAEL, no observed adverse effect level; NOEL, no-observed effect level; NZW, New Zealand White.

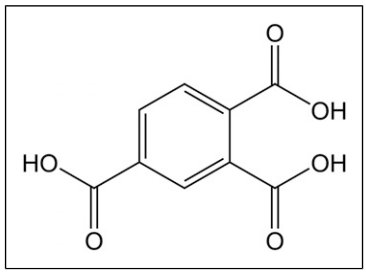

Figure 1. Trimellitic acid.

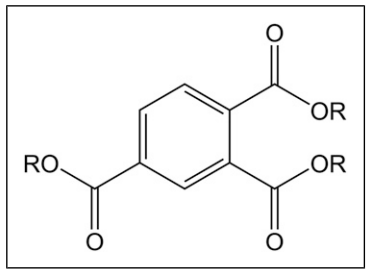

Figure 2. Trialkyl trimellitates, wherein R is the alkyl residue of a fatty alcohol.

di-(2-ethylhexyl)terephthalate; the amount of this impurity present in the test material was not specified.[2]

Use

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the reported use in cosmetics. The Panel utilizes data received from the US Food and Drug Administration (FDA) and from the cosmetics industry in determining safety based on the expected cosmetic use. The data received from the FDA are those collected from manufacturers on the use of individual ingredients in cosmetics by product category in its Voluntary Cosmetic Registration Program (VCRP). Data from the cosmetic industry are submitted in response to a survey of maximum use concentration by product category conducted by the Personal Care Products Council (Council).

Data obtained from the FDA VCRP in 2015[20] and submitted by industry in response to the Council survey in 2014[21] indicate that 4 of the 5 ingredients included in this safety assessment are used in cosmetic formulations; tricaprylyl/capryl trimellitate is the only ingredient in this group that is not reported to be used. Tridecyl trimellitate has the greatest frequency and concentration of use; it is reported to be used in 409 formulations, and the maximum reported concentration of use is 57.1% in lipstick formulations (Table 4).

The 5 trialkyl trimellitates named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[22] In Australia, according to a NICNAS report, tridecyl trimellitate cannot be classified according to the *Globally Harmonised System for Classification and Labelling of Chemicals* or the *Approved Criteria for Classifying Hazardous Substances* because limited toxicity data are available. However, it not considered to pose an unreasonable risk to the health of workers, and when used at ≤40% in foundation, lipstick, eye shadow, and eyeliner formulations and ≤9% in hand and face creams, it is not considered to pose an unreasonable risk to public health.[9] (These concentrations were provided to NICNAS as intended use concentrations).

Non-Cosmetic

Triethylhexyl trimellitate is a primary plasticizer used in polyvinyl chloride (PVC) plastic.[23] It has high temperature

Table 3. Chemical and Physical Properties.

Property	Description	Reference
	Tricaprylyl/Capryl Trimellitate	
physical characteristics	yellowish liquid (97.15% pure)	29
formula weight	661.01	65
melting point	−53°C	29
boiling point	346°C	29
solubility	<.13 mg/L	9
density	.97 g/cm³ (20°C)	29
vapor pressure	1.34 x 10^{-7} Pa (25°C; experimental)	29
log P_{ow}	10.6 (55°C; pH 6.6)	29
	17.2-24.8 (25°C; pH 7)	9
	>5.94	
	Tridecyl Trimellitate	
physical characteristics	Colorless to slightly yellow viscous liquid (20°C and 25°C)	9,66
molecular weight	757.19	67
purity	99.97%	9
solubility	compatible with most oil phase ingredients; insoluble in water	66,68
relative density	.965 gr/cm³ (20°C)	68
refractive index	1.4850	68
saponification value	315-335	66
	210-230	68
acid value	.1 (max)	66
	.5 (max)	68
	Triethylhexyl Trimellitate	
physical characteristics	pale yellow liquid with a faint odor (98.29% pure)	32
	colorless, odorless viscous liquid (>99.9% pure)	18
molecular weight	546.78	69
melting point	−43°C	32
boiling point	355°C	32
	417°C	70
solubility	insoluble (<.1 mg/L) to slightly soluble (.13 mg/L) in water (25°C)	32
	10-50 mg/L in DMSO and ethanol (20°C); >100 mg/L in acetone (20°C) soluble in most organic solvents; miscible with alcohol, ether, and most oils	71 17
density	.9885 g/cm³ (20°C)	32
vapor pressure	6.8 x 10^{-8} Pa (25°C; experimental)	32
	5.2 x 10^{-9} Pa (25°C)	23
partial pressure (experimental)	2.13 x 10^{-8} Pa	72
log P_O (saturation vapor pressure; estimated)	−12.29 Pa (SPARC); −5.91 (EPI Suite)	72
log K_{OA} (octanol-air partition coefficient; estimated)	16.24 (EPI Suite)	72
vapor density	18.9 (air = 1)	18
decomposition	emits acrid smoke and irritating vapors when heated to decomposition	71
refractive index	1.485 (n^{20}_D)	19
specific gravity	.987 (25°C/25°C)	19
log P_{ow}	4.35 (determined by gas-liquid chromatography)	73
	5.94 (25°C)	14,74
	8 (25°C; pH 4.81)	32
	8.88 (55°C; pH 6.3)	32
	Triisodecyl Trimellitate	
physical characteristics	yellow liquid (>98% pure)	56
	colorless odorless liquid	75
molecular weight	630.94	76
melting point	−35°C	75

(continued)

Table 3. (continued)

Property	Description	Reference
boiling point	335 - 420°C (at 100.5 kPa)	56
density	.959 (20°C)	56
vapor pressure	5.8 x 10^{-10} Pa (25°C; experimental)	56
solubility	slightly soluble in water (≤1.24 x 10^{-3} g/L at 20°C)	56
log P_{ow}	>9.4	56
	Triisotridecyl Trimellitate	
physical characteristics	liquid, faint odor (99.60% pure)	36
molecular weight	757.19	77
boiling point	737°C (760 mmHg)	78
solubility	insoluble (solvent not named)	79
density	.948 g/cm^3	78
vapor pressure	< 1 x 10^{-10} Pa (20°C; calculated)	36
refractive index	1.483	78
saponification value	222-232	79
log P_{ow}	14.65770	78

Table 4. Frequency and Concentration of use According to Duration and Type of Exposure.

	# of Uses[20]	*Max Conc of Use (%)*[21]	*# of Uses*[20]	*Max Conc of Use (%)*[21]	*# of Uses*[20]	*Max Conc of Use (%)*[21]
	Tridecyl Trimellitate		**Triethylhexyl Trimellitate**		**Triisodecyl Trimellitate**	
Totals*	**409**	**0.25-57.1**	**65**	**0.02-5.1**	**16**	**12.4-15**
Duration of Use						
Leave-On	*395*	*0.25-57.1*	*65*	*0.36-5.1*	*16*	*12.4-15*
Rinse-Off	*13*	*0.4-12.8*	*NR*	*0.02*	*NR*	*NR*
Diluted for (Bath) Use	*1*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	9	0.25-17	1	NR	NR	NR
Incidental Ingestion	231	1.7-57.1	44	0.36-0.99	6	12.4-15
Incidental Inhalation-Spray	47[a]; 24[b]	0.3-2.8[a]	NR	NR	NR	NR
Incidental Inhalation-Powder	14 24[b]; 1[c]	0.5-3.4[c]	NR	NR	NR	NR
Dermal Contact	151	0.25-17	21	0.02-5.1	10	12.4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	26	0.3-2.8	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	232	1.7-57.1	44	0.36-0.99	6	12.4-15
Baby Products	1	NR	NR	NR	NR	NR

	Triisotridecyl Trimellitate	
Totals*	**NR**	**4**
Duration of Use		
Leave-On	*NR*	*4*
Rinse-Off	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	4
Incidental Inhalation-Spray	NR	NR
Incidental Inhalation-Powder	NR	NR
Dermal Contact	NR	NR
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	4
Baby Products	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] Includes products that can be sprays, but it is not known whether the reported uses are sprays
[b] Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation
[c] Includes products that can be powders, but it is not known whether the reported uses are powders
NR – no reported use

applications, with primary use in high-specification electrical cable insulation and sheathing. It also has applications as a plasticizer in medical products, specifically blood bags, infusion sets, catheters, and hemodialysis tubing.[24,25]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

Tridecyl Trimellitate. Tridecyl trimellitate has a molecular weight of 757 Da, low water solubility, and high log *P* value; therefore, systemic availability from dermal exposure is expected to be limited.[9]

Triethylhexyl Trimellitate. The in vitro hydrolysis of triethylhexyl trimellitate (92% pure) was determined by adding [hexyl 2-^{14}C]triethylhexyl trimellitate (.19 μCi/mL) to rat intestinal homogenates prepared from male Sprague-Dawley rats.[26] There was no evidence that triethylhexyl trimellitate was hydrolyzed in the intestinal homogenates, and 2-ethylhexanol was not released.

The absorption, metabolism, and excretion of orally administered triethylhexyl trimellitate (97.1% pure) was determined in 4 fasted male Sprague-Dawley rats.[2] The rats were administered a single dose by gavage of 100 mg/kg bw [hexyl-2-^{14}C]triethylhexyl trimellitate (16-18 μCi) in corn oil, and placed in metabolism cages. Urine, feces, and expired air were collected at various intervals for up to 144 h, after which time the animals were killed, several organs were removed, and the radioactivity in these tissues was determined. The overall recovery of radioactivity was 94.4% of the dose. Approximately 75% of the dose was excreted in the feces (actual values ranged from 62.3-93.1% in the individual animals), 16% in the urine as metabolites (8.3-25.1% in the individual animals), and 1.9% as expired $^{14}CO_2$ (.8-3.5% in the individual animals). Peak rates of excretion for expired $^{14}CO_2$ were at 2-3 h and 8-12 h after dosing. Less than .6% of the radioactivity remained in the tissues; the liver and adipose tissues contained the greatest amounts. In the feces, 85% of the radioactivity was excreted as unchanged triethylhexyl trimellitate, and the remaining radioactivity as mono-(2-ethylhexyl) trimellitate (1%), di-(2-ethylhexyl)trimellitate (7%), and unidentified polar metabolites. In the urine, the metabolites were identified as mono-(2-ethylhexyl)trimellitate, 2-ethylhexanol, 2-ethylhexanoic acid, and 2-heptanone. Elimination in the urine and in CO_2 was biphasic, with half-lives of 3.1 and 42 h and 4.3 and 31 h, respectively. Figure 3 depicts the metabolic fate of triethylhexyl trimellitate in rats.

The distribution and excretion of triethylhexyl trimellitate was determined in male Sprague-Dawley rats.[27] Serial blood sampling was conducted with 5 rats dosed intravenously (i.v.) with 10.5 mg/kg [^{14}C-carbonyl]triethylhexyl trimellitate (>98% radiochemically pure; 59.9 μCi/kg) in 2.5-3.5 mL of a soybean oil-water (10:90) emulsion. Blood samples were collected prior to dosing, and at 10 time points from .5 to 336 h (14 days) after dosing. The animals were placed in metabolism cages, and urine and fecal samples were collected at various intervals for 14 days. The distribution half-life, disposition half-life, apparent distribution volume, and plasma clearance were 46.2 min, 5.34 days, 7.49 L/kg, and 40.5 mL/kg·h, respectively, indicating a fairly rapid initial distribution and slow clearance of triethylhexyl trimellitate from the body. Over the 14-day period, 3.3% of the radioactivity was recovered in the urine and 16.9% was recovered in the feces; renal clearance was 13 mL/kg·h.

Twenty-eight rats were then dosed i.v. with 15.6 mg/kg [^{14}C-carbonyl]triethylhexyl trimellitate (28.0 μCi/kg) in 2.6-3.6 mL of the vehicle; groups of 4 rats were killed at 1, 6, 24, 48, 72, 168, and 336 h after dosing. Blood samples, urine, and feces were collected, and at necropsy, several organs were removed and analyzed for radioactivity. The majority of the radioactivity was distributed in the liver, lungs, and spleen. The peak radioactivity in the liver was 71.6% of the dose at 24 h, in the lungs 18.6% at 1 h, and in the spleen 5.3% at 24 h; the radioactivity in the liver and lungs declined after peaking, and in the spleen, the amount of radioactivity recovered mostly remained constant for 14 days.

Dermal Absorption

Triethylhexyl Trimellitate. The in vitro skin absorption of triethylhexyl trimellitate was determined via analytical methods in Franz cells using full-thickness skin samples excised from female nude mice and specific pathogen-free pigs.[28] The receptor medium contained 40% ethanol, and the donor medium was 5.4 mM triethylhexyl trimellitate in 40% ethanol/pH 7.4 buffer. The skin samples were removed from the cells after a 12 h exposure and tape-stripped. The accumulation of triethylhexyl trimellitate was 1.32 ± .53 nmol/mg in nude mouse and .35 ± .19 nmol/mg in pig skin; the flux was 0 nmol/cm^2/h for both mouse and pig skin. Triethylhexyl trimellitate was not found in the receptor medium after 12 h, indicating no biologically relevant availability for dermal absorption.

Toxicological Studies

Single Dose (Acute) Toxicity

The acute dermal toxicity of tricaprylyl/capryl trimellitate (in rats)[29] and triethylhexyl trimellitate (in guinea pigs and rabbits)[30,31] and the acute oral toxicity of tricaprylyl/capryl trimellitate (in rats),[29] tridecyl trimellitate (in rats),[9] triethylhexyl trimellitate (in mice and rats),[32-35] and triisodecyl trimellitate (in rats)[36] was not remarkable (Table 5). Mixed results were observed with triethylhexyl trimellitate in single-exposure inhalation studies in rats; 100% mortality was reported with a 6-h whole body exposure to heated vapor with 2640 and 4170 mg/m^3 in one study,[37] but no mortality was observed with a 4-h exposure to 2600 mg/m^3 in another study.[38]

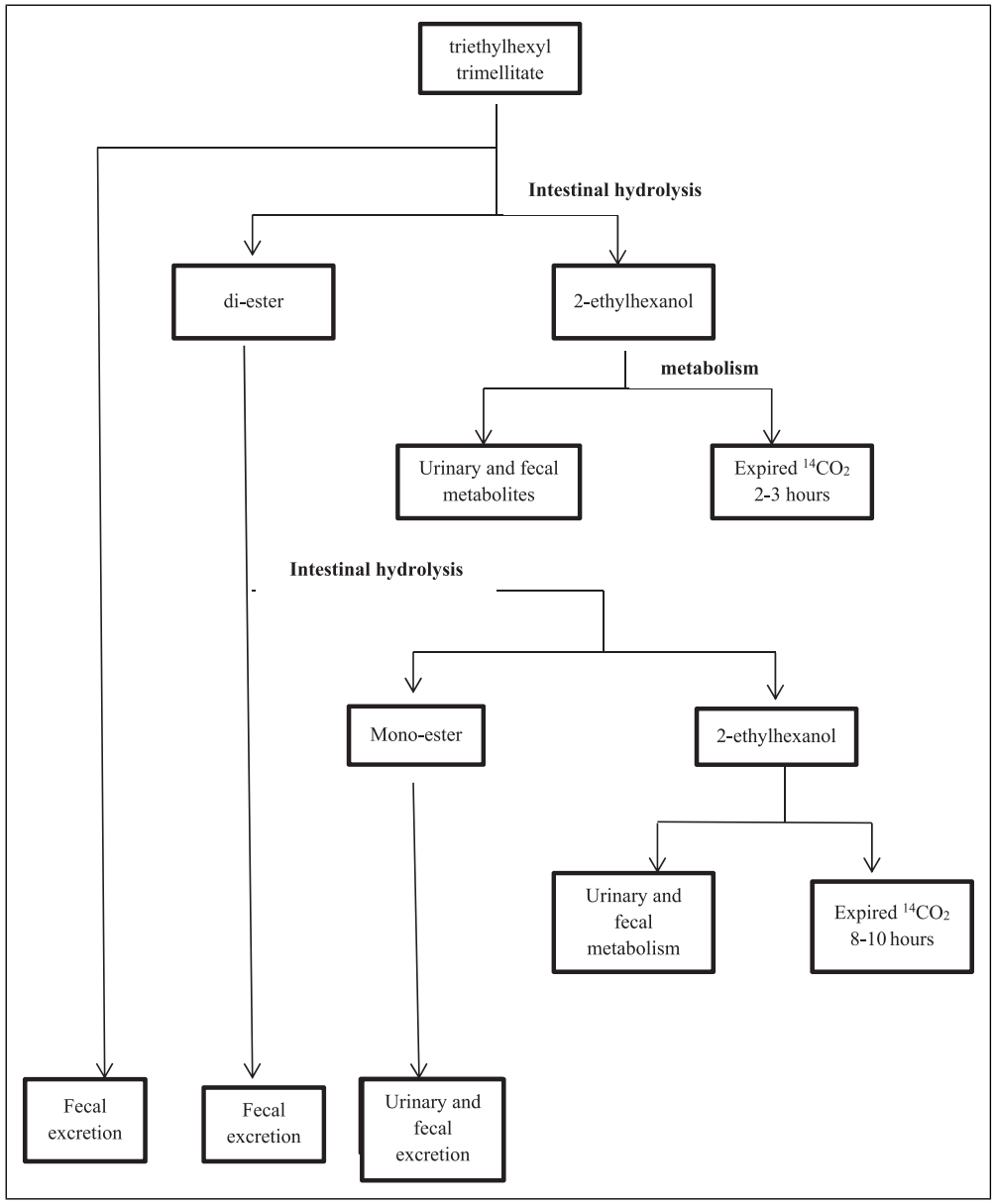

Figure 3. Metabolic fate of Triethylhexyl Trimellitate following oral dosing in the rat.[2]

Repeated Dose Toxicity

In repeated dose oral toxicity studies in rats, the no-observed-adverse-effect-level (NOAEL) of tricaprylyl/capryl trimellitate was 300 mg/kg/day in a 28-day gavage study (a slight but statistically significant increase in absolute and relative liver weights was observed in males and females dosed with 1000 mg/kg/day), and it was 500 mg/kg/day in a 13-wk gavage study[29] (Table 6). Triethylhexyl trimellitate was administered to rats by gavage for 21 days (up to 2000 mg/kg/day)[39,40] or 28 days (up to 1000 mg/kg/day),[39,41,42] and in the diet (up to 2%) for 28 days and (up to 1000 mg/kg/bw) for 90 days.[32] In the feed study, hepatomegaly was reported with .67 and 2.0% triethylhexyl trimellitate; no significant test-article related effects were reported in the other studies. The NOAEL in the 90-day study was 225 mg/kg bw/day; some effects were observed in liver and spleen weights.

Hepatotoxicity

In Vitro

Triethylhexyl Trimellitate. Hepatocytes from male Wistar rats were incubated with 50 µg/mL triethylhexyl trimellitate in polysorbate 80, and viability was evaluated by the Trypan blue exclusion test.[43] Cell viability was similar to controls over a 3 h period.

Table 5. Acute Toxicity Studies.

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
				DERMAL		
tricaprylyl/ capryl trimellitate	Sprague-Dawley rats	5M/5F	undiluted	Single 24 h semi-occlusive patches; 2 g/kg bw applied	>2 g/kg No mortality and no signs of toxicity.	29
triethylhexyl trimellitate	guinea pigs	1 (sex not specified)	undiluted	Single 24 h occlusive patch; 5, 10, or 20 mL/kg	>20 mL/kg no mortality	30
triethylhexyl trimellitate	NZW rabbits	3M/3F	undiluted	Single 24 h occlusive patch; 2.0 mL/kg was applied	>2.0 mL/kg No signs of toxicity; no gross pathology	31
				ORAL		
tricaprylyl/ capryl trimellitate	Wistar rats	5M/5F	undiluted	3 g/kg bw by gavage	>3 g/kg No mortality and no signs of toxicity	29
tricaprylyl/ capryl trimellitate	Sprague-Dawley rats	5 or 10 M	undiluted	10 mL/kg bw (5 M) or 13.3-31.6 mL/kg bw (10 M) by gavage	24.9 mL/kg bw 17.8 mL/kg: 3 animals died 6-7 days after dosing; 23.7 mL/kg: 3 animals died 3-6 days after dosing; 31.6 mL/kg: 8 animals died 3-9 days after dosing; Signs of toxicity, primarily reduced spontaneous activity and soft feces, were observed in all groups.	29
tridecyl trimellitate	Wistar albino rats	5M/5F	undiluted	5 g/kg bw by gavage	>5 g/kg No mortality and no signs of toxicity.	9
triethylhexyl trimellitate	mice	2M/2F	not provided	10 mL/kg by gavage	>3.2 g/kg	32
triethylhexyl trimellitate	mice	not provided	not provided	3 and 60 g/kg bw by gavage	>6 g/kg	32
triethylhexyl trimellitate	Crj:CD (SD) rats	10 (M and F)	corn oil	0 and 2 g/kg by gavage; 40.0 w/v% for 2 g/kg dose	>2 g/kg No mortality and no signs of toxicity	33
triethylhexyl trimellitate	Sprague-Dawley rats	2M/2F	undiluted	10 mL/kg bw by gavage	>3.2 g/kg piloerection observed in males at 1 and 2 h	32
triethylhexyl trimellitate	Sprague-Dawley rats	5M/5F	undiluted	5 g/kg bw by gavage	>5 g/kg No mortality and no signs of toxicity.	34
triethylhexyl trimellitate	Sprague-Dawley rats	2M/2F	undiluted	10 mL/kg bw by gavage	9.85 g/kg piloerection observed in males at 2 and 3 h; no signs of toxicity after 3 h	32,35
triisodecyl trimellitate	Sprague-Dawley rats	2M/2F	undiluted	10 mL/kg by gavage	>9.59 g/kg bw (>10 mL/kg) No mortality and no signs of toxicity.	56
				INHALATION		
triethylhexyl trimellitate	rats	3 (sex not specified)		230, 2640, or 4170 mg/m^3 heated to 180°C to generate a mixture of aerosol and heated vapor; whole-body inhalation; 6-h exposure	LC_{50} not determined 100% mortality at >2640 mg/m^3	37
triethylhexyl trimellitate	Sprague-Dawley rats	5M/5F		2600 mg/m^3; 4-h exposure	>2600 mg/m^3 No mortality and no signs of toxicity	38

Abbreviations: NZW, New Zealand White.

Table 6. Repeated Dose Toxicity Studies.

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/ Concentration	Results	Reference
			ORAL			
tricaprylyl/ capryl trimellitate	Sprague-Dawley rats, 5M/5F	28-day, with 2-wk high-dose and control recovery groups	corn oil	0, 100, 300, or 1000 mg/kg/day by gavage	All animals survived until study termination Treatment-related effects were observed in males and, to a minor extent in females, of the high dose group included hair loss in 6/10 females; a decrease in mean body weights that continued until the end of the recovery period; reversible, slight but statistically significant increases in absolute and relative liver weights in males and females and a reversible increase in the absolute and relative adrenal weights in males; and reversible microscopic changes in the adrenal glands of high dose males. No microscopic changes were observed in the reproductive organs NOAEL was 300 mg/kg/day	[29]
tricaprylyl/ capryl trimellitate	Sprague-Dawley rats, 10M/10F; 5M/5F recovery animals	13 wk, with 4-wk high-dose and control recovery groups	corn oil	0, 50, 200, or 500 mg/kg/day, by gavage	Clinical and neurobehavioral observations, body wts and feed consumption were recorded, clinical chemistry, hematology, and urinalysis parameters were measured, vaginal smears were taken from wk 12 until study termination, a detailed evaluation of testes was performed on all control and high dose males, including an examination of the spermatogenic cycle, and gross and microscopic examinations at necropsy, including microscopic examination of the testes, epididymides, and seminiferous epithelium; any observed changes, including wt and microscopic changes in the liver, were fully reversible and therefore not considered toxicologically significant NOAEL was 500 mg/kg/day	[29]
triethylhexyl trimellitate	Fischer F344 rats, 5M/5F	21-day	corn oil	0, 200, 700, or 2000 mg/kg/day	No effect on feed consumption or body weight gains. A statistically significant, non–dose related, increase in relative liver weights was observed in females of all dose groups; no effect on relative liver weights was observed in the males of any dose group; only remarkable microscopic effects in the livers was a reduction in the quantity of neutral lipids	[39,40]

(continued)

Table 6. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/ Concentration	Results	Reference
triethylhexyl trimellitate	Crj:CD (SD) rats, 5M/5F	28-day	corn oil	0, 100, 300, or 1000 mg/kg	None of the animals died during the study, and no signs of toxicity, test article-related changes were observed in mean body weights, feed consumption, clinical chemistry, hematology, or organ weights. NOAEL was >1000 mg/kg/day in male and female rats	[41]
triethylhexyl trimellitate	Fischer 344 albino rats, 5M	28-day	corn oil	1000 mg/kg/day	None of the animals died during the study, and there were no significant effects on body weight, absolute liver weights, or relative liver-to-body weight ratios. The only remarkable effect was a significant decrease in triglyceride values in the test animals	[42]
triethylhexyl trimellitate	Fischer F344 rats, 5M/5F	28-day	feed	0, .2, .67, or 2.0%	No statistically significant effects on feed consumption or body weight gains were observed. Hepatomegaly was observed in males and females of the mid and high dose groups; a slight reduction in the cytoplasmic basophilia in 2/5 females of the high dose group the only microscopic change reported in the livers; NOAEL was .2%; LOAEL was .67%	[39]
triethylhexyl trimellitate	Sprague-Dawley rats; 10M/10F	90-day, with high dose recovery group	feed	0, 50, 225, or 1000 mg/kg/day	No signs of toxicity; no effect on feed consumption or body weight gains; dose-related statistically significant increase in absolute liver weights in high dose females, and a statistically significant increase in relative liver weights in high dose males and females; absolute and relative spleen weights were decreased in high dose males; some microscopic lesions in the liver and spleen were observed; no significant effect on the estrous or spermatogenic cycles; absolute and relative liver weights were slightly increased in females, but not males, at the end of recovery; no other significant changes were observed at the end of treatment or recovery periods NOAEL was 225 mg/kg bw/day; LOAEL was 1000 mg/kg bw/day	[32]

Abbreviations: LOAEL, lowest observable adverse effect level; NOAEL, no-observable adverse effect level.

Non-Human

OralTriethylhexyl Trimellitate

A group of 12 male albino rats was dosed by gavage with 300 mg/kg/day triethylhexyl trimellitate in corn oil, 6 days/wk, for 4 wk; 6 of the animals were killed one day after administration of the last dose, and the other 6 served as a 4-wk recovery group.[44] Two control groups of 6 male rats each were used; one group was administered distilled water, and the other 5 mL corn oil, by gavage 6 days/wk for 4 wks. Liver specimens were taken from each animal at study termination. Triethylhexyl trimellitate had mild reversible effects in the liver. In the test animals, a preserved lobular architecture with generalized vascular dilation and congestion and many shrunken hepatocytes with euchromatic nuclei and lipid

globules were observed. In the recovery group, a normal lobular architecture and normal hepatocytes with rounded vesicular nuclei were reported. The immunoperoxidase technique was used to evaluate the Hep Par-1 immune reaction; positive patchy immunoreactivity was observed in the test group, and moderate immunoreaction in the cytoplasm of most hepatocytes was observed in the recovery animals.

ParenteralTriethylhexyl Trimellitate

Six male albino rats were dosed intraperitoneally with 1.0 mg/kg bw triethylhexyl trimellitate for 7 days, and the control group was administered the same volume of saline.[25] The animals were killed 16 h after the last dose, and the livers were removed. The test animals did not exhibit any signs of toxicity, and body weights and liver weights of the test animals were similar to those of control animals. The effect of triethylhexyl trimellitate on the activity of several enzymes was evaluated; triethylhexyl trimellitate did not cause any change in the activities of aminopyrine-*N*-demethylase, aryl hydrocarbon hydroxylase, or glutathione-*S*-transferase, and it did not affect glutathione levels.

Peroxisome Proliferation

Triethylhexyl Trimellitate. The induction of peroxisome proliferation by triethylhexyl trimellitate has been studied because triethylhexyl trimellitate has been considered as an alternative to diethylhexyl phthalate (DEHP). In 21- and 28-day oral studies in Fischer 344 rats (described earlier), the ability of triethylhexyl trimellitate (and DEHP and 2-ethylhexanoic acid) to induce peroxisomes was evaluated using 3 enzyme markers, i.e., cyanide-insensitive palmitoyl CoA oxidation, catalase, and carnitine acetyltransferase, and the effect on numbers of hepatic peroxisomes was evaluated.[39] Peroxisome induction in rats given 2% triethylhexyl trimellitate was less than that observed with .67% DEHP or in those given a metabolically equivalent dose of 2-ethylhexanoic acid. The researcher also noted that a "monoester effect" attributed to mono(2-ethylhexyl)phthalate (MEHP) was not seen with triethylhexyl trimellitate.

A molecular modelling study of triethylhexyl trimellitate–peroxisome proliferator-activated receptors (PPAR) interactions was also conducted.[45] Using a 3-dimensional model of triethylhexyl trimellitate, in which flexible docking of the compound into the receptor active site was performed using GOLD 3.0.1 software, triethylhexyl trimellitate was not able to fit in the binding site of either $PPAR_{\alpha}$ or $PPAR_{\gamma}$; the researchers attributed this result to the size of the molecule.[45]

2-Ethylhexanoic acid appears to be a proximate peroxisome proliferator in both mice and rats; however, even though 2-ethylhexanoic acid is a metabolite of triethylhexyl trimellitate, triethylhexyl trimellitate appears only to have a weak effect on peroxisome proliferation. Peroxisome proliferation causes an increase in liver weights and can induce hepatocarcinogenicity in rats and mice. However, peroxisome proliferation is not believed to pose the risk of inducing hepatocarcinogenesis in humans, as a species difference in response to peroxisome proliferators exists, and in a previous safety assessment the Panel noted that humans do not react to peroxisome proliferators in the same manner that rodents do.[4] There is no effect on organelle proliferation and induction of peroxisomal and microsomal fatty acid-oxidizing enzymes in species other than rats and mice, including humans. Consequently, even if triethylhexyl trimellitate were to have an effect on peroxisome proliferation in rats or mice, these results would have no relevance to humans.

Reproductive and Developmental Toxicity

In an oral developmental toxicity study, tricaprylyl/capryl trimellitate had a NOAEL of 300 mg/kg bw/day for maternal toxicity and of 1000 mg/kg bw/day for fetotoxicity in rats dosed with up to 1000 mg/kg/day on days 6-15 of gestation[29] (Table 7). In a reproductive and developmental toxicity study, orally administered triethylhexyl trimellitate had a no-observed effect level (NOEL) of 100 mg/kg/day in male rats and 1000 mg/kg/day in female rats and offspring; spermatocytes and spermatids were decreased with doses of 300 and 1000 mg/kg/day.[32] Two oral developmental toxicity studies with triethylhexyl trimellitate in rats (by gavage with up to 1000 and 1050 mg/kg bw/day on days 14-18 and 6-19 of gestation, respectively) did not produce any toxicologically significant effects.[32,46] Neither tricaprylyl/capryl trimellitate nor triethylhexyl trimellitate, at doses of 500 mg/kg bw/day, had a significant repressive effect on genes in the testicular mal-development (TMD) pathway.[29,32]

In Vitro Tests for Endocrine Activity

Triethylhexyl Trimellitate. Triethylhexyl trimellitate was screened in an in vitro competitive binding assay measuring its binding affinity for the human estrogen receptor alpha (ERα).[47] Triethylhexyl trimellitate in dimethyl sulfoxide (DMSO; 10^{-10} to 10^{-4} mol/l) had no affinity for ERα in this assay. It also did not have estrogenic activity in a yeast two-hybrid assay (an assay based on the ligand-dependent interaction of ERα and the coactivator TIF2) at final concentrations of 10^{-3} to 10^{-7} mol/l in DMSO.[48] The 10% relative effective concentration (i.e., the concentration producing 10% of the agonist activity of the highest activity level of 17 β-estradiol; REC_{10}) was >.001 mmol/l triethylhexyl trimellitate. The estrogenic activity of the metabolites of triethylhexyl trimellitate (which were not identified) was also measured; the metabolite solution was prepared by incubating triethylhexyl trimellitate in S9 mix. The REC_{10} of the metabolite solution was >.0005 mmol/l.

Triethylhexyl trimellitate in DMSO did exhibit estrogenic activity in an in vitro test using human osteoblastic (US-O2) reporter gene cell lines for ERα and ERβ.[49] The lowest effective concentrations of triethylhexyl trimellitate in the ERα

Table 7. Reproductive and Developmental Toxicity Studies.

Test Article	Animals/ Group	Vehicle	Dose/ Concentration	Procedure	Results	Reference
ORAL						
tricaprylyl/ capryltrimellitate (alcohol side-chains consisted of 40-60% linear C8-alcohol and 40-60% linear C10-alcohol)	24 gravid Sprague-Dawley rats	corn oil	0, 100, 300, or 1000 mg/kg bw/ day	Animals were dosed by gavage on GD 6-19, and killed on GD 20. The animals were observed for clinical signs of toxicity during the study, the ovaries and uterine content were examined at study termination, and fetal examinations were performed.	1000 mg/kg bw group: increase in staining on the body, primarily around the head; statistically significant decreases in body wt (from day 12), body wt gains (from day 9), feed consumption (from day 9), terminal body wts, uterine wts, and absolute body wts, fetal wts and consequently litter wts compared to the controls; a delay in ossification was considered a result of the maternal toxicity observed at this dose; no other embryotoxic or teratogenic effects were reported NOAELs were 300 mg/kg bw/day for maternal toxicity and 1000 mg/kg bw/day for fetal toxicity	[29]
tricaprylyl/capryl trimellitate	24 gravid Han Wistar rats	corn oil	0 or 500 mg/kg bw/day	Examined effect on TMD. Dams were dosed on GD 12-19, and killed on GD 19. Testes from a minimum of 5 litters/ group were examined for changes in gene expression in pathways relevant to TMD by transcription profiling analysis of RNA. DEHP was used as a positive control	No significant repressive effect on genes in the TMD pathway; positive control caused a repression of genes involved in testes development and cholesterol and testosterone biosynthesis	[29]
triethylhexyl trimellitate	3-4 gravid Sprague-Dawley rats	corn oil	0, 250, 500, or 1000 mg/kg bw/day	Animals were dosed by gavage on GD 14-18, and killed approximately 2h after the last dose. Fetuses were removed immediately and necropsied within 2h. (2 trials)	No statistically significant effects on testicular testosterone production, fetal viability, or maternal body wt gains	[46]

(continued)

Table 7. (continued)

Test Article	Animals/ Group	Vehicle	Dose/ Concentration	Procedure	Results	Reference
triethylhexyl trimellitate	Crj:CD:SD rats, 12M/ 12F	corn oil	0, 100, 300,or 1000 mg/kg/ day	Males were dosed by gavage for 46days, starting 14days prior to mating, and females were dosed 14days prior to mating through LD 3	No effects on appearance, body wt, feed consumption, gross pathology, reproductive organ wts; no microscopic effects in the kidneys; number of spermatocytes and spermatids was slightly reduced in 2/12 and 11/12 males of the mid- and high-dose groups, respectively, and moderately decreased in 1 high-dose male NOELs for reproductive and developmental effects were 100 mg/kg/day for males and 1000 mg/kg/day for females and offspring	32
triethylhexyl trimellitate	20 gravid Sprague-Dawley rats (main study) 15 recovery animals (control and high-dose)	corn oil	0, 100, 500, or 1050 mg/kg bw/day	Dams were dosed by gavage on GD 6-19, and recovery dams were dosed on GD 6 through LD 20	No treatment-related signs of maternal toxicity, no effects on fetal body wts or litter viability, no teratogenic effects, and no effects upon sexual maturation or development of the reproductive tract in male or female pups; an increase in the number of fetuses with displaced testes was in the high dose group, however the values were within historical control ranges; slight but statistically significant increase in the number of offspring with retained areolar regions in the high-dose group at PND 13, but not PND 18 - this effect was not considered toxicologically significant. NOAELs were 1050 mg/kg bw/day for maternal and developmental toxicity, and 500 mg/kg bw/ day for postnatal development	32

(continued)

Table 7. (continued)

Test Article	Animals/ Group	Vehicle	Dose/ Concentration	Procedure	Results	Reference
triethylhexyl trimellitate	gravid Han Wistar rats	corn oil	0 or 500 mg/kg bw/day	Examined effect on TMD (as above). DEHP and MEHP were used as a positive controls	No significant repressive effect on genes in the TMD pathway; positive controls caused a repression of genes involved in testes development and cholesterol and testosterone biosynthesis	[32]

Abbreviations: DEHP, diethylhexyl phthalate; GD, gestation day; LD, lactation day; MEHP, mono-2-ethylhexyl phthalate; NOAEL = no-observable adverse effect level; NOEL, no-observable effect level; PND, postnatal day; TMD, testicular mal-development.

and ERβ reporter cells were 8.1 and 4.9 μM, respectively. The estradiol equivalence factors (EEF_{10}; i.e., $EC_{10\ estradiol}/EC_{10\ triethylhexyl\ trimellitate}$) in the ERα and ERβ were 1.2×10^{-7} and 1.6×10^{-6}, respectively; the $EEF_{10}\alpha/EEF_{10}\beta$ ratio was .0075. When compared to estradiol, the maximum estrogenic effect of triethylhexyl trimellitate in ERα cells was 113% of that found with estradiol, and in the ERβ cells, it was 76% of that found with estradiol.

Genotoxicity

Tricaprylyl/capryl trimellitate and triethylhexyl trimellitate were not genotoxic in the Ames test using *Salmonella typhimurium*, a mammalian cell gene mutation assay in mouse lymphoma cells, or a chromosomal aberration assay in human lymphocytes or Chinese hamster lung fibroblasts (for triethylhexyl trimellitate), and triethylhexyl trimellitate was not genotoxic in a forward mutation assay in Chinese hamster ovary cells, unscheduled DNA synthesis assay in rat primary hepatocytes, or dominant lethal assay in mice[29,32,50-54] (Table 8). Also, when the mutagenicity of urine from rats dosed with triethylhexyl trimellitate was evaluated in the Ames test, there was no evidence that mutagenic substances were excreted in the urine by rats.[55]

Carcinogenicity

Carcinogenicity data on the trialkyl trimellitate ingredients were not found in the published literature, nor were unpublished data provided.

Irritation and Sensitization

Dermal Irritation and Sensitization

Undiluted tricaprylyl/capryl trimellitate, 10% tridecyl trimellitate, and triisodecyl trimellitate were slightly irritating to rabbit skin following a single occlusive application, but undiluted tridecyl trimellitate was non-irritating to mouse skin[9,29,56] (Table 9). A single occlusive application of undiluted triethylhexyl trimellitate produced reversible moderate erythema and moderate to severe edema in guinea pig skin[30]; triethylhexyl trimellitate was a reversible primary dermal irritant in Californian rabbits,[57] but it was not a primary irritant in New Zealand White rabbits.[58] Tricaprylyl/capryl trimellitate (10% at induction/undiluted at challenge) was not a sensitizer in a guinea pig maximization study,[29] and undiluted triethylhexyl trimellitate was not a sensitizer in a Buehler sensitization assay in guinea pigs.[59] Up to 100% tridecyl trimellitate was negative in a local lymph node assay.[9] In human repeated insult patch tests, tridecyl trimellitate (57.1% in a lipstick formulation and undiluted)[9,60] and 1% triethylhexyl trimellitate in acetone were not sensitizers.[61]

Phototoxicity

Human

Tridecyl Trimellitate. The phototoxicity potential of a lipstick containing 22.3% tridecyl trimellitate was evaluated in 10 fair-skinned subjects with skin types I, II, or III.[62] On day 1 of the study, occlusive patches containing approximately .1 g of the test material, a dark red waxy solid, were applied (neat) to both volar forearms of each subject. On day 2, the patches were removed and one arm of each subject was irradiated with a dose of ~.22 J/cm^2/min ultraviolet A (UVA) from 4 F40BL florescent tubes (the wavelength range was 320-400 nm, and over 95% of the relative energy at 360 nm) for 15 min, for a total dose of 3.3 J. The responses at the test sites on both arms were evaluated on days 3 and 4. No reactions were observed at the irradiated or non-irradiated sites. A lipstick formulation containing 22.3% tridecyl trimellitate was not irritating and did not induce a phototoxic response.

Ocular Irritation

Tricaprylyl/capryl trimellitate, triethylhexyl trimellitate, and triisodecyl trimellitate were not irritating to rabbit eyes,[29,56,63]

Table 8. Genotoxicity Studies.

Test Article	Concentration/ Vehicle	Procedure	Test System	Results	Reference
		IN VITRO			
tricaprylyl/capryl trimellitate	8-5000 μg/plate in DMSO	Ames test, with or without metabolic activation; appropriate positive controls were used.	*S. typhimurium* TA97, TA98 and TA100	negative	29
tricaprylyl/capryl trimellitate	156-2500 μg/mL in ethanol	Mammalian cell gene mutation assay, with and without metabolic activation; vehicle and appropriate positive controls were used	L5178Y cells	negative	29
tricaprylyl/capryl trimellitate	313-1250 μg/mL in ethanol	Chromosomal aberration assay; 24h harvest time; vehicle and appropriate positive controls were used 3h exposure with and without metabolic activation	in human peripheral blood lymphocytes	not genotoxic with either exposure time	29
	625-2500 μg/mL in ethanol	24h exposure without metabolic activation			
triethylhexyl trimellitate	0-5000 μg/plate in acetone	Ames test, with and without metabolic activation; appropriate positive controls were used.	*S. typhimurium* TA98 TA100, TA1535, and TA1537; *E. coli* WP2 uvrA	negative	50
triethylhexyl trimellitate	0-10,000 μg/plate in DMSO	Ames test, with or without metabolic activation; appropriate positive controls were used.	*S. typhimurium* TA97, TA98 TA100, and TA1535	negative	51
triethylhexyl trimellitate	0-2500 μg/mL in ethanol	mammalian cell gene mutation assay; appropriate positive controls were used	mouse lymphoma L5178Y cells	negative	32
triethylhexyl trimellitate	0-5000 μg/plate in ethanol	chromosomal aberration assay, with and without metabolic activation; 2 assays, one with a 3h and one with a 24h treatment; appropriate controls were used	human lymphocytes	negative	32
triethylhexyl trimellitate	0-5.0 mg/mL in acetone	chromosomal aberration assay, with and without metabolic activation; short-term (6h) and continuous (24 or 48h) treatments; appropriate controls were used	Chinese hamster lung fibroblasts (V79 cells)	negative	32,52
triethylhexyl trimellitate	0-200 nL/mL in ethanol	CHO/HGPRT forward mutation assay, with and without metabolic activation; appropriate positive controls were used	CHO cells	negative	53
triethylhexyl trimellitate	0-5000 nL/mL in ethanol	unscheduled DNA synthesis assay; appropriate positive controls were used	rat primary hepatocytes	negative	54
urine from rats dosed with triethylhexyl trimellitate	≤2 mL undiluted test material	Ames test using a direct plating procedure, with and without metabolic activation at least 6 male Sprague-Dawley rats were dosed by gavage with 2000 mg/kg bw/day for 15 days; urine samples were collected daily; a vehicle (corn oil) and a positive control (8-hydroxyquinoline) was used	*S. typhimurium* TA97, TA98 TA100, TA1535, and/or TA1537	negative	55
		IN VIVO			
triethylhexyl trimellitate	1400 mg/kg bw (vehicle not specified)	dominant lethal assay; details not provided	male Swiss mice	negative	32

Abbreviations: CHO – Chinese hamster ovary; DMSO - dimethyl sulfoxide; *E.* – *Escherichia*; *S.* - *Salmonella*.

Table 9. Dermal Irritation and Sensitization.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
tricaprylyl/ capryl trimellitate	as supplied; .5 mL	3 White Russian rabbits (sex not specified)	A 2.5 cm^2 semi-occlusive patch with was applied to a shaved area on the trunk for 4 h; test sites were evaluated at 24, 48, and 72h	slightly irritating; PII = 1.67/8 At 24h, slight to well-defined erythema was observed in all animals and slight edema in 2 animals; all reactions were reversible within 6-8days	29
tricaprylyl/ capryl trimellitate	intradermal induction: 10% in FCA and maize germ oil (1:1) dermal induction and challenge: undiluted	Dunkin-Hartley guinea pigs, 20 F	GPMT intradermal induction: administered in a mixture of FCA and maize germ oil (1:1) dermal induction: animals were pretreated with 10% sodium dodecyl sulfate on day 6; 48h patches were applied on day 7 challenge: 24-h occlusive patch applied on day 21	not a sensitizer intradermal induction: all control and test animals had irritation at injection sites; severe erythema, edema and necrosis were observed dermal induction: at 1 h after patch removal, both test and control animals had erythema and edema in the whole application area, with inflamed or bloody lesions; 24h after patch removal, some animals had erythema and eschar formation in the application area Challenge: no reactions were observed at 48 or 72h	29
tridecyl trimellitate	10% in corn oil; .5 mL	NZW rabbits 2 (sex not specified)	24-h single occlusive patch to intact and abraded skin; sites scored at 24 and 72h	slightly irritating erythema/eschar mean score – .25/1 and .5/1 for intact and abraded skin, respectively; resolved by 72h no edema	9
tridecyl trimellitate	as supplied	NZW rabbits, 3M	similar to OECD 404 (ie, acute dermal irritation/corrosion test); patch type and duration not stated; no details provided	non-irritating no erythema or edema at 24, 48, or 72h	9
tridecyl trimellitate	5, 10, 25, 50, or 100% acetone/olive oil	CBA/J mice, 4F	OECD TG 429; LLNA; two experiments were performed HCA was used as a positive control	negative SI >3 at 10 and 100% in experiment 1, but not in experiment 2	9
triethylhexyl trimellitate	as supplied; 5, 10, or 20 mL/kg	1 guinea pig/ dose (sex not specified)	single 24-h occlusive patch applied to shaved skin	moderate erythema and moderate to severe edema; all animals appeared normal after 1wk	30
triethylhexyl trimellitate	as supplied; .5 mL	Californian rabbits, 2M/2F	single 4-h occlusive patch applied to shaved skin	Reversible primary dermal irritant slight erythema was observed n all rabbits 30-60 min after patch removal; no effects were observed at day 7	57
triethylhexyl trimellitate	as supplied; .5 mL	6 NZW rabbits (sex not specified)	single 24-h occlusive patch applied to intact and abraded skin	not a primary skin irritant; PII = 1.04	58

(continued)

Table 9. (continued)

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
triethylhexyl trimellitate	as supplied; .5 mL	albino guinea pigs, 10M	modified Buehler sensitization assay induction: 10 24-h occlusive patches were applied, with a 24-h rest period between patches Challenge: after a 2-wk non-treatment period, a 24-h occlusive patch was applied to a previously untreated site	not a primary irritant, fatiguing agent, or sensitizer	59
triisodecyl trimellitate	undiluted; .5 mL	NZW rabbits, 3M/3F	24-h single occlusive patch to intact and abraded skin; sites were scored at 24 and 72 h	slightly irritating; PII = 1.1 24 h: slight/well-defined erythema at 3 intact and 4 abraded sites; very slight edema at 5 intact and 4 abraded sites; slight edema at 1 abraded site 72 h: very slight edema at 3 intact and abraded sites All reactions were resolved at day 6.	56
			HUMAN		
tridecyl trimellitate	57.1% in a lipstick formulation	53 subjects	modified Draize HRIPT induction: 24-h occlusive patches with test material, applied 3x/wk Challenge: 24-h challenge patch applied to a previously untreated site after a 2-wk non-treatment period; test sites were evaluated 24 and 72 h after application	not an irritant or a sensitizer	60
tridecyl trimellitate	undiluted; .2 mL	51 subjects	HRIPT (same procedure as above)	not an irritant or a sensitizer	9
triethylhexyl trimellitate	1% in acetone	203 subjects	HRIPT (as above, except semi-occlusive patches were used; challenge reactions were evaluated at 48 and 96 h)	not a sensitizer induction: erythema in 4 subjects on 4-6 occasions Challenge: slight erythema in 2 subjects at 48 h; 1 at 48 and 96 h; and 1 at 96 h (these subjects did not have irritation during induction)	61

Abbreviations: FCA, Freund's Complete Adjuvant; GPMT, guinea pig maximization test; HCA, α-hexylcinnamaldehyde; HRIPT, human repeated insult patch test; LLNA, local lymph node assay; NZW, New Zealand White; OECD, Organisation for Economic Development; PII, primary irritation index; SI, stimulation index; TG, test guidelines.

and tridecyl trimellitate was slightly irritating to rabbit eyes[9] (Table 10).

Summary

This report addresses the safety of 5 trialkyl trimellitates as used in cosmetics. The trialkyl trimellitates are structurally-related as alkyl esters of trimellitic acid, most commonly manufactured by esterifying trimellitic anhydride, and the only structural difference between these ingredients is the length/branching of the alkyl chains. According to the *International Cosmetic Ingredient Dictionary and Handbook*, these ingredients are reported to function in cosmetics as skin conditioning agents, and, tricaprylyl/capryl trimellitate and triethylhexyl trimellitate are also reported to function in cosmetics as plasticizers.

VCRP data obtained from the FDA, and data received in response to a survey of the maximum reported use concentration by product category conducted by the Council, indicate that 4 of the 5 ingredients included in this safety assessment

Table 10. Ocular Irritation Studies.

Test Article	Concentration/ Dose	Animals	Method	Results	Reference
NON-HUMAN STUDIES					
tricaprylyl/ capryl trimellitate	as supplied; .1 mL	small White Russian rabbits, 3	the test material was instilled into the conjunctival sac of 1 eye; the eyes were rinsed after 72 h	non-irritating No signs of irritation at 24, 48, or 72 h	29
tridecyl trimellitate	not specified (assumed to be undiluted)	NZW rabbits, 3	study conducted using methods similar to those of the OECD TG 405 (i.e., acute eye irritation/corrosion test; additional details were not provided)	slightly irritating Severe conjunctival effects observed at 1 h; effects diminished in severity by 24 h, and were resolved by 72 h	9
triethylhexyl trimellitate	as supplied; .1 mL	6 NZW rabbits (sex not specified)	the test material was instilled into the conjunctival sac of the right eye; the eyes were not rinsed	not a primary ocular irritant; average ocular irritation score was 2.3/110 on day 1, 1.7/110 on day 2, and 0 on days 3-7	63
triisodecyl trimellitate	as supplied; .1 mL	NZW rabbits, 3M/ 3F	the test material was instilled into the conjunctival sac of 1 eye; the eyes of 3 animals were rinsed after 30 sec	not irritating Very slight conjunctival reactions were observed in 2 rinsed and 3 unrinsed eyes at 1 h; all rinsed eyes and 1 unrinsed eye were normal at 24 h; all eyes were normal at 48 h	56

Abbreviations: NZW, New Zealand White; OECD, Organisation for Economic Development; TG, test guideline.

are used in cosmetic formulations; tricaprylyl/capryl trimellitate is the only ingredient in this group that is not reported to be used. Tridecyl trimellitate has the greatest frequency and concentration of use; it is reported to be used in 409 formulations, and the maximum reported concentration of use is 57.1% in lipstick formulations.

Tridecyl trimellitate has a molecular weight of 757 Da, low water solubility, and high log *P* value; therefore, systemic availability is expected to be limited under conditions of cosmetic use. In rats, approximately 75% of a single oral dose of 100 mg/kg bw [hexyl-2-^{14}C]triethylhexyl trimellitate was excreted in the feces, 16% in the urine as metabolites, and 1.9% as expired $^{14}CO_2$. In the feces, 85% of the radioactivity was excreted as unchanged triethylhexyl trimellitate, and the remainder as mono-(2-ethylhexyl) trimellitate (1%), di-(2-ethylhexyl)trimellitate (7%), and unidentified polar metabolites. The urinary metabolites were identified as mono-(2-ethylhexyl)trimellitate, 2-ethylhexanol, 2-ethylhexanoic acid, and 2-heptanone. In rats dosed i.v. with [^{14}C-carbonyl] triethylhexyl trimellitate, there was a fairly rapid initial distribution and slow clearance of triethylhexyl trimellitate from the body; over the 14-day period, 3.3% of the radioactivity was recovered in the urine and 16.9% was recovered in the feces. In a 28-day i.v. study examining the distribution of triethylhexyl trimellitate in rats, the majority of the radioactivity was distributed in the liver, lungs, and spleen.

In in vitro dermal absorption studies with skin from nude mice and specific pathogen-free pigs, the accumulation of triethylhexyl trimellitate in the skin was 1.32 ± .53 nmol/mg and .35 ± .19 nmol/mg, respectively. Triethylhexyl trimellitate was not found in the receptor medium after 12 h, indicating no systemic availability for dermal absorption.

The acute dermal toxicity of tricaprylyl/capryl trimellitate and triethylhexyl trimellitate, and the acute oral toxicity of tricaprylyl/capryl trimellitate, tridecyl trimellitate, triethylhexyl trimellitate, and triisodecyl trimellitate, were not remarkable. Mixed results were observed with triethylhexyl trimellitate in single-exposure inhalation studies in rats; 100% mortality was reported with a 6-h whole body exposure to heated vapor with 2640 and 4170 mg/m^3 in one study, but no mortality was observed with a 4-h exposure to 2600 mg/m^3 in another study.

In repeated dose oral toxicity studies in rats, the NOAEL of tricaprylyl/capryl trimellitate was 300 mg/kg/day in a 28-day gavage study (a slight but statistically significant increase in absolute and relative liver weights was observed in males and females dosed with 1000 mg/kg/day), and was 500 mg/kg/day in a 13-wk gavage study. Triethylhexyl trimellitate was administered to rats by gavage for 21-days (up to 2000 mg/kg/day)[39,40] or 28-days (up to 1000 mg/kg/day), and in the diet (up to 2%) for 28 days and (up to 1000 mg/kg/bw) for 90 days. In the feed study, hepatomegaly was reported with .67 and 2.0% triethylhexyl trimellitate. The NOAEL in the 90-day

study was 225 mg/kg bw/day; some effects were observed in liver and spleen weights.

Oral administration of 300 mg/kg/day triethylhexyl trimellitate, 6 days/wk for 4 wk, produced mild reversible effects in the liver of rats; evaluation of the Hep Par-1immune reaction reported positive patchy immunoreactivity in the test group, and moderate immunoreaction in the cytoplasm of most hepatocytes was observed in recovery animals. Intraperitoneal administration of 1.0 mg/kg bw triethylhexyl trimellitate for 7 days did not have an effect on hepatic enzymes.

Orally administered triethylhexyl trimellitate (21- or 28-days) did not have a remarkable effect on peroxisome proliferation in rats.

In an oral developmental toxicity study, tricaprylyl/capryl trimellitate had a NOAEL of 300 mg/kg bw/day for maternal toxicity and of 1000 mg/kg bw/day for fetotoxicity in rats dosed with up to 1000 mg/kg/day on days 6-15 of gestation. In a reproductive and developmental toxicity study, orally administered triethylhexyl trimellitate had a NOEL for reproductive and developmental effects of 100 mg/kg/day in male rats and 1000 mg/kg/day in female rats and offspring; spermatocytes and spermatids were decreased with doses of 300 and 1000 mg/kg/day. Two oral developmental toxicity studies with triethylhexyl trimellitate in rats (by gavage with up to 1000 and 1050 mg/kg bw/day on days 14-18 and 6-19 of gestation, respectively) did not produce any toxicologically significant effects. Neither tricaprylyl/capryl trimellitate nor triethylhexyl trimellitate, at doses of 500 mg/kg bw/day, had a significant repressive effect on genes in the TMD pathway.

Several studies were performed to evaluate whether triethylhexyl trimellitate had endocrine disrupting activity. Triethylhexyl trimellitate (10^{-10} to 10^{-4} mol/l, in DMSO) had no affinity for ERα in a competitive binding assay, and it did not have estrogenic activity in a yeast two-hybrid assay (10^{-1} to 10^{-5} mol/l, in DMSO). However, in a study evaluating estrogenic potency using ERα and ERβ reporter gene cell lines, triethylhexyl trimellitate in DMSO was shown to be estrogenic in both cell lines.

Tricaprylyl/capryl trimellitate and triethylhexyl trimellitate were not genotoxic in the Ames test using *Salmonella typhimurium*, a mammalian cell gene mutation assay in mouse lymphoma cells, or a chromosomal aberration assay in human lymphocytes or Chinese hamster lung fibroblasts (for triethylhexyl trimellitate), and triethylhexyl trimellitate was not genotoxic in a forward mutation assay in Chinese hamster ovary cells, unscheduled DNA synthesis assay in rat primary hepatocytes, or dominant lethal assay in mice. Also, urine from rats dosed with triethylhexyl trimellitate was not mutagenic in the Ames test.

Undiluted tricaprylyl/capryl trimellitate, 10% tridecyl trimellitate, and triisodecyl trimellitate were slightly irritating to rabbit skin following a single occlusive application, but undiluted tridecyl trimellitate was non-irritating to mouse skin. A single occlusive application of undiluted triethylhexyl trimellitate produced reversible moderate erythema and moderate to severe edema in guinea pig skin; triethylhexyl trimellitate was a reversible primary dermal irritant in Californian rabbits, but it was not a primary irritant in New Zealand White rabbits. In clinical testing, a lipstick formulation containing 22.3% tridecyl trimellitate was not irritating, and did not induce a phototoxic response.

Tricaprylyl/capryl trimellitate (10% at induction/undiluted at challenge) was not a sensitizer in a guinea pig maximization study, and undiluted triethylhexyl trimellitate was not a sensitizer in a Buehler sensitization assay in guinea pigs. Up to 100% tridecyl trimellitate was negative in a local lymph node assay. In human repeated insult patch tests, tridecyl trimellitate (57.1% in a lipstick formulation and undiluted) and 1% triethylhexyl trimellitate were not sensitizers.

Tricaprylyl/capryl trimellitate, triethylhexyl trimellitate, and triisodecyl trimellitate were not irritating to rabbit eyes, and tridecyl trimellitate was slightly irritating to rabbit eyes.

Discussion

The trialkyl trimellitates form a family of cosmetic ingredients in that they are all structurally related as alkyl esters of the aromatic triprotic acid, trimellitic acid. The only structural difference between the ingredients included in this family is the length/branching of the alkyl chains.

The Panel discussed the fact that triethylhexyl trimellitate exhibited estrogenic activity in an in vitro test using human osteoblastic (US-O2) reporter gene cell lines for ERα and ERβ. However, trialkyl trimellitates are not significantly absorbed through the skin, thus the Panel was not concerned with potential endocrine effects.

It was noted that some studies suggested the induction of peroxisome proliferation by triethylhexyl trimellitate in rats. However, triethylhexyl trimellitate appeared only to have a weak effect on peroxisome proliferation. The Panel further noted that even if there was an effect, peroxisome proliferation is not believed to pose the risk of inducing hepatocarcinogenesis in humans because humans do not react to peroxisome proliferators in the same manner as rodents.

The Panel noted that no carcinogenicity data were available. They concluded that carcinogenicity is not a concern with cosmetic use because tricaprylyl/capryl trimellitate and triethylhexyl trimellitate are not genotoxic, there is a lack of structural alerts for carcinogenicity, and the dermal absorption is expected to be poor.

There was concern that the potential exists for dermal irritation with the use of products formulated using trialkyl trimellitates. Therefore, the Panel specified that products containing these ingredients must be formulated to be non-irritating.

Finally, the Panel recognized that there were little toxicity data available for the branched ingredient triisodecyl trimellitate. However, an analogous ingredient, triethylhexyl trimellitate, was found to have no biologically relevant availability for dermal absorption in mouse or pig skin samples. Therefore, the Panel had little concern about the safety of triisodecyl trimellitate as used in cosmetics.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that Tridecyl Trimellitate, Tricaprylyl/Capryl Trimellitate,* Triethylhexyl Trimellitate, Triisodecyl Trimellitate, and Triisotridecyl Trimellitate are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

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

Author's Note

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

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References

1. Nikitakis J, Breslawec HP. *International Cosmetic Ingredient Dictionary and Handbook*. 15 ed. Washington, DC: Personal Care Products Council; 2014.
2. Eastman Kodak Company. Absorption and metabolism of [hexyl-2-14C] tri-(2-ethylhexyl)trimellitate in the rat; 1984. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0206636; OTS0507501.
3. Organisation for Economic Development (OECD). Trimellitic anhydride & trimellitic acid (CAS No. 552-30-7; 528-44-9). https://www.inchem.org/documents/sids/sids/TLANA.pdf. Last Updated 2002. Date Accessed 9-4-2014.
4. Fiume MM, Heldreth BA, Bergfeld WF, et al. Final report of the Cosmetic Ingredient Review Expert Panel on the safety assessment of dicarboxylic acids, salts, and esters. *Int J Toxicol*. 2012;31(Suppl 1 (July/Aug)):5S-76S.
5. European Chemicals Agency (ECHA). Octan-1-ol (CAS No. 111-87-5; caprylyl alcohol). https://apps.echa.europa.eu/registered/data/dossiers/DISS-9c82fa92-822d-1adc-e044-00144f67d249/DISS-9c82fa92-822d-1adc-e044-00144f67d249_DISS-9c82fa92-822d-1adc-e044-00144f67d249.html. Last Updated 2015. Date Accessed 2-5-0015.
6. European Chemicals Agency (ECHA). 2-Ethylhexan-1-ol (CAS No. 104-76-7). https://apps.echa.europa.eu/registered/data/dossiers/DISS-9d83af48-c78c-4dcf-e044-00144f67d249/DISS-9d83af48-c78c-4dcf-e044-00144f67d249_DISS-9d83af48-c78c-4dcf-e044-00144f67d249.html. Last Updated 2014. Date Accessed 2-6-2015.
7. The Good Scents Company. 1-Tridecanol. https://www.thegoodscentscompany.com/data/rw1156881.html. Last Updated 2015. Date Accessed 2-5-0015.
8. European Chemicals Agency (ECHA). Isotridecan-1-ol (CAS No. 27458-92-0). https://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea4b34e-9041-2989-e044-00144f67d031/DISS-9ea4b34e-9041-2989-e044-00144f67d031_DISS-9ea4b34e-9041-2989-e044-00144f67d031.html. Last Updated 2014. Date Accessed 8-7-2015.
9. National Industria Chemicals Notification and Assessment Scheme (NICNAS). 1,2,4-Benzenetricarboxylic acid, 1,2,4-tritridecyl ester (INCI name: tridecyl trimellitate). File No: LTD/1654. www.nicnas.gov.au/__data/assets/word_doc/0005/7394/LTD1654-FR-Final.docx. Last Updated 2013. Date Accessed 11-13-2014.
10. European Chemicals Agency (ECHA). European chemicals agency. https://echa.europa.eu. Last Updated 2014. Date Accessed 9-4-2014.
11. Environmental Protection Agency (EPA). HIgh production volume challenge. https://www.epa.gov/hpv/. Last Updated 2013. Date Accessed 9-4-2014.
12. Organisation for Economic Development (OECD). OECD existing chemicals database. https://webnet.oecd.org/hpv/ui/Search.aspx. Last Updated 2014. Date Accessed 9-4-2014.
13. National Technical Information Service (NTIS). National technical reports library. https://www.ntis.gov/products/ntrl/. Last Updated 2015. Date Accessed 1-20-2015.
14. American Chemistry Council. High production volume (HPV) test plan for the trimellitate category, as part of the Phthalate Esters Panel test plans for phthalate and trimellitate esters. https://www.epa.gov/chemrtk/pubs/summaries/trime/c13468.pdf. Last Updated 2001. Date Accessed 9-4-2014.
15. He T, Shen W, Zou M, Wu Y, inventor. Method for industrialized composite catalytic synthesis of trioctyl trimellitate with trimellitic anhydride and isooctanol as main raw materials. (Abstract only). CN102030652A. 4-27-2011.
16. Jiang PP, Ji X, Yu XJ, Wang MH. Synthesis of tri(2-ethylhexyl) trimellitate. (Abstract only). *Huaxue Xuebao*. 2002;60(6):1102-1105.
17. ExxonMobil Biomedical Sciences, Inc. High production volume (HPV) chemical challenge program test plan for the trimellitate category. https://www.epa.gov/hpv/pubs/summaries/trime/c13468tp.pdf. Last Updated 12-13-2001. Date Accessed 9-4-2014.
18. Eastman Chemical Company. Safety data sheet: Eastman™ TOTM Plasticizer (3319-31-1). https://ws.eastman.com/

ProductCatalogApps/PageControllers/MSDSShow_PC.aspx. Last Updated 2014. Date Accessed 1-28-2015.
19. BASF. Technical data sheet: Palatinol® TOTM Tri Octyl Trimellitate. https://www2.basf.us/plasticizers/pdfs/pala-tot.pdf. Last Updated 2001. Date Accessed 1-20-2015.
20. Food and Drug Administration (FDA). *Frequency of Use of Cosmetic Ingredients*. FDA Database; 2015.
21. Personal Care Products Council. 1-6-2015. Concentration of Use by FDA Product Category: Trimellitates. Unpublished data submitted by Personal Care Products Council. 1 pages.
22. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. https://ec.europa.eu/consumers/cosmetics/cosing/. Last Updated 2014. Date Accessed 7-14-2014.
23. Versar, Inc. and Syracuse Research Corporation (SRC). Review of exposure toxicity data for phthalate substitutes. https://www.cpsc.gov/PageFiles/126546/phthalsub.pdf. Last Updated 1-15-2010. Date Accessed 9-4-2014.
24. van Vliet EDS, Reitano EM, Chhabra JS, Beren GP, Whyatt RM. A review of alternatives to di(2-ethyhexyl)phthalate-containing medical devices in the neonatal intensive care unit. *J Perinatol*. 2011;31(8):551-560.
25. Rathinam K, Srivastava SP, Seth PK. Hepatic studies of intraperitoneally administered tris(2-ethyl hexyl)trimellitate (TOTM) and di(2-ethyl hexyl)phthalate in rats. *J Appl Toxicol*. 1990;10(1):39-41. PM:2335710.
26. Eastman Kodak Company. The in vitro hydrolysis of selected plasticizers by rat gut homogenates. 1984. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0510633; OTS0206391:91-112.
27. Martis L, Freid E, Woods E. Tissue distribution and excretion of tris-(2-ethylhexyl) trimellitate in rats. *J Toxicol Environ Health*. 1987;20(4):357-366.
28. Pan T-L, Wang P-W, Aljuffali IA, Hung Y-Y, Lin C-F, Fang J-Y. Dermal toxicity elicited by phthalates: evaluation of skin absorption, immunohistology, and functional proteomics. *Food Chem Toxicol*. 2014;65:105-114.
29. European Chemicals Agency (ECHA). 1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters (CAS No. 90218-76-1; tricaprylyl/capryl trimellitate). https://apps.echa.europa.eu/registered/data/dossiers/DISS-97d9b500-cdcd-0f33-e044-00144f67d031/DISS-97d9b500-cdcd-0f33-e044-00144f67d031_DISS-97d9b500-cdcd-0f33-e044-00144f67d031.html. Last Updated 9-12-2014. Date Accessed 11-13-2014.
30. Eastman Kodak Company. Tri(2-ethylhexyl)trimellitate. Acute dermal toxicity in guinea pigs. Unpublished report. https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionId=24962414&epcount=9&epname=Acute+Toxicity&epdiscp=Mammalian+Health+Effects+SIDS&selchemid=null&CategorySingle=null. Last Updated 1971. Date Accessed 8-19-2014.
31. Midwest Research Institute. *Acute Dermal Toxicity Test of Tenneco Chemicals, Inc (TCI) Compound Nuoplaz 6959 in Rabbits*. MRI Project No. 7180-B(4); 1981. Date Accessed 1-20-2015. Available electronically at:https://ntrl.ntis.gov: OTS0206575, pages 5, 13-20, 61.
32. European Chemicals Agency (ECHA). Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate (CAS No. 3319-31-1; trie-thylhexyl trimellitate). https://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea6ef4e-cd0e-73f3-e044-00144f67d031/DISS-9ea6ef4e-cd0e-73f3-e044-00144f67d031_DISS-9ea6ef4e-cd0e-73f3-e044-00144f67d031.html. Last Updated 7-29-2013. Date Accessed 9-4-2014.
33. Biosafety Research Center, Food, Drugs and Pesticides (An-pyo Centxx), Japan. Acute oral toxicity study of 1,2,4-benzene-tricarboxylic acid, tris(2-ethylhexyl) ester (3319-31-1) in rats. https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionId=24962414&epcount=9&epname=Acute+Toxicity&epdiscp=Mammalian+Health+Effects+SIDS&selchemid=null&CategorySingle=null. Toxicity Testing Reports of Environmental Chcmicals, Ministry of Health & Welfare Japan. Last Updated 1996. Date Accessed 1-22-2015.
34. Biosearch Inc. *Acute Oral Toxicity of Nuoplaz TOTM in Rats*. Project No. 81-2672A; 1981. Date Accessed 1-20-2015. Available electronically at: OTS0206575, pages 5, 41-44, 61.
35. Ciba-Geigy Pharmaceuticals. Acutre oral median lethal dose (LD50) in rats of Reomol OTM (1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester, CASRN 3313-31-1); 1984. Date Accessed 1-20-2015. Report No. 84R004. Available electronically at: https://ntrl.ntis.gov: OTS0513265.
36. European Chemicals Agency (ECHA). Triisotridecyl benzene-1,2,4-tricarboxylate (CAS No. 72361-35-4; triisotridecyl trimellitate). https://apps.echa.europa.eu/registered/data/dossiers/DISS-dffb4072-e37d-47ae-e044-00144f67d031/DISS-dffb4072-e37d-47ae-e044-00144f67d031_DISS-dffb4072-e37d-47ae-e044-00144f67d031.html. Last Updated 7-10-2013. Date Accessed 11-13-2014.
37. Eastman Kodak Company. Tri(2-ethylhexyl)trimellitate. Acute inhalation toxicity. Unpublished report. https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=6&v_rs_list=25046905,25045058,25045040,25046953,25045070,25046899. Last Updated 1971. Date Accessed 8-19-2014.
38. Midwest Research Institute. *Acute Inhalation Toxicity Test in Sprague-Dawley Rats Using Compound Nuoplaz 6959*. MRI Project No. 7180-B(5); 1982. Date Accessed 1-20-2015. Available electronically at:https://ntrl.ntis.gov: OTS0206575, pages 5-12, 61.
39. Hodgson JR. Results of peroxisome induction studies on tri(2-ethylhexyl) trimellitate and 2-ethylhexanol. *Toxicol Ind Health*. 1987;3(2):49-61.
40. British Industrial Biological Research Assocation. *A 28-day Toxicity Study with Tris(2-Ethylhexyl)trimellitate in the Rat*. BIBRA Project No. 3.0496; 1985. Date Accessed 1-20-2015. Report No. 0496/1/85. Available electronically at: https://ntrl.ntis.gov: OTS0510637.
41. Biosafety Research Center, Food, Drugs and Pesticides, Japan. 1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (3319-31-1); 28-day oral (gavage) toxicity study in rats. https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=3&v_rs_list=25047513,25047404,25063987. Toxicity Testing Reports of Environmental Chemicals, Ministry of Health & Welfare, Japan. Last Updated 1996. Date Accessed 8-19-2014.

42. Biosearch Inc. *28-Day Hepatotoxicity Study in Rats Conducts for Tenneco Chemicals, Inc, with Samples Nuoplaz TOTM and Nuoplaz DOP*. Project No. 81-2672A; 1981. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0206575, pages 5, 21-40, 61.
43. Kambia K, Dine T, Gressier B, Dupin-Spriet T, Luyckx M, Brunet C. Evaluation of the direct toxicity of trioctyltrimellitate (TOTM), di(2-ethylhexyl) phthalate (DEHP) and their hydrolysis products on isolated rat hepatocytes. *Int J Artif Organs*. 2004;27(11):971-978.
44. Shehata AS, Abd El-Rehim Mohamed Z, Abd El-Haleem MR, Samak MA. Effects of exposure to plasticizers di-(2-ethylhexyl) phthalate and trioctyltrimellitate on the histological structure of adult male albino rats' liver. *J Clin Toxicol*. 2013;3(4):1000169/1-1000169/9.
45. Kambia N, Renault N, Dilly S, et al. Molecular modelling of phthalates - PPARs interactions. *J Enzyme Inhib Med Chem* 2008;23(5):611-616. PM:18821250.
46. Furr JR, Lambright CS, Wilson VS, Foster PM, Gray LE Jr. A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. *Toxicol Sci*. 2014;140(2):403-424.
47. Ohashi A, Kotera H, Hori H, et al. Evaluation of endocrine disrupting activity of plasticizers in polyvinyl chloride tubes by estrogen receptor alpha binding assay. *J Artif Organs*. 2005;8(4):252-256.
48. Ogawa Y, Kawamura Y, Wakui C, Mutsuga M, Nishimura T, Tanamoto K. Estrogenic activities of chemicals related to food contact plastics and rubbers tested by the yeast two-hybrid assay. *Food Addit Contam*. 2006;23(4):422-430.
49. Ter Veld MGR, Schouten B, Louisse J, et al. Estrogenic potency of food-packaging-associated plasticizers and antioxidants as detected in ERα and ERβ reporter gene cell lines. *J Agric Food Chem*. 2006;54(12):4407-4416.
50. Halano Rcscarti Institute, Food and Drug Safety Center, Japan. Bacterial reverse mutation assay of 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester (3319-31-1). https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionId=24962414&epcount=9&epname=Genetic+Toxicity+in+vitro&epdiscp=Mammalian+Health+Effects+SIDS&selchemid=null&CategorySingle=null. Toxicity Testing Reports of Environmental Chemicals, Ministry of Health and Welfare, Japan. Last Updated 2014. Date Accessed 8-19-2014.
51. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity tests. IV. Results from the testing of 300 chemicals. *Environ Mol Mutagen*. 1988;11(12):1-157.
52. Anonymous. In vitro mammalian chromosome aberration test of 1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester (3319-31-1). https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionId=24962414&epcount=9&epname=Genetic+Toxicity+in+vitro&epdiscp=Mammalian+Health+Effects+SIDS&selchemid=null&CategorySingle=null. Last Updated 1996. Date Accessed 8-19-2014.
53. Litton Bionetics. Evaluaiton of tris(2-ethyl hexy) trimellitate (TOTM) in the CHO/HGPRT forward mutation assay. LBI Project No. 22207. 1985. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0510642.
54. Litton Bionetics. Evaluation of tris(2-ethyl hexyl) trimellitate in the rat primary hepatocyte unscheduled DNA synthesis assay. LBI Project No. 20991. 1985. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0510641; OTS0508501:326-347.
55. Divincenzo GD, Hamilton ML, Mueller KR, Donish WH, Barber ED. Bacterial mutagenicity testing of urine from rats dosed with 2-ethylhexanol derived plasticizers. *Toxicology*. 1985;34(3):247-259.
56. European Chemicals Agency (ECHA). Triisodecyl benzene-1,2,4-tricarboxylate (CAS No. 36631-30-8; triisodecyl trimellitate). https://apps.echa.europa.eu/registered/data/dossiers/DISS-d977b0c3-ea5c-1552-e044-00144f67d031/AGGR-2a0abd02-a4c6-49c9-bc13-5fab8a68e7f0_DISS-d977b0c3-ea5c-1552-e044-00144f67d031.html#AGGR-2a0abd02-a4c6-49c9-bc13-5fab8a68e7f0. Last Updated 2014. Date Accessed 11-13-2014.
57. Ciba-Geigy Pharmaceuticals. Primary dermal irritation test in Californian rabbits of Reomol OTM (1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester, CASRN 3313-31-1). 1984. Date Accessed 1-20-2015. Report No. 84L004. Available electronically at: https://ntrl.ntis.gov: OTS0513266.
58. Biosearch Inc. Primary skin irritation of Nuoplaz TOTM in rabbits. Project No. 81-2672A. 1981. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0206575, 5, 45-49, 61.
59. Biosearch Inc. Guinea pig contact dermal irritation/sensitization - modified Buehler method - with Nuoplaz TOTM. Project No. 81-2672-A. 1981. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0206575, 5, 56-61.
60. Consumer Product Testing Co. 2014. Summary of an HRIPT on a lipstick containing 57.1% Tridecyl Trimellitate. Unpublished data submitted by Personal Care Products Council. 1 pages.
61. David RM, Lockhart LK, Ruble KM. Lack of sensitization for trimellitate, phthalate, terephthalate and isobutyrate plasticizers in a human repeated insult patch test. *Food Chem Toxicol*. 2003;41(4):589-593. PM:12615132.
62. Harrison Research Laboratories, Inc. 1995. Phototoxicity test of a lipstick containing 22.3% tridecyl trimellitate. Unpublished data submitted by the Personal Care Products Council (7/21/15).
63. Biosearch Inc. Primary eye irritation of Nuoplaz TOTM in rabbits. Project No. 81-2672A. 1981. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov: OTS0206575, pages 5, 50-56, 61.
64. Opdyke DLJ. Monographs on fragrance raw materials: alcohol C-8. *Fd Cosmet Toxicol*. 2015;11(1):101-102.
65. Chemical Book. 1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters, CAS No. 90218-76-1 (tricaprylyl/capryl trimellitate). https://www.chemicalbook.com/ChemicalProductProperty_EN_CB9941058.htm. Last Updated 2010. Date Accessed 11-13-2014.

66. Tempo. Liponate® TDTM (tridecyl trimellitate) product description. https://tempo.ca/wp-content/uploads/2013/06/LIPONATE-TDTM-SELL-SHEET-11-07-13.pdf. Last Updated 7-13-2011. Date Accessed 11-13-2014.
67. National Library of Medicine (NLM). Tri(tridecyl) benzene-1,2,4-tricarboxylate (94109-09-8; tridecyl trimellitate). https://chem2.sis.nlm.nih.gov/chemidplus/rn/94109-09-8. Last Updated 2015. Date Accessed 1-22-2015.
68. AIC. Specification sheet, Soldoc TM13® (tridceyl trimellitate). https://www.aicma.com/products/Tridecyl_Trimellitate_Soldoc_TM_13_TM13SL.pdf. Last Updated 6-17-2014. Date Accessed 11-13-2014.
69. National Institute of Standards and Technology (NIST). Tri(2-ethylhexyl) trimellitate. https://webbook.nist.gov/cgi/cbook.cgi?ID=3319-31-1. Last Updated 2015. Date Accessed 1-20-2015.
70. Eastman Kodak Company. Toxicity and health hazard summary, with cover letters, for tri(2-ethylhexyl) trimellitate. 1983. Date Accessed 1-20-2015. Available electronically at: https://ntrl.ntis.gov; OTS0206572.
71. National Center for Biotechnology Information, U.S. National Library of Medicine. PubChem: Compound summary for CID 18725 (triethylhexyl trimellitate). https://pubchem.ncbi.nlm.nih.gov/compound/18725?from=summary. Last Updated 2014. Date Accessed 2-12-2015.
72. Schossler P, Schripp T, Salthammer T, Bahadir M. Beyond phthalates: gas phase concentrations and modeled gas/particle distribution of modern plasticizers. *Sci Total Environ*. 2011; 409(19):4031-4038.
73. Analytical Biochemistry Laboratories, Inc. Determination of octanol/water partition coefficient of TOTM, a supplementary study. 1985. Date Accessed 1-20-2015. Report No. ABC Final Report #31890. Available electronically at: https://ntrl.ntis.gov: OTS0510639.
74. Chemicals Evaluation and Research Institute, Japan. Partition coefficient: 1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (3319-31-1). https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=24962414&epcount=59&epname=null&epdiscp=null&selchemid=100417&CategorySingle=Category. Last Updated 1998. Date Accessed 1-22-2015.
75. Chem Service Inc. Material safety data sheet (MSDS): triisodecyl trimellitate. https://chemservice.com/media/product/msds/NG-13692.pdf. Last Updated 2012. Date Accessed 1-23-2015.
76. National Library of Medicine (NLM). 1,2,4-Benzenetricarboxylic acid, 1,2,4-triisodecyl ester (36631-30-8;triisodecyl trimellitate). Last Updated 2015. Date Accessed 1-22-2015.
77. National Library of Medicine (NLM). 1,2,4-Benzenetricarboxylic acid, 1,2,4-triisotridecyl ester (72361-35-4; triisotridecyl trimellitate). https://chem2.sis.nlm.nih.gov/chemidplus/rn/72361-35-4. Last Updated 2015. Date Accessed 1-22-2015.
78. Molbase. Properties: Tris(11-methyldodecyl) Benzene-1,2,4-tricarboxylate. https://www.molbase.com/en/properties_72361-35-4-moldata-1658141.html#tabs. Last Updated 2015. Date Accessed 1-23-2015.
79. Parchem. Product specifications: tri-isotridecyl trimellitate. https://www.parchem.com/chemical-supplier-distributor/Tri-isodecyl-Trimellitate-016092.aspx. Last Updated 2015. Date Accessed 1-23-2015.