# Safety Assessment of Trialkyl Trimellitates as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian Gill.*

The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst and Bart A Heldreth, Ph.D., Chemist.



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## INTRODUCTION

This scientific literature review is the initial step in preparing 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

These ingredients all 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, 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 therein. 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.

It is possible that the trialkyl trimellitates can be metabolized via hydrolysis back to the parent alcohol and acid. The parent alcohols and acid may be present as residual starting materials from the synthesis of these ingredients. Therefore, brief summaries of data on trimellitic acid, trimellitic anhydride (although this reactive starting material is unlikely to survive in the product),[2] and the alcohols[3-6] 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 the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) public report of tridecyl trimellitate, triethylhexyl trimellitate should be considered as an acceptable analogue for read-across based on structure and properties.[7] 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 could be extrapolated to address the safety of tridecyl trimellitate, and based on this line of reasoning, all 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),[8] the Environmental Protection Agency (EPA) High Production Volume (HPV) challenge testing system,[9] the Organisation for Economic Development (OECD),[10] and from NICNAS.[7] 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). However, several of the original reports summarized in these dossiers were available through the National Technical Information Service,[11] 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).

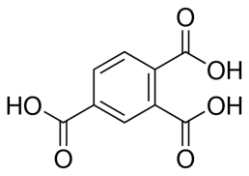


**Figure 1.** trimellitic acid

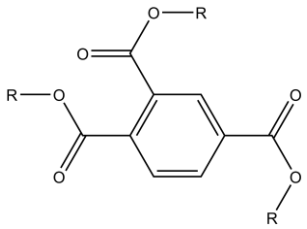

**Figure 2.** trialkyl trimellitates, wherein R is the alkyl residue of a fatty alcohol

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, and low volatility (Table 3). Although they are insoluble with water, these ingredients are readily soluble in most organic solvents and oils.[12]

### Method of Manufacture

The trialkyl trimellitates can be synthesized under traditional esterification conditions from trimellitic acid, the acid chloride, or the anhydride,[13] with the corresponding alcohol (e.g. trimellitic anhydride with 2-ethylhexanol to synthesize triethylhexyl trimellitate).[14] Most commonly, these trialkyl trimellitates are manufactured by esterifying trimellitic anhydride.[12,15]

There is also a fair amount of 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*

Tridecyl trimellitate is reportedly 99.97% pure and contains <0.03% isodecanol and <0.03% tridecanol.[7]

*Triethylhexyl Trimellitate*

One supplier reports that triethylhexyl trimellitate is >99.9% pure,[16] and another supplier indicates that industrial triethylhexyl trimellitate is available with 0.1% by weight 1,1,3-tris(2-methyl-4-hydroxy-5-*t*-butylphenyl) butane.[17] In a study that used 97.1% pure triethylhexyl trimellitate, the major impurity was di-(2-ethylhexyl)terephthalate; the amount of this impurity present in the test material was not specified.[18]

## USE

### Cosmetic

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

Data obtained from the FDA VCRP in 2015[19] and submitted by industry in response to the Council survey in 2014[20] 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.[21] 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.[7] (These concentrations were provided to NICNAS as intended use concentrations.)

### Non-Cosmetic

Triethylhexyl trimellitate is a primary plasticizer used in polyvinyl chloride (PVC) plastic.[22] It has high temperature applications, with primary use in high specification electrical cable insulation and sheathing. It also has applications in medical products, specifically blood bags, infusion sets, catheters, and hemodialysis tubing.[23,24]

## TOXICOKINETICS

### Absorption, Distribution, Metabolism, and Excretion

*Tridecyl Trimellitate*

Tridecyl trimellitate has a relatively high molecular weight, low water solubility, and high log P value; therefore, absorption through skin and in the gastrointestinal tract is likely to be limited.[7]

*Triethylhexyl Trimellitate*

The in vitro hydrolysis of triethylhexyl trimellitate (92% pure) was determined by adding [hexyl 2-$^{14}$C]triethylhexyl trimellitate (0.19 µCi/ml) to rat intestinal homogenates prepared from male Sprague-Dawley rats.[25] 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.[18] 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 $^{14}CO_2$ (0.8-3.5% 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 0.6% 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.[26] 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 times points from 0.5 h to 336 h (14 days) after dosing. The animals were placed in metabolism cages, and urine and fecal samples were collected at various intervals 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 in Franz cells using full-thickness skin samples excised from female nude mice and specific pathogen-free pigs.[27] 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 ± 0.53 nmol/mg in nude mouse and 0.35 ± 0.19 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 after 12 h, indicating no in vivo availability into systemic absorption.

## TOXICOLOGICAL STUDIES

### Single Dose (Acute) Toxicity

The acute dermal toxicity of tricaprylyl/capryl trimellitate (in rats)[28] and triethylhexyl trimellitate (in guinea pigs and rabbits)[29,30] and the acute oral toxicity of tricaprylyl/capryl trimellitate (in rats),[28] tridecyl trimellitate (in rats),[7] triethylhexyl trimellitate (in mice and rats),[31-34] and triisodecyl trimellitate (in rats)[35] was not remarkable (Table 5). Mixed results were observed with triethylhexyl trimellitate in single-exposure inhalation studies in rats; 100% mortality was reported with 2640 and 4170 mg/m$^3$ in one study,[36] but no mortality was observed with 2600 mg/m$^3$ in another study.[37]

### Repeated Dose Toxicity

In repeated dose oral toxicity studies in rats, the no-observable 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[28] (Table 6). Triethylhexyl trimellitate was administered to rats by gavage for 21-days (up to 2000 mg/kg/day)[38,39] or 28-days (up to 1000 mg/kg/day),[38,40,41] and in the diet (up to 2%) for 28 days;[31] in one 28-day gavage study, the NOAEL was >1000 mg/kg/day, and in the feed study, hepatomegaly was reported with 0.67 and 2.0% triethylhexyl trimellitate.

### 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.[42] Cell viability was similar to controls over a 3 h period.

#### Non-Human

**Oral**

*Triethylhexyl Trimellitate*

A group of 12 male albino rats was dosed by gavage with 300 mg/kg/day in corn oil, 6 days/wk, for 4 wks; 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.[43] Two control groups of 6 male rats 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-1immune 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.

**Parenteral**

*Triethylhexyl Trimellitate*

Six male albino rats were dose intraperitoneally with 1.0 mg/kg bw triethylhexyl trimellitate for 7 days, and the control group was administered the same volume of saline.[24] 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; it 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 acetyl transferase, and the effect on numbers of hepatic peroxisomes was evaluated.[38] Peroxisome induction in rats given triethylhexyl trimellitate was less than that observed with 0.67% 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 was not seen with triethylhexyl trimellitate.

A molecular modelling study of triethylhexyl trimellitate - peroxisome proliferator-activated receptors (PPAR) interactions was also conducted.[44] 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.[44]

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 the Panel has noted that humans do not react to peroxisome proliferators in the manner that rodents do.[3] 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 study of up to 1000 mg/kg/day, 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[28] (Table 7). Orally administered triethylhexyl trimellitate had a no-observed effect level (NOEL) in rats of 100 mg/kg/day in males and 1000 mg/kg/day in females and offspring for reproductive and developmental effects; spermatocytes and spermatids were decreased with doses of 300 and 1000 mg/kg/day.[31] Two additional oral reproductive and developmental toxicity studies with triethylhexyl trimellitate in rats did not produce any toxicologically significant effects.[31,45] Neither tricaprylyl/capryl trimellitate or triethylhexyl trimellitate had a significant repressive effect on genes in the TMD pathway.[28,31]

### 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).[46] 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.[47] 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 >0.001 mmol/l triethylhexyl trimellitate. The estrogenic activity of the metabolite(s) 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 >0.0005 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.[48] The lowest effective concentrations of triethylhexyl trimellitate in the ERα 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 $1.2 \times 10^{-7}$ and $1.6 \times 10^{-6}$, respectively; the $EEF_{10}\alpha/EEF_{10}\beta$ ratio was 0.0075. 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, a mammalian cell gene mutation assay, or a chromosomal aberration assay, and triethylhexyl trimellitate was not genotoxic in a forward mutation assay, unscheduled DNA synthesis assay, or dominant lethal assay[28,31,49-53] (Table 8). Also, urine from rats dosed with triethylhexyl trimellitate was not mutagenic in the Ames test.[54]

## 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[7,28,55] (Table 9). A single occlusive application of undiluted triethylhexyl trimellitate produced reversible moderate erythema and moderate to severe edema in guinea pig skin;[29] triethylhexyl trimellitate was a reversible primary dermal irritant in Californian rabbits,[56] but it was not a primary irritant in New Zealand White rabbits.[57] Tricaprylyl/capryl trimellitate (10% at induction/undiluted at challenge) was not a sensitizer in a guinea pig maximization study,[28] and undiluted triethylhexyl trimellitate was not a sensitizer in a Buehler sensitization assay in guinea pigs.[58] Up to 100% tridecyl trimellitate was negative in a local

lymph node assay.[7] In human repeated insult patch tests, tridecyl trimellitate (57.1% in formulation and undiluted)[7,59] and 1% triethylhexyl trimellitate were not sensitizers.[60]

### Ocular Irritation

Tricaprylyl/capryl trimellitate, triethylhexyl trimellitate, and triisodecyl trimellitate were not irritating to rabbit eyes,[28,55,61] and tridecyl trimellitate was slightly irritating to rabbit eyes[7] (Table 10).

## INFORMATION SOUGHT

The CIR requests that interested parties submit any available data on the trialkyl trimellitates, especially on those for which data are not currently included in this report. Although these ingredients do not appear to be genotoxic, carcinogenicity data would enhance this safety assessment.

## 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 therein. These ingredients are all 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 category conducted by the Council, 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.

Because the trialkyl trimellitates have high molecular weights, low water solubility, and high log P values, absorption through skin and in the gastrointestinal tract is likely to be limited. 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; in the urine, the 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 mouse and pig skin, the accumulation of triethylhexyl trimellitate in the skin was 1.32 ± 0.53 nmol/mg and 0.35 ± 0.19 nmol/mg, respectively. Triethylhexyl trimellitate was not found in the receptor after 12 h, indicating no in vivo availability into systemic 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, was not remarkable. Mixed results were observed with triethylhexyl trimellitate in single-exposure inhalation studies in rats; 100% mortality was reported with 2640 and 4170 mg/m$^3$ in one study, but no mortality was observed with 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 it was 500 mg/kg/day in a 13-wk gavage study. Triethylhexyl trimellitate was administered to rats by gavage for 21- (up to 2000 mg/kg/day) or 28-days (up to 1000 mg/kg/day), and in the diet (up to 2%) for 28 days; in one 28-day gavage study, the NOAEL was >1000 mg/kg/day, and in the feed study, hepatomegaly was reported with 0.67 and 2.0% triethylhexyl trimellitate.

Oral administration of 300 mg/kg/day triethylhexyl trimellitate, 6 days/wk for 4 wks, 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 study of up to 1000 mg/kg/day, 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. Orally administered triethylhexyl trimellitate had a NOEL in rats of 100 mg/kg/day in males and 1000 mg/kg/day in females and offspring for reproductive and developmental effects; spermat-

ocytes and spermatids were decreased with doses of 300 and 1000 mg/kg/day. Two additional oral reproductive and developmental toxicity studies in rats did not produce any toxicologically significant effects. Neither tricaprylyl/capryl trimellitate or triethylhexyl trimellitate 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, a mammalian cell gene mutation assay, or a chromosomal aberration assay, and triethylhexyl trimellitate was not genotoxic in a forward mutation assay, unscheduled DNA synthesis assay, or dominant lethal assay. 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. 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 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.

## TABLES AND FIGURES

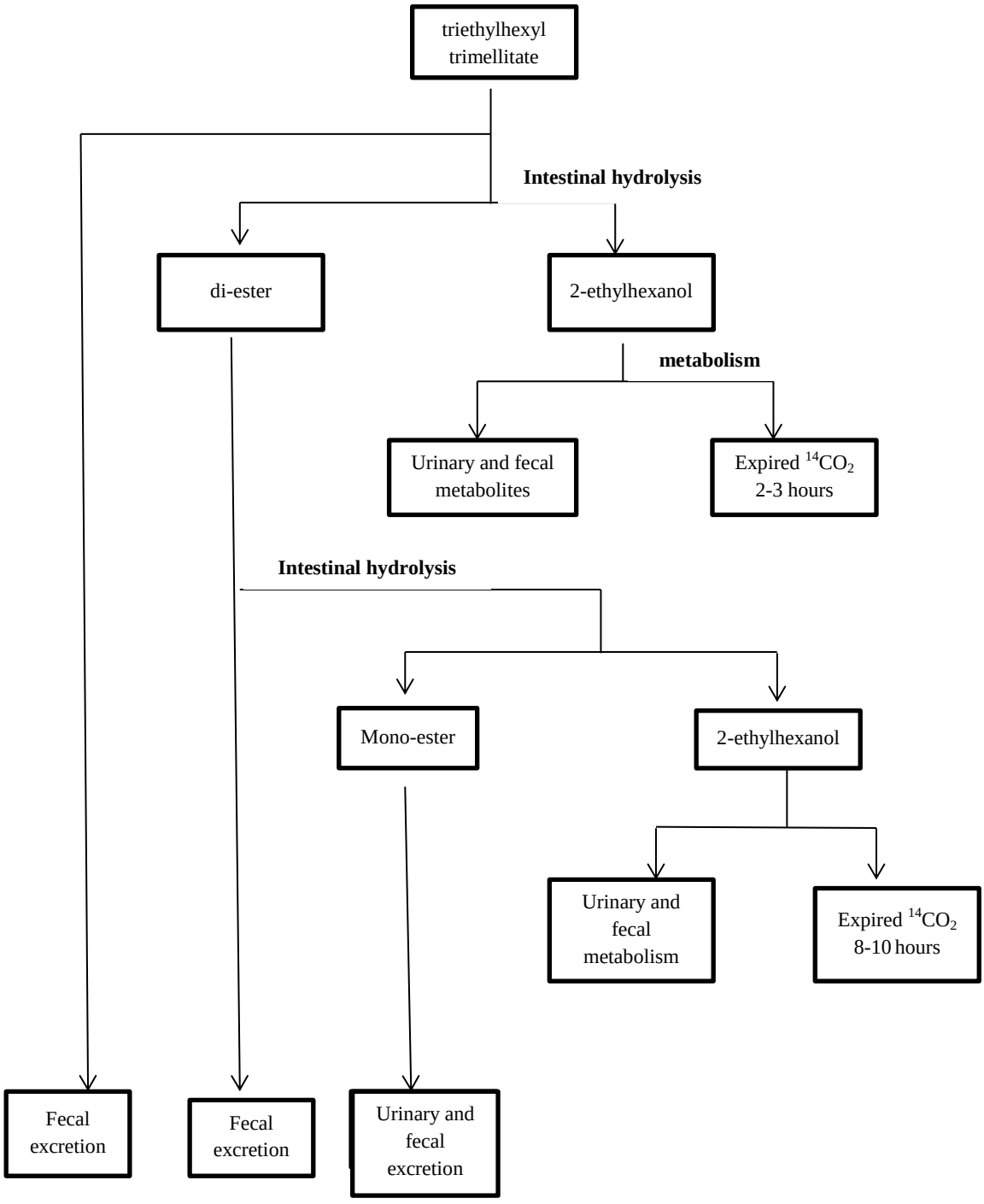


**Figure 3. Metabolic fate of triethylhexyl trimellitate following oral dosing in the rat [18]**

**Table 1. Definitions, Structures, and 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/Caprylyl 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 |

**Table 2. Data on trimellitic acid, trimellitic anhydride, and constituent alcohols**

| Acid or Alcohol | Summary Data | Reference |
|---|---|---|
| Trimellitic Acid | 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<br>single dose (acute) toxicity-inhalation: $LC_{50}$ >3750 mg/m$^3$ , with necropsy findings considered within normal limits<br>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<br>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 0.05, 0.1, or 0.3 mg/m$^3$ for 6 h/day, 5days/wk for 13 wks<br>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)<br>dermal irritation and sensitization: mild skin irritation potential<br>ocular irritation: severe eye irritation potential | [2] |
| Trimellitic Anhydride | single dose (acute) toxicity-dermal: $LD_{50}$ = 5600 mg/kg<br>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<br>single dose (acute) toxicity-inhalation: the inhalation $LC_{50}$ value in rats was >2330 mg/m$^3$, with lung lesions appearing as the most consistent lesion upon necropsy<br>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<br>repeated dose toxicity-inhalation: – in mice, exposure to 0.010, 0.070, or 0.150 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 0.3 mg/m$^3$ for 6 h/day, 5 days/wk for 2 wks; in rats exposed to 0.1 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 0.010, 0.030, 0.10 or 0.30 mg/m$^3$ for 6 h/day, 5 days/wk for 1-2 wks, and the lung foci completely resolved within 12 days after the last exposure, but reappeared following exposure to a single challenge concentration; exposure to 0.5 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 wks – 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, bronchoalveoloar pneumonia) and antibody levels was observed; in rats exposed to 0.002, 0.015, or 0.054 mg/m$^3$ for 6 h/day, 5 days/wk for up to 13 wks, and these effects were more pronounced in rats following 6.5 wks of exposure than observed in animals following 13 wks 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<br>reproductive and developmental toxicity: in gravid rats exposed to 0.5 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 in a study in an inhalation study in which guinea pigs were exposed to 0.5 mg/m$^3$ on days 6-15 of gestation<br>genotoxicity: negative in Ames test, chromosomal aberration assay, and assay for HGPRT mutations, with | [2] |

**Table 2. Data on trimellitic acid, trimellitic anhydride, and constituent alcohols**

| Acid or Alcohol | Summary Data | Reference |
|---|---|---|
| | and without metabolic activation<br>dermal irritation and sensitization: mild skin irritation potential; 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<br>ocular irritation: severe eye irritation potential<br>genotoxicity: three in vitro assays were negative<br>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 | |
| Caprylic Alcohol | dermal irritation – non-human: produced a mild irritation when applied undiluted to intact or abraded rabbit skin<br>irritation – human: produced no irritation in a 48 h closed-patch test in 25 human subjects when tested at 2% in petrolatum | [3] |
| 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<br>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<br>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<br>genotoxicity: ≤2500 µg/plate was not mutagenic in an Ames test using *Salmonella typhimurium* TA 98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation; ≤5000 µg/plate was not mutagenic in an Ames test using *Salmonella typhimurium* TA98 and, TA100 with and without metabolic activation<br>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<br>dermal irritation – non-human: slightly irritating when applied undiluted to 3 female NZW rabbits using 4-h semi-occlusive patches<br>dermal irritation and sensitization – human: non-irritating; not a sensitizer in a maximization study in 25 subjects<br>ocular irritation: irritating to the eyes of NZW rabbits (n=3) when instilled undiluted | [4] |
| Decyl Alcohol | dermal irritation – human: 3% in petrolatum was not irritating in a 48-h occlusive patch test in 25 subjects<br>single dose (acute) toxicity–dermal: $LD_{50}$ in rabbits, 3.5 ml/kg<br>single dose (acute) toxicity-oral: $LD_{50}$ in rats, 9800 mg/kg<br>single dose (acute) toxicity-inhalation: no deaths with exposure to concentrated vapors for 8 h<br>irritation – human: produced no irritation in a 48 h closed-patch test in 25 human subjects when tested at 3% in petrolatum | [3] |
| Ethylhexyl Alcohol | absorption, distribution, metabolism, and excretion: in vitro dermal absorption rates were 0.22 mg/cm$^2$/h for rats and 0.038 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, mitochondrial beta-oxidation of fatty acids was inhibited 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<br>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; in a study in which 10 rats were dosed with a single dermal application of 1600 mg/kg bw, absolute and relative thymus weights, liver granulomas, brochiectasis in the lung, renal tubular epithelial necroses, edematous heart and testes, and spermatogenesis, all decreased<br>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<br>single dose (acute) toxicity-inhalation: $LC_{50}$ in rats was >0.89 mg/l but <5.3 mg/l; $LC_{50}$ >227 ppm in mice, rats, and guinea pigs<br>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<br>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 | [3,5] |

**Table 2. Data on trimellitic acid, trimellitic anhydride, and constituent alcohols**

| Acid or Alcohol | Summary Data | Reference |
|---|---|---|
| | repeated dose toxicity-inhalation: NOAEC was 120 ppm (i.e., 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<br>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.<br>estrogenic activity: in an E-SCREEN assay using T47D human breast cancer cells, weak estrogenic activity was observed<br>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 acid-soluble DNA incorporated into the thymidine; 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<br>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, weak hepatocellular carcinoma increased in females of the 750 mg dose group body wt gain decreased and mortality increased; 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, and mortality was 52% in females of the 750 mg/kg dose group<br>dermal irritation – non-human: 4-h occlusive patches were irritating to rabbit skin (n= 3 males); application of 0.5 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<br>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<br>ocular irritation: instillation of 20 µg into the conjunctival sac of rabbit eyes caused moderately severe irritation of the cornea | |
| Isodecyl Alcohol | single dose (acute) toxicity-dermal: $LD_{50}$ of a mixture of C9-11 branched alkyl alcohols in rats, >2600 mg/kg<br>single dose (acute) toxicity-oral: $LD_{50}$ of a mixture of C9-11 branched alkyl alcohols in rats, 4600 mg/kg<br>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 | [3] |
| Tridecyl Alcohol | single dose (acute) toxicity-dermal: dermal $LD_{50}$ in rabbits, 5600 mg/kg<br>single dose (acute) toxicity-oral: oral $LD_{50}$ in rats, 17,200 mg/kg | [6] |

Abbreviations: 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

**Table 3. Chemical and Physical Properties**

| Property | Description | Reference |
|---|---|---|
| | **Tricaprylyl/Capryl Trimellitate** | |
| physical characteristics | yellowish liquid (97.15% pure) | 28 |
| formula weight | 661.01 | 62 |
| melting point | -53ºC | 28 |
| boiling point | 346 ºC | 28 |
| solubility | <1.0 mg/l (23 °C) | 28 |
| density | 0.97 g/cm³ (20ºC) | 28 |
| vapor pressure | 0.000000134 Pa (25°C; experimental) | 28 |
| Log $P_{ow}$ | 10.6 (55ºC; pH 6.6) | 28 |
| | 17.2-24.8 (25ºC; pH 7) | |
| | **Tridecyl Trimellitate** | |
| physical characteristics | colorless to slightly yellow viscous liquid (20ºC and 25ºC) | 7,63 |
| molecular weight | 757.19 | 64 |
| purity | 99.97% | 7 |
| solubility | compatible with most oil phase ingredients; insoluble in water | 63,65 |
| relative density | 0.965 gr/cm³ (20° C) | 65 |
| refractive index | 1.4850 | 65 |
| saponification value | 315-335 | 63 |
| | 210-230 | 65 |
| acid value | 0.1 (max) | 63 |
| | 0.5 (max) | 65 |
| | **Triethylhexyl Trimellitate** | |
| physical characteristics | pale yellow liquid with a faint odor (98.29% pure) | 31 |
| | colorless, odorless viscous liquid (>99.9% pure) | 16 |
| molecular weight | 546.78 | 66 |
| melting point | -43ºC | 31 |
| boiling point | 355ºC | 31 |
| | 417ºC | 67 |
| solubility | insoluble (<0.1 mg/l) to slightly soluble (0.13 mg/l) in water (25ºC) | 31 |
| | 10-50 mg/l in DMSO and ethanol (20ºC); >100 mg/l in acetone (20ºC) | 68 |
| | soluble in most organic solvents; miscible with alcohol, ether, and most oils | 15 |
| density | 0.9885 g/cm³ (20ºC) | 31 |
| vapor pressure | 6.8 x $10^{-8}$ Pa (25 °C; experimental) | 31 |
| | 3.9 x $10^{-11}$ mm Hg (25°C) | 22 |
| partial pressure (experimental) | 2.13 x $10^{-8}$ Pa | 69 |
| log $P_O$ (saturation vapor pressure; estimated) | -12.29 Pa (SPARC); -5.91 (EPI Suite) | 69 |
| log $K_{OA}$ (octanol-air partition coefficient; estimated) | 16.24 (EPI Suite) | 69 |
| vapor density | 18.9 (air = 1) | 16 |
| decomposition | emits acrid smoke and irritating vapors when heated to decomposition | 68 |
| refractive index | 1.485 ($n^{20}_D$) | 17 |
| specific gravity | 0.987 (25ºC/25ºC) | 17 |
| log $P_{ow}$ | 4.35 (determined by gas-liquid chromatography) | 70 |
| | 5.94 (25ºC) | 12,71 |
| | 8 (25ºC; pH 4.81) | 31 |
| | 8.88 (55ºC; pH 6.3) | 31 |
| | **Triisodecyl Trimellitate** | |
| physical characteristics | yellow liquid (>98% pure) | 55 |
| | colorless odorless liquid | 72 |
| molecular weight | 630.94 | 73 |
| melting point | -35ºC | 72 |
| boiling point | 335 - 420°C (at 100.5 kPa) | 55 |
| density | 0.959 (20 °C) | 55 |
| vapor pressure | 5.8 x $10^{-10}$ Pa (25 °C; experimental) | 55 |
| solubility | slightly soluble in water (≤1.24 x $10^{-3}$ g/L at 20°C) | 55 |
| log $P_{ow}$ | >9.4 | 55 |
| | **Triisotridecyl Trimellitate** | |
| physical characteristics | liquid, faint odor (99.60% pure) | 35 |
| molecular weight | 757.19 | 74 |
| boiling point | 737ºC ( 760 mmHg) | 75 |
| solubility | insoluble (solvent not named) | 76 |
| density | 0.948 g/cm$^3$ | 75 |
| vapor pressure | < 0.0000000001 Pa (20 °C; calculated) | 35 |
| refractive index | 1.483 | 75 |
| saponification value | 222-232 | 76 |
| log P | 14.65770 | 75 |

**Table 4. Frequency and concentration of use according to duration and type of exposure**

| | *# of Uses*[19] | *Max Conc of Use (%)*[20] | *# of Uses*[19] | *Max Conc of Use (%)*[20] | *# of Uses*[19] | *Max Conc of Use (%)*[20] |
|---|---|---|---|---|---|---|
| | **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<br>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

**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<br>No mortality and no signs of toxicity. | [28] |
| triethylhexyl trimellitate | guinea pigs | 1 (sex not specified) | undiluted | Single 24 h occlusive patch; 5, 10, or 20 ml/kg | >20 ml/kg<br>no mortality | [29] |
| triethylhexyl trimellitate | NZW rabbits | 3M/3F | undiluted | Single 24 h occlusive patch; 2.0 ml/kg was applied | >2.0 ml/kg<br>No signs of toxicity; no gross pathology | [30] |
| **ORAL** | | | | | | |
| tricaprylyl/capryl trimellitate | Wistar rats | 5M/5F | undiluted | 3 g/kg bw by gavage | >3 g/kg<br>No mortality and no signs of toxicity. | [28] |
| 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<br>17.8 ml/kg: 3 animals died 6-7 days after dosing;<br>23.7 ml/kg: 3 animals died 3-6 days after dosing;<br>31.6 ml/kg: 8 animals died 3-9 days after dosing;<br>Signs of toxicity, primarily reduced spontaneous activity and soft feces, were observed in all groups. | [28] |
| tridecyl trimellitate | Wistar albino rats | 5M/5F | undiluted | 5 g/kg bw by gavage | >5 g/kg<br>No mortality and no signs of toxicity. | [7] |
| triethylhexyl trimellitate | mice | 2M/2F | not provided | 10 ml/kg by gavage | >3.2 g/kg | [31] |
| triethylhexyl trimellitate | mice | not provided | not provided | 3 and 60 g/kg bw by gavage | >6 g/kg | [31] |
| 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<br>No mortality and no signs of toxicity | [32] |
| triethylhexyl trimellitate | Sprague-Dawley rats | 2M/2F | undiluted | 10 ml/kg bw by gavage | >3.2 g/kg<br>piloerection observed in males at 1 and 2 h | [31] |
| triethylhexyl trimellitate | Sprague-Dawley rats | 5M/5F | undiluted | 5 g/kg bw by gavage | >5 g/kg<br>No mortality and no signs of toxicity. | [33] |
| triethylhexyl trimellitate | Sprague-Dawley rats | 2M/2F | undiluted | 10 ml/kg bw by gavage | 9.85 g/kg<br>piloerection observed in males at 2 and 3 h; no signs of toxicity after 3 h | [31,34] |
| triisodecyl trimellitate | Sprague-Dawley rats | 2M/2F | undiluted | 10 ml/kg by gavage | >9.59 g/kg bw (>10 ml/kg)<br>No mortality and no signs of toxicity. | [35] |
| **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 | $LC_{50}$ not determined<br>100% mortality at >2640 mg/m$^3$ | [36] |
| triethylhexyl trimellitate | Sprague-Dawley rats | 5M/5F | | 2600 mg/m$^3$; 4-h exposure | >2600 mg/m$^3$<br>No mortality and no signs of toxicity. | [37] |

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.<br>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<br>NOAEL was 300 mg/kg/day | 28 |
| tricaprylyl/capryl trimellitate | Sprague-Dawley rats, 10M/10F; 5M/5F recovery animals | 13 wks, 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<br>NOAEL was 500 mg/kg/day | 28 |
| 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.<br>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 | 38,39 |
| 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.<br>NOAEL was >1000 mg/kg/day in male and female rats | 40 |
| 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 rations. The only remarkable effect was significantly decreased in triglyceride values were the test animals | 41 |
| triethylhexyl trimellitate | Fischer F344 rats, 5M/5F | 28-day | feed | 0, 0.2, 0.67, 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 0.2%; LOAEL was 0.67% | 38 |
| 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<br>NOAEL was 225 mg/kg bw/day; LOAEL was 1000 mg/kg bw/day | 31 |

Abbreviations: LOAEL – lowest observable adverse effect level; NOAEL = no-observable adverse effect level

**Table 7. Reproductive and Developmental Toxicity Studies**

| Test Article | Animals/Group | Vehicle | Dose/Concentration | Procedure | Results | Reference |
|---|---|---|---|---|---|---|
| | | | **ORAL** | | | |
| tricaprylyl/capryl trimellitate (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<br>NOAELs were 300 mg/kg bw/day for maternal toxicity and 1000 mg/kg bw/day for fetal toxicity | 28 |
| 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 | 28 |
| 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 2 h after the last dose. Fetuses were removed immediately and necropsied within 2 h. (2 trials) | No statistically significant effects on testicular testosterone production, fetal viability, or maternal body wt gains | 45 |
| triethylhexyl trimellitate | Crj:CD:SD rats, 12M/12F | corn oil | 0, 100, 300,or 1000 mg/kg/day | Males were dosed by gavage for 46 days, starting 14 days prior to mating, and females were dosed 14 days 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<br>NOELs for reproductive and developmental effects were 100 mg/kg/day for males and 1000 mg/kg/day for females and offspring | 31 |
| triethylhexyl trimellitate | 20 gravid Sprague-Dawley rats (main study)<br>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 with 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.<br>NOAELs were 1050 mg/kg bw/day for maternal and developmental toxicity, and 500 mg/kg bw/day for postnatal development | 31 |

**Table 7. Reproductive and Developmental Toxicity Studies**

| 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 | 31 |

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

**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 | 28 |
| 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 | 28 |
| tricaprylyl/capryl trimellitate | 313-1250 µg/ml in ethanol<br>625-2500 µg/ml in ethanol | Chromosomal aberration assay; 24 h harvest time; vehicle and appropriate positive controls were used<br>3 h exposure with and without metabolic activation<br>24 h exposure without metabolic activation | in human peripheral blood lymphocytes | not genotoxic with either exposure time | 28 |
| 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 | 49 |
| 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 | 50 |
| triethylhexyl trimellitate | 0-2500 µg/ml in ethanol | mammalian cell gene mutation assay; appropriate positive controls were used | mouse lymphoma L5178Y cells | negative | 31 |
| 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 24 h treatment; appropriate controls were used | human lymphocytes | negative | 31 |
| triethylhexyl trimellitate | 0-5.0 mg/ml in acetone | chromosomal aberration assay, with and without metabolic activation; short-term (6 h) and continuous (24 or 48 h) treatments; appropriate controls were used | Chinese hamster lung fibroblasts (V79 cells) | negative | 31,51 |
| 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 | 52 |
| triethylhexyl trimellitate | 0-5000 nl/ml in ethanol | unscheduled DNA synthesis assay; appropriate positive controls were used | rat primary hepatocytes | negative | 53 |
| urine from rats dosed with triethylhexyl trimellitate | ≤2 ml undiluted test material | Ames test using a direct plating procedure, with and without metabolic activation<br>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 | 54 |

**Table 8. Genotoxicity studies**

| Test Article | Concentration/Vehicle | Procedure | Test System | Results | Reference |
|---|---|---|---|---|---|
| | | **IN VIVO** | | | |
| triethylhexyl trimellitate | 1400 mg/kg bw (vehicle not specified) | dominant lethal assay; details not provided | male Swiss mice | negative | [31] |

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; 0.5 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 72 h | slightly irritating; PII = 1.67/8<br>At 24 h, slight to well-defined erythema was observed in all animals and slight edema in 2 animals; all reactions were reversible within 6-8 days | [28] |
| tricaprylyl/capryl trimellitate | intradermal induction: 10% in FCA and maize germ oil (1:1)<br>dermal induction and challenge: undiluted | Dunkin-Hartley guinea pigs, 20 F | GPMT<br>intradermal induction: administered in a mixture of FCA and maize germ oil (1:1).<br>dermal induction: animals were pretreated with 10% sodium dodecyl sulfate on day 6; 48 h patches were applied on day 7<br>challenge: 24-h occlusive patch applied on day 21 | not a sensitizer<br>intradermal induction: all control and test animals had irritation injection sites; severe erythema, edema and necrosis were observed<br>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; 24 h after patch removal, some animals had erythema and eschar formation in the application area<br>challenge: no reactions were observed at 48 or 72 h | [28] |
| tridecyl trimellitate | 10% in corn oil; 0.5 ml | NZW rabbits 2 (sex not specified) | 24-h single occlusive patch to intact and abraded skin; sites scored at 24 and 72 h | slightly irritating<br>erythema/eschar mean score – 0.25/1 and 0.5/1 for intact and abraded skin, respectively; resolved by 72 h<br>no edema | [7] |
| tridecyl trimellitate | as supplied | NZW rabbits, 3M | similar to OECD 404 (i.e., acute dermal irritation/corrosion test); patch type and duration not stated; no details provided | non-irritating<br>no erythema or edema at 24, 48, or 72 h | [7] |
| tridecyl trimellitate | 5, 10, 25, 50, or 100% acetone/olive oil | CBA/J mice, 4F | OECD TG 429; LLNA; two experiments were performed<br>HCA was used as a positive control | negative<br>SI >3 at 10 and 100% in experiment 1, but not in experiment 2 | [7] |
| 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 1 wk | [29] |
| triethylhexyl trimellitate | as supplied; 0.5 ml | Californian rabbits, 2M/2F | single 4-h occlusive patch applied to shaved skin | reversible primary dermal irritant<br>slight erythema was observed n all rabbits 30-60 min after patch removal; no effects were observed at day 7 | [56] |
| triethylhexyl trimellitate | as supplied; 0.5 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 | [57] |
| triethylhexyl trimellitate | as supplied; 0.5 ml | albino guinea pigs, 10M | modified Buehler sensitization assay<br>induction: 10 24-h occlusive patches were applied, with a 24-h rest period between patches<br>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 | [58] |

**Table 9. Dermal irritation and sensitization**

| Test Article | Concentration/Dose | Test Population | Procedure | Results | Reference |
|---|---|---|---|---|---|
| triisodecyl trimellitate | undiluted; 0.5 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<br>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<br>72 h: very slight edema at 3 intact and abraded sites<br>All reactions were resolved at day 6. | 55 |
| | | | **HUMAN** | | |
| tridecyl trimellitate | 57.1% in a lipstick formulation | 53 subjects | modified Draize HRIPT<br>induction: 24-h occlusive patches with test material, applied 3x/wk<br>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 | 59 |
| tridecyl trimellitate | undiluted; 0.2 ml | 51 subjects | HRIPT (same procedure as above) | not an irritant or a sensitizer | 7 |
| 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<br>induction: erythema in 4 subjects on 4-6 occasions<br>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) | 60 |

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

**Table 10. Ocular irritation studies**

| Test Article | Concentration/Dose | Animals | Method | Results | Reference |
|---|---|---|---|---|---|
| | | | **NON-HUMAN STUDIES** | | |
| tricaprylyl/capryl trimellitate | as supplied; 0.1 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<br>No signs of irritation at 24, 48, or 72 h | 28 |
| 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<br>Severe conjunctival effects observed at 1 h; effects diminished in severity by 24 h, and were resolved by 72 h | 7 |
| triethylhexyl trimellitate | as supplied; 0.1 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 | 61 |
| triisodecyl trimellitate | as supplied; 0.1 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<br>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 | 55 |

Abbreviations: NZW – New Zealand White; OECD - Organisation for Economic Development; TG – test guideline

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