CPSC Staff Statement on University of Cincinnati Report
"Toxicity Review for Trioctyltrimellitate (TOTM)"[1]

October 2018

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct toxicology assessments for six dialkyl o-phthalate (o-DAP) substitutes: acetyl tri-n-butyl citrate (ATBC); bis(2-ethylhexyl) adipate (DEHA); di-2-ethylhexyl terephthalate (DEHT); 1,2-cyclohexanedicarboxylic acid, dinonyl ester, branched and linear (DINX); trioctyltrimellitate (TOTM); and 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TPIB). The reports will be used to inform staff's assessment of products that may contain these compounds and is the first step in the risk assessment process.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. First, it must be "toxic" under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards of products under the FHSA.

The first step in the risk assessment process is hazard identification, which consists of a review of the available toxicity data for the chemical. If it is concluded that a substance may be "toxic", then a quantitative assessment of exposure and risk is performed to evaluate whether a specified product may be considered a "hazardous substance".

The toxicity review for TOTM follows.

[1] This statement was prepared by the CPSC staff, and the attached report was produced by the University of Cincinnati for CPSC staff. The statement and report have not been reviewed or approved by, and do not necessarily represent the views of, the Commission.

TOXICITY REVIEW FOR TRIOCTYLTRIMELLITATE (TOTM)

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1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with trioctyltrimellitate (TOTM). It is an update of a previous contractor report to CPSC (Versar, 2010).

Literature searches for physico-chemical, toxicological, exposure, and risk information were performed in November 2017 using the CAS number and synonyms (see Appendix 1 for the full list of search terms), and using the following databases:

- EPA SRS
- PUBMED
- RTECS
- TSCATS (included in TOXLINE)
- TOXNET databases, including
    - TOXLINE
    - CCRIS
    - DART/ETIC
    - GENE-TOX
    - HSDB

Searches of the PubMed and Toxline databases covered all dates through the date of the search (November, 2017). However, studies dated up to 2007 were screened out of the library during the screening process using the Endnote files, as the current report supplements and updates a staff report prepared in 2010 (Versar, 2010). Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Searches for authoritative reviews addressing general toxicity and physicochemical information were conducted with the following databases using the CAS number for TOTM and synonyms. These sites included:

- ANSES Information on Chemicals (https://www.anses.fr/en)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)
- ECHA Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
- EFSA (https://www.efsa.europa.eu/)
- EPA (https://www.epa.gov/)
- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA IRIS (https://www.epa.gov/iris)
- FDA (https://www.fda.gov/)
- Google
- Health Canada (https://www.canada.ca/en/health-canada.html)
- IARC (https://www.iarc.fr/)

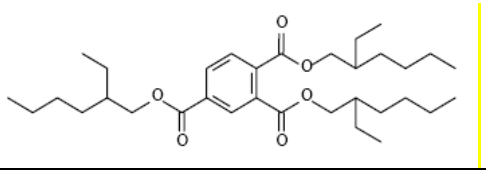
- INCHEM (http://www.inchem.org/)
- JEFCA (http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/)
- NICNAS (https://www.nicnas.gov.au/)
- NTP (https://ntp.niehs.nih.gov/)
- OECD (http://www.oecd.org/)
- WHO (http://www.who.int/en/)

Several new TOTM toxicology studies were identified in the literature searches. These included original Japanese studies (JECDB, 1996); a new 90-day feed study (Anonymous, 2012, as cited by ECHA, 2018), the published version of the Huntingdon Life Sciences (2002) study (Renaut and Whitley, 2017), and a developmental study (Furr et al., 2014). New studies identified in the primary literature also included studies on toxicokinetics, mechanism, and exposure, as well as several reviews. Several of the key toxicity studies were unpublished and not available as the primary studies. Therefore, these studies were evaluated based on authoritative reviews and data compilations, including OECD (2002), ECHA (2018), U.S. EPA (undated HPV dossier) and SCENIHR (2016).

2 Physico-Chemical Characteristics

Physical-chemical properties and identification information for this compound are highlighted in Table 1.

Table 1: Physicochemical Properties and Identification Information for Trioctyltrimellitate

Chemical Name	Trioctyltrimellitate
Synonyms	Tri-(2-ethylhexyl)trimellitate (TEHTM); Tris(2-ethylhexyl) trimellitate; Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate; Trioctyltrimellitate; tri(2-ethylhexyl)trimellitate; 1,2,4-benzenetricarboxylic acid; Trioctyl ester; Tris(2-ethylhexyl) ester; Trioctyl benzene-1,2,4-tricarboxylate
CAS Number	3319-31-1
Structure	
Chemical Formula	$C_{33}H_{54}O_6$
Molecular Weight	546.78 g/mol
Physical State	Liquid
Color	Yellow

Melting Point	-38°C (CMA, 1983); -50°C (SCENIHR, 2016)
Boiling Point	414°C; 283°C at 4 hPa (SCENIHR, 2016)
Vapor Pressure	3.9×10^{-11} at 25°C
Water Solubility	100 mg/L at 25°C[1]
Log K_{ow}	5.94 (HSDB, 2018; SCENIHR, 2016)
Flashpoint	N/A
Density	N/A
K_{oc} (the organic carbon normalized solid-water partition coefficient)	350 L/kg
Henry's Law Constant	4.45×10^{-7} (atm m^3/mol) (Versar, 2010)
Sources	ChemID*plus* 2018, (unless otherwise stated)

See Appendix B for more detail on the characteristics.

There appears to be considerable uncertainty regarding the water solubility of TOTM, with reported values ranging from 100 mg/L to 0.1 mg/L or even 1 µg/L. If TOTM is released into water, is expected to adsorb to suspended solids and sediment in water based upon an estimated K_{oc} value of 350. Volatilization from water surfaces or from moist soil surfaces is not expected to occur based upon an estimated Henry's Law constant of 4.4×10^{-7} (HSDB, 2008). If released to air, an estimated vapor pressure of 3.9×10^{-11} mm Hg (25ºC) indicates that TOTM will exist solely in the particulate phase in the ambient atmosphere (to be removed by wet and dry deposition). Volatilization from dry soil surfaces is not expected due to its low vapor pressure (HSDB, 2008). A measured BCF of less than 1 to 2.7 in carp suggest that bioconcentration in aquatic organisms is low (HSDB, 2018).

3 Manufacture, Supply, and Use

Manufacture and Supply

Trimellitate esters, such as TOTM, are produced by the esterification of a range of alcohols with trimellitic anhydride (TMA). The structure of TOTM is similar to that of di(2-ethylhexyl) phthalate (DEHP), with the exception that TOTM contains a third functionality on the aromatic ring. The presence of three alcohols makes trimellitates significantly more viscous then adipates or phthalates (Hatco, 2008, as cited by Versar, 2010). TOTM is an EPA High Production Volume chemical (HPVIS, 2008, as cited by Versar, 2010) with an estimated global production of 40,000-100,000 tons/year (SCENIHR, 2016).

Use

[1] CMA (1983) reported the solubility as 6 mg/L. SCENIHR (2016) reports the water solubility as "0.13 (0.00039) (sic) mg/L at 25°C / 1.08 µg/L at 25°C (measured)." The reason for this discrepancy is not known.

TOTM is the plasticizer of choice for high temperature applications, or when low volatility and high viscosity are important. When trimellitate esters, such as TOTM, are processed with PVC, their principle feature is low volatility, even under high temperatures. Consequently, TOTM's main use is in high specification electrical cable insulation and sheathing (ECPI, 2009, as cited by Versar, 2010). Additionally, as a branched molecule, TOTM is more viscous than the essentially linear adipates and phthalates, and its higher molecular weight and bulky structure result in improved extraction and migration resistance. Thus, TOTM can be used where high viscosity or migration resistance is needed, such as in gear lubricants and greases (Hatco, 2008, as cited by Versar, 2010), and in pesticide formulations as a release-rate control agent (Federal Register, 1998, as cited by Versar, 2010). The extraction and migration resistance of trimellitates are also significantly improved relative to phthalate plasticizers, leading to TOTM's use in gaskets and medical tubing and photograph storage (SCENIHR, 2016).

Due to its low extractability and limited migration, TOTM is used as a plasticizer for food contact materials and in medical devices (Kambia et al., 2001; SCENIHR, 2016). TOTM is used in PVC products in the hospital sector, packing, and floor/wall coverings (ECHA, 2014; Stuer-Lauridsen et al., 2001; as cited by Bui et al., 2016) and in plastic packaging (HSDB, 2018). It is used in cosmetics and as an emollient and skin conditioning agent (CIR, 2015). NICNAS (undated) reported additional uses for TOTM including: laundry detergents, automotive care products, fragrances and air fresheners, furniture, toys, curtains, foot-wear, leather products, paper, and cardboard. Commercial uses also include: lubricants, greases and hydraulic fluids, in construction and building materials, and in paints, coatings, and adhesives (NICNAS, undated).

Due to its low volatility, high viscosity, and subsequently low migration rates, TOTM may be an alternative to *o*-DAP plasticizers in children's articles. While TOTM has not been found in children's products tested by CPSC, Bui et al. (2016) reported TOTM has been measured in PVC toys and children's products (Biedermann-Brem et al., 2008; as cited by Bui et al., 2016).

4 Toxicokinetics

No data were located on the toxicokinetics of TOTM in humans.

Much of the data on TOTM toxicokinetics are from a single study in which TOTM radiolabeled on the 2-carbon atom of a 2-ethylhexyl group was administered to male SD rats by gavage in corn oil at 100 mg/kg (Eastman Kodak Co., 1984a, as cited by Versar, 2010; OECD, 2002; ECHA, 2018). These data are supplemented by a study with rats administered a single intravenous (i.v.) injection of TOTM that was ^{14}C-labeled on the carbonyl group, providing information on the disposition of the trimellitic acid core (Martis et al., 1987).

Absorption

Based on the pattern of excretion, at least 18% of the orally administered dose in the Eastman study was absorbed systemically. Measures of the extent of absorption are complicated by the

potential for biliary excretion[2], and the difference in the part of the molecule labeled in the oral and i.v. studies. Biliary excretion following i.v. dosing makes estimating absorption difficult because half of the radiolabel in the i.v. study was still in the body at the last time point of 14 days.

The dermal absorption of TOTM was evaluated *in vitro* using Franz cells and full thickness skin samples from female nude mice and from specific pathogen-free pigs (Pan et al., 2014). After a 12-hour exposure, TOTM was not detectable in the receptor medium with either skin sample, indicating that TOTM is not systemically absorbed after dermal exposure.

No data were located on the toxicokinetics of TOTM in rats following inhalation exposure. The observation of toxicity following inhalation exposure (see Section 5.1) suggests that absorption does occur.

Distribution

A study with rats administered a single intravenous (i.v.) injection of TOTM that was ^{14}C-labeled on the carbonyl group provides information on the disposition of the trimellitic acid core (Martis et al., 1987). In an initial study with rats administered 10.5 mg/kg, plasma concentrations of TOTM followed a biphasic decay pattern (half-lives of 46.2 minutes and 5.34 days), suggesting rapid distribution and slow clearance from the body. The authors also reported an apparent distribution volume of 7.49 L/kg, plasma clearance of 40.5 mL/kg-hr, and renal clearance of 13 mL/kg-hr. The large volume of distribution reflected extensive uptake of TOTM by the tissues. The difference between the plasma clearance and renal clearance indicates that the rapid decrease of plasma TOTM in the first phase of elimination is a result of the distribution to tissues rather than as a result of excretion. Analysis of tissues found that TOTM distributed primarily to the liver, lung, and spleen; almost 72% of the administered dose was found in the liver 24 hours after i.v. dosing with 15.6 mg/kg (Martis et al., 1987). At 14 days after dosing with 15.6 mg/kg, only 21% of the i.v. dose was in the feces and 3% in the urine, while 45% of the original dose was in the liver.

Metabolism

TOTM does not appear to be hydrolyzed in the intestine, but it is not clear whether hydrolysis occurs elsewhere in the gastrointestinal tract, such as the stomach. In an *in vitro* study with rat intestinal homogenates prepared from male Sprague-Dawley rats, no hydrolysis of [hexyl 2-^{14}C]triethylhexyl trimellitate] was observed, and release of 2-ethylhexanol (EH) was not detected (Eastman Kodak Company, 1984b, as cited by CIR, 2015).

Additional information about the metabolism of TOTM was obtained from the analysis of metabolites in the excreta. The urinary metabolites were identified as primarily 2-ethylhexanol and its metabolites 2-ethylhexanoic acid and 2-heptanone, as well as some mono-(2-ethyl-hexyl)trimellitate (MOTM). Parent TOTM was not found in the urine. In the feces, parent

[2]Versar (2010) stated that "the available data suggest that only 2-ethylhexanol and one of the mono esters are actually absorbed." However, the basis for this statement was not clear from that report or any of the other secondary sources, and the original study was not available.

TOTM accounted for 86% of the radioactivity, and the remaining radioactivity was present as mono-(2-ethylhexyl) trimellitate (1%; the same mono-ester as in the feces), di-(2-ethyl-hexyl)trimellitate (7%), and unidentified polar metabolites. Thus, absorbed 2-ethylhexanol undergoes additional oxidative metabolism in the body, but the mono-ester of trimellitic acid apparently does not.

Elimination

In the gavage study, approximately 75% of the administered dose was excreted unchanged in the feces within 6 days, while 16% of the radioactivity was found in the urine as metabolites, and 1.9% was expired in air as CO_2. The pattern of radiolabel in the expired air was used to estimate that the absorption was relatively rapid, with a half-time of 0.7 hours. The authors noted that there were two peaks for radiolabeled CO_2 in expired air, one at 2-3 hours and one at 8-12 hours. The authors suggested that the two peaks reflect sequential hydrolysis of TOTM, each step releasing 2-ethylhexanol, followed by metabolism of 2-ethylhexanol to CO_2. Release of 2-ethylhexanol from TOTM results in the formation of mono-and di-esters of trimellitic acid. Elimination in both the expired air and the urine was biphasic, with half-lives of 3-4 and 30-40 hours. Only a trace amount of the dose (<0.6%) was left in the tissues of animals at 6 days after dosing. The highest levels were in the liver and fat.

The biphasic decay patter following oral dosing, with half-lives of 3-4 and 30-40 hours, contrasts with the biphasic decay pattern (half-lives of 46.2 minutes and 5.34 days) seen following i.v. dosing. These apparent discrepancies in the elimination rate between the oral and i.v. study reflect the differences in the part of the TOTM molecule that was labeled, and thus the differences in disposition of those functional groups. The oral study, which provided information on the disposition of 2-ethylhxanol group of TOTM, found that almost all of the radioactivity was eliminated within 6 days, while the i.v., study found that the trimellitic acid core is excreted slowly, with almost half of the original dose still in the liver after 14 days.

5 Hazard Information[3]

5.1 Acute Single Dose Toxicity

Studies on TOTM acute oral, inhalation, and dermal toxicity, skin sensitization, and eye irritation are available.

5.1.1 Acute Oral Toxicity

The acute oral lethality of TOTM is low. No deaths were recorded among groups of 5 Sprague-Dawley-derived rats of each sex given a single dose of 2000 mg/kg of TOTM by gavage in corn

[3] Where available, this report provides significance level p values in all sections. However, source secondary references often report only that a change was significant without reporting the p level. If no p level is reported in this text, the p level was not available in the cited secondary reference, but the significance is presumed to be statistical.

oil and observed for two weeks (Japan Ministry of Health and Welfare, 1996, as cited by OECD, 2002). Similarly, there were no deaths in groups of 5 Sprague-Dawley-derived rats of each sex given a single dose of 5000 mg/kg of TOTM by gavage (Nuodex, 1983a, as cited by OECD, 2002) in a GLP study conducted according to OECD test guideline. There were also no deaths in groups of two Sprague-Dawley rats of each sex given a single dose of 10 mL/kg (9850 mg/kg, based on a density of 0.985 g/mL) of TOTM by gavage (Ciba-Geigy, 1984, as cited by OECD, 2002). In both of these latter studies, the rats were also observed for 2 weeks, but the vehicle was not identified. The only reported effect in any of these studies was piloerection in the two male rats treated with 9850 mg/kg, which was seen 2-3 hours after treatment but not subsequently (Ciba-Geigy, 1984, as cited by OECD, 2002). Eastman Kodak Co. (1983b, as cited by OECD, 2002) reported oral LD_{50} values of >3200 mg/kg for TOTM in both rats and mice, but no experimental details were provided.

5.1.2 Acute Dermal Toxicity

In a GLP-compliant study, there were no signs of toxicity, body weight changes, or death in a group of 3 male and 3 female New Zealand albino white rabbits treated by application of 2.0 mL/kg TOTM (1970 mg/kg, based on a density of 0.985 g/cm^3) to abraded skin. Treatment areas were occluded for 24 hours and followed by observation for 14 days (Nuodex, 1983c, as cited by OECD, 2002). Eastman Kodak Co. (1983b, as cited by ECHA, 2018) reported a dermal LD_{50} value of >20 mL/kg (19,700 mg/kg), based on the absence of deaths in guinea pigs treated with 20 mL/kg, but further experimental details were not available.

5.1.3 Acute Inhalation Toxicity

Results of TOTM acute inhalation studies were inconsistent. In a GLP-compliant study, no deaths occurred among a group of 5 male and 5 female Sprague-Dawley rats exposed via whole-body inhalation to 2600 mg/m^3 of TOTM aerosol (98.95% purity; particle size distribution not provided) for 4 hours followed by observation for 14 days (Nuodex, 1983b, as cited by OECD, 2002; ECHA, 2018). The test animals were reported to all have matted, drenched coats for the first 2 days, but no other visible effects. Necropsy revealed generalized lung involvement (reddening patches on lungs) of uncertain toxicological significance in 8/10 test animals. In contrast to the low toxicity with the TOTM aerosol, Eastman Kodak Co. (1971[4], as cited by U.S. EPA, undated; ECHA, 2018) reported much higher toxicity in a study with an unidentified strain of rats. In that study, the test atmosphere was generated by heating the TOTM solution to 180ºC. U.S. EPA (undated) considered it likely that the test atmosphere contained a mixture of vapor and aerosol. In this study, exposure was to 230, 2640, or 4170 mg/m^3 for 6 hours, and the rats were observed for 14 days post-exposure. ECHA (2018) reported moderate irritation in this study at 16 ppm, but this concentration in ppm does not correspond to any of the reported test concentrations in mg/m^3. Mortality occurred in 100% of the rats within 1-3 days after exposure to 2640 or 4170 mg/m^3. ECHA (2018) considered this latter study "not reliable," but it appears

[4] Cited by Versar (2010) as Eastman Kodak, Co. (1983a, 1983b).

that the U.S. EPA had the original study report, while ECHA was using a 1983 summary. The reason for the difference between the results of the Nuodex and Eastman inhalation studies is not clear, but may have been due to the different forms of exposure (aerosol vs. vapor), with the vapor exposure resulting in higher deposition in the lungs and thus higher toxicity.

5.1.4 Irritation/Sensitization

TOTM was tested for dermal irritation and sensitization in 201 men and women volunteers ranging in age from 18 to 81 years (David et al., 2003). The chemical (1% v/v in acetone) was applied to the skin under a semi-occlusive patch for 3 consecutive weeks, and the reaction to a challenge application noted following a 2-week rest period. TOTM produced only slight erythema in four subjects on four-six occasions during induction; none of these subjects exhibited irritation during the challenge phase. Four individuals exhibited a reaction of slight or mild responses during the challenge phase. Because none of the subjects had a score of 1.5 or higher (1 = mild erythema, 2 = moderate erythema), the authors concluded that based on Food and Drug Administration (FDA) criteria, there was no sensitization of human subjects in this study. Furthermore, the positive responses in the induction phase were slight to mild and intermittent. Thus, David et al. (2003) concluded that TOTM is non-irritating and non-sensitizing to humans.

TOTM was slightly irritating in animal studies. Tests in animals (all as cited in OECD, 2002; Versar, 2010) determined that TOTM is only slightly irritating to rabbit (Ciba-Geigy, 1984b; Nuodex, 1981) and guinea pig skin (Nuodex, 1983d; Eastman Kodak Co., 1983a,b), and not sensitizing to guinea pig skin (Eastman Kodak Co., 1983a,b; Nuodex, 1983d).

Neat TOTM (0.1 mL) was instilled into the right eyes of six young adult New Zealand White rabbits, with the left eyes serving as corresponding controls (Nuodex, 1983e, as cited by Versar, 2010). Only slight redness of the conjunctivae was observed during the first 2 days following treatment. No irritation was noted in the rabbit eyes 3 days post-instillation. Eastman Kodak Co. (1983a,b, as cited by Versar, 2010) also reported only slight, transient irritation in rabbit eyes following TOTM application.

5.2 Repeated Dose Toxicity

Oral repeated-dose toxicity data for TOTM are available from several short-term gavage (Nuodex, 1983f; Japan Ministry of Health and Welfare, 1996; CMA, 1987; Hodgson, 1987) and feeding (CMA, 1986; Hodgson, 1987) studies in rats.

The TOTM Consortium of Japan (a group of four Japanese corporations) conducted a 28-day study that was submitted to the United Nations Environment Programme (UNEP) for the OECD (2002) report (Japan Ministry of Health and Welfare, 1996, as cited by OECD, 2002; JECDB,

1996[5]). In this study, Sprague-Dawley rats (5/sex/dose) were administered TOTM (99% purity) via gavage in corn oil at 0, 100, 300 or 1000 mg/kg-day for 28 days. The study was done according to the Japanese 28-day repeat dose toxicity testing guidelines, and recovery groups for both the control and 1000 mg/kg-day group were included. No treatment-related effects were reported for clinical signs, body weights, food and water consumption, hematology, clinical chemistry, urinalysis, organ weights, or gross or histological pathology. A NOAEL of 1000 mg/kg-day was identified for both sexes. OECD (2002) considered the study to be reliable without restrictions, even though it did not have access to the full study.

In another 4-week study, male Fischer-344 albino rats (5/dose) were administered TOTM (purity not given) via gavage in corn oil at 0 (vehicle control) or 1000 mg/kg-day, 5 days/week for 4 weeks (Nuodex, 1983f, as cited by Versar, 2010). Triglyceride levels were significantly reduced in the treated rats compared to corn oil controls ($p<0.05$ by one-way ANOVA), consistent with effects seen from the activation of PPARα. Body weight and organ weights (liver, kidney, brain, spleen, testes) in treated rats did not differ from controls and no deaths occurred in either group. No other endpoints were investigated in this study.

Other repeated-dose studies were performed primarily to evaluate potential TOTM-induced liver effects, especially those related to peroxisome proliferation. Peroxisome proliferation is a well-known effect of DEHP, a compound structurally similar to TOTM. For example, in a short-term feeding study (OECD Guideline 407), Fischer-344 rats (5/sex/dose) were fed TOTM (98% purity) at dietary levels of 0, 0.2, 0.67 or 2% for 28 days (CMA, 1986; Hodgson, 1987). Corresponding doses reported by the researchers were 0, 184, 642 and 1826 mg/kg-day for males, and 0, 182, 666 and 1641 mg/kg-day for females. In high-dose females, food consumption was significantly decreased for the first 7 days of treatment. After that, food consumption increased, but still remained below control levels (CMA, 1986). At the high dose, final body weight was decreased by 17% (males) and 30% (females), with corresponding decreases of 4% and 13%, respectively, in the food consumption. Although none these changes were statistically significant, the observation of a substantially larger decrease in final body weight than in food consumption suggests a treatment-related effect.

In the same study (CMA, 1986), there were statistically significant reductions in hemoglobin in both males and females at concentrations at or greater than 0.67% ($p<0.01$ for 0.67% groups of both sexes and $p<0.001$ for 2.0% groups of both sexes). Small but statistically significant decreases in red blood cell counts were seen in all TOTM-treated male rats ($p<0.05$), but only in the 0.67% treatment group in female rats ($p<0.01$). Female rats also had statistically significant ($p<0.001$) decreases in mean cell volume and hematocrit at 0.2 and 0.67% dose groups, but not the 2% dose group. Although these data would suggest a pattern of hematological effects, the overall changes were small (<10% for all endpoints), and in many cases not dose-related. This assessment, therefore, considers these effects not toxicologically significant. Dose-related and statistically significant ($p<0.05$) increases in white blood cells (by about 20%) and decreases in percent eosinophils and monocytes (by about 50%) were seen in males at the mid- and high dose. The toxicological significance of these changes is unclear. Serum chemistry analyses showed

[5] The English-language summary from the Japanese Ministry of Health and Welfare was supplemented by the full study report, including tabular data, obtained from the JECDB, and translated with Google Translate. The document was undated, but the date is presumed to be 1996, based on the date reported for the study in OECD (2002).

statistically significant increases in serum albumin in mid- and high-dose males and females ($p<0.05$% for mid-dose males, $p<0.001$ for high-dose males and mid and high-dose females). As with red blood cells, mean cell volume, and hematocrit, the changes in albumin were marginal and not clearly related to dose. There was no effect of treatment on triglyceride or lipid levels, although there was a significant increase in cholesterol in males at the mid ($p<0.05$) and high ($p<0.001$) doses. There was a dose-related increase in relative liver weight in both sexes in the mid- and high-dose groups (25-35% larger than controls at the high dose; $p<0.001$ for mid-and high dose males and females).

This study included biochemical and electron microscopic assays for peroxisome proliferation. In the biochemical studies, TOTM induced significant dose-related increases in the liver activity of the peroxisome markers cyanide-insensitive palmitoyl CoA (pCoA) and carnitine acetyl transferase in both males and females, and catalase activity in males. Some of these biochemical changes were found at the lowest dose group in males.

Only the high-dose group and controls were examined for histopathology and electron microscopy. Electron microscopy study of the high-dose livers revealed slight increases in centrilobular and periportal peroxisomes when compared to controls. The peroxisome number, but not their size, was increased in these samples. Light microscopy revealed a slight reduction in liver cytoplasmic basophilia in 2/5 high-dose females. There were no treatment-related changes in other organs.

Based on these results, TOTM appears to be a peroxisome proliferator. Although the effects produced by TOTM in the 28-day oral rat study (CMA, 1986; Hodgson, 1987) were similar in pattern to those produced by DEHP, TOTM was much less potent. Therefore, the low dose in males (184 mg/kg-day) and the mid dose in females (666 mg/kg-day) were LOAELs for rats, based on peroxisome proliferation. As discussed further in Section 5.8, peroxisome proliferation is a rodent-specific effect that is of questionable relevance to hazard characterization for humans (Cattley et al., 1998; Chevalier and Roberts, 1998; Doull et al., 1999; IARC, 2000a; Klaunig et al. 2003; Lake, 1995, Melnick 2001; Felter et al., 2018).

Increased cholesterol was also determined in male rats, with a NOAEL of 184 mg/kg-day and a LOAEL of 642 mg/kg-day. There was no effect on cholesterol in the females and so the human-relevant NOAEL in females was 1641 mg/kg-day in females. This effect is not related to PPAR, since PPAR agonists such as fibrates act to lower cholesterol, not raise it (Ferri et al., 2017).

The same researchers conducted a non-guideline, 21-day gavage study that investigated many of these same endpoints (CMA, 1987; Hodgson, 1987). Fischer-344 rats (5/sex/dose) were administered TOTM via gavage in corn oil at 0 (corn oil), 200, 700 or 2000 mg/kg-day for 21 days. There was no significant effect on body weight gain or feed consumption in treated rats. Serum triglyceride and cholesterol levels did not differ significantly from controls. Significant increases in absolute (p-value not given) and relative liver weights ($p<0.001$ for low- and high-dose groups, $p<0.05$ for mid-dose group) were observed among female rats at all dose levels, but these changes did not increase with dose. Only slight, non-significant changes in liver weights were observed among male rats. The only remarkable histological change was a reduction in the quantity of neutral lipid in the livers of all treated rats. Liver biochemistry revealed significant

increases in pCoA activity at the high dose in males ($p<0.001$) and females ($p<0.01$), and significant increases in lauric acid 12-hydroxylase activity in males at all dose levels ($p<0.05$ for low-dose, $p<0.01$ for mid dose, $p<0.001$ for high-dose). A slight increase in the number of hepatic peroxisomes was observed in high-dose males, but no change compared to controls was observed in females. For the purposes of this review, the low dose of 200 mg/kg-day in males is a LOAEL for rodents, based on increased markers for peroxisome proliferation, while the LOAEL in females is the high dose of 2000 mg/kg-day. In this study, the high dose of 2000 mg/kg-day was the human-relevant NOAEL. This is because the only effects observed were related to peroxisome proliferation, a process not directly relevant to humans (Felter et al., 2018).

Hodgson (1987) compared the potency of TOTM for peroxisome proliferation with that of equimolar doses of DEHP and their shared metabolite, EH. TOTM was less potent than either of the two other chemicals. The implications of this finding are limited, since potency estimations did not account for potential differences in absorption, or in metabolism to EH.

In another unpublished study[6] (Anonymous 2012, as cited by ECHA, 2018), groups of Sprague-Dawley rats (10/sex/dose) were administered TOTM in feed for 90 days at nominal doses of 0, 50, 225, or 1000 mg/kg-day. Based on body weight and food intake, the authors calculated that the mean daily dosages over the 13-week treatment period were 0, 52, 226 and 992 mg/kg-day for males and 0, 52, 233 and 1023 mg/kg-day for females. Additional control and high-dose rats (10/sex/dose) were maintained for a post-exposure recovery period of 4 weeks. The study was GLP compliant and conducted according to OECD guideline 408. Endpoints evaluated included feed consumption, body weight, clinical signs (including a functional observational battery [FOB] for neurological signs of toxicity), ophthalmological exam, hematology, clinical chemistry, urinalysis, neurobehavioral examination, reproductive cycle staging, and histopathology. ECHA (2018) provided a detailed description of the study, but limited quantitative results.

There were no clinical signs of toxicity in this study. The only change in the FOB was a "slight decrease" in mean grip strength and increase in landing foot splay (significance not reported) in high-dose females, but the results were not considered toxicologically significant, because of their low magnitude and high individual variability. There was no TOTM-induced effects in the neurobehavioral examination. The high-dose males had a slight decrease in body weight and body weight gain (about 5% compared to controls) throughout the treatment periods. These changes were not statistically significant and not considered toxicologically meaningful. The platelet count was slightly but significantly increased in treated animals (sex not specified) at the high dose. High-dose males also had a significant (41%) increase in neutrophils. Females had a slight (<6%) but statistically significant decrease in erythrocytes, hemoglobin and hematocrit, but it was not clear which dose(s) was affected; the authors considered these change of minimal severity and not toxicologically significant. Significant increases were seen in mid- and high-dose males (but not in females) of alkaline phosphatase (15% and 28%, respectively), γ-glutamyl transferase (61% and 167%). In females, there were significant *decreases* at the mid and high doses in alanine aminotransferase and aspartate aminotransferase (18% to 29%), bilirubin (45% and 39%, respectively), total protein (approximately 5%), and globulin (11%, high dose group only). Based on the magnitude of the change, different targets in males and females, and the

[6] The p level for statistical significance was not reported for any endpoint in this study.

opposing direction of the effects in males and females, this assessment did not consider these effects to be toxicologically significant. In contrast, the significant decrease in bile acids in females (48%, high dose group only) and increased cholesterol in males (21% and 41% at the mid-and high doses) are considered potentially adverse by this assessment. Relative liver weight was significantly increased in high-dose males (by 20%) and females (by 14%), while relative spleen weight was decreased in these groups, by 22% and 14%, respectively. Diffused hepatocytic hypertrophy, and increased incidence of extramedullary hematopoiesis was observed in the high-dose males and females. The study authors considered these results to be adaptive[7]. Mild extramedullary hematopoiesis was also observed in the spleen in high-dose females. No toxicologically significant effects were seen in the recovery groups. Results of the evaluations of reproductive tissues are described in Section 5.4.

As was noted for the Hodgson (1987) study, this assessment considers the effects related to peroxisome proliferation (increased liver weight and hypertrophy) to be potentially adverse for rats, but not humans. However, the increased cholesterol in males is considered adverse, meaning that the low dose is a NOAEL in males; the decreased bile acids in high-dose females are also considered potentially adverse. Other changes were of insufficient magnitude to be adverse, or adaptive.[8]

5.3 Chronic Toxicity/Carcinogenicity

No chronic toxicity studies were available for TOTM. CMA (1983, as cited by Versar, 2010) described *in vivo* oncogenicity screening study conducted by the FDA. In this study, TOTM was negative for tumors in strain A mice, a strain that has a propensity to form pulmonary adenomas. The lack of further detailed information limits the interpretation of these results. This study was not described by ECHA (2018).

5.4 Reproductive Toxicity

In a screening reproductive toxicity study (OECD Guideline 421), Sprague-Dawley rats (12/sex/dose) were administered TOTM (99% purity) via gavage at 0, 100, 300 or 1000 mg/kg-day (Japan Ministry of Health and Welfare, 1998; JECDB, 1998[9]). Treatment began 14 days prior to mating for both males and females, and continued through mating for males (total of 46 days), and through LD 3 for females. No effects were observed in either sex on general appearance, body weights, food consumption, or weights of reproductive organs. No histological changes in ovaries from treated females were observed. Histological examination of the testes

[7] The underlying reasoning was not provided, but may relate to the idea that extramedullary hematopoiesis is typically secondary to disease in other organs, and no evidence was found for such disease. It is also noted that extramedullary hematopoiesis does not appear to be consistent with decreased spleen weight.

[8] CIR (2015) considered the mid-dose of 225 mg/kg-day (nominal) to be a NOAEL and 1000 mg/kg-day (nominal) to be a LOAEL, based on increased liver weight, decreased spleen weight, and microscopic lesions at the high dose. ECHA (2018) did not address adversity, and considered the mid dose to be a NO(A)EL, based on changes in blood chemistry, organ weight, and microscopic pathology.

[9] The English-language summary from the Japanese Ministry of Health and Welfare was supplemented by the full study report, including tabular data, obtained from the Japan Existing Chemical Database (JECDB), and translated with Google Translate. The document was undated, but the date is presumed to be 1998, based on the date reported for the study in OECD (2002).

revealed dose-related decreases in spermatocytes and spermatids among mid-dose ($p<0.05$) and high-dose ($p<0.01$) males. There were no effects on reproductive ability, delivery of pups, maternal behavior of dams, or the viability, general appearance, birth weights or necropsy findings of offspring. Although the males were not exposed for the entirety of the spermatogenic cycle, the observation that the late stages of development (i.e., the spermatocytes and spermatids, not the spermatogonia) were affected supports the conclusion that observed decreases would not affect the fertility of rats, although they might affect the fertility of humans, who have less reserve. A NOAEL of 100 mg/kg-day was identified for reproductive toxicity in males based on the decreases in spermatocytes and spermatids in male rats at 300 mg/kg-day and higher. The NOAEL for reproductive toxicity in females, and for developmental toxicity, was 1000 mg/kg-day.

In the subchronic study described in Section 5.3, groups of Sprague-Dawley rats (10/sex/dose) were provided TOTM in feed for 90 days at nominal doses of 0, 50, 225, or 1000 mg/kg-day (ECHA, 2018). A detailed qualitative examination of the staging of the spermatogenic cycle was conducted in the testes of control and high-dose males. No effect was observed on the spermatogenic cycle or the integrity of the cell types within the various stages. There was also no effect on the estrous cycle of females, or on the reproductive organ weight or histopathology.

5.5 Prenatal, Perinatal, and Post-natal Toxicity

In a GLP-compliant OECD Guideline 414 study, pregnant CD (Sprague-Dawley) rats (35/dose) were administered 0, 100, 500, or 1050 mg/kg-day in corn oil via oral gavage on gestational days (GD) 6-19 (Renaut and Whitley, 2017; previously available as an unpublished study - Huntington Life Sciences, 2002, as cited by Versar, 2010). A positive control group of 25 animals was treated on the same schedule with 750 mg/kg-day of DEHP. On GD 20, 20 rats/dose (10/dose of the positive control) were sacrificed and subjected to necropsy and evaluation of uterine content. Treatment of the other 15 rats/dose continued through lactational day (LD) 20. For both the teratology phase (sacrificed GD 20) and the littering phase, particular attention was paid to sexual developmental markers. Female offspring were necropsied at 6 weeks of age and male offspring at 15 weeks of age.

The general condition of treated dams was similar in all groups with no mortalities or significant clinical signs. TOTM did not have any biologically or statistically significant effect on body weight or food consumption at any dose. There were no treatment-related effects on maternal liver weight, or on the number of corpora lutea, implantations, pre-implantation loss, embryo-fetal survival, or litter size. There was also no effect on the sex ratio, anogenital distance (AGD) of males or AGD divided by the cube root of fetal body weight (AGD is a measure of sexual differentiation), or fetal body weight. The only effects seen in detailed skeletal and visceral examination of the fetuses were slight dose-related increases in the number of litters with displaced testes and in the number of litters with 13/14 or 14/14 ribs. The unpublished Huntingdon Life Sciences (2002) study and the Versar (2010) report also noted increases in the numbers of fetuses from treated dams exhibiting renal cavitation and hydroureter when compared to concurrent controls. These incidences were within historical control ranges for these findings. More importantly, the apparent increase in renal cavitation was seen only among the pups examined for visceral abnormalities prior to the skeletal evaluation, but renal cavitation was not seen in any pups examined by the more detailed serial sectioning; renal cavitation was not

noted in the published study. Because the apparent effect was not seen at all in the more detailed evaluation, the apparent increase is unlikely to have been treatment-related.

Among the females that littered, TOTM treatment had no effect on gestational length, sex ratio, litter size, or live birth index. In the 1050 mg/kg-day group, average mean female offspring survival from LD 1 to LD 20 (viability index) was slightly decreased, due to one litter that was killed on PND 2 because the pups were cold, unfed, and underactive. There was also no effect on pup body weight, auditory startle reflex, or pupil closure response. Pup body weights in the TOTM-treated groups tended to be lower at all time points, but there was no dose-response and the change was not statistically significant. However, there was a statistically significant ($p<0.01$) decrease in male offspring body weight at age 4 weeks at the mid and high doses. In addition, the number of litters with the areolar region visible at PND 13/14 was significantly increased[10] at 1050 mg/kg-day. The retained areolar regions were no longer present by PND 18. Thus, this effect may represent a slight developmental delay, but was not considered to be toxicologically significant by the study authors. No apparent effect of treatment was seen in the sexual maturation of male or female offspring in response to TOTM. The mean days to sexual maturation as assessed by vaginal opening was slightly but significantly ($p<0.05$) delayed in the 500 and 1050 mg/kg-day groups, by 0.6 and 0.3 days respectively, but the authors stated that this effect was considered to be marginal and not of biological significance. Furthermore, the body weight at termination was comparable to that of the controls. Mean age at completion of balano-preputial separation was slightly but significantly decreased ($p<0.05$, difference of 0.8 days) at 1050 mg/kg-day. Body weight was significantly lower at the start of separation at the high dose ($p<0.05$), and significantly lower at termination at the mid and high doses ($p<0.01$). The difference in balano-preputial separation times was not considered treatment-related, because the difference was less than a day (observations were performed once/day) and associated with decrements in body weight (growth). In addition, the direction of change was the opposite of that seen with DEHP.

No findings related to maternal TOTM treatment were observed in necropsy of female offspring at 6 weeks or males at 15 weeks. There were no treatment-related changes in male reproductive organ weights at any dose; sporadic statistically significant increases were small in magnitude and generally not dose-related, and so were not considered biologically significant. In contrast to the absence of effects with TOTM, an equimolar dose of the positive control, DEHP, caused the expected effects of "phthalate syndrome," including testicular abnormalities, decreased male reproductive organ weight, and delayed sexual development. Therefore, the high-dose of 1050 mg/kg-day was identified as a NOAEL in this study for both maternal and developmental effects.

As part of the development of a screening assay to detect chemicals affecting fetal testosterone production, Furr et al. (2014) treated pregnant Sprague-Dawley rats (2-3/dose) by gavage with 0, 200, 500, 750, or 1000 mg/kg-day TOTM on GD 14 to 18. Within two hours of the final dose, dams were sacrificed, and the fetuses were necropsied and fetal testosterone measured. In this study, TOTM had no effect on fetal testosterone production, fetal viability, or maternal weight gain.

[10] Level of significance unclear. Two different significance levels were shown in the table, $p<0.05$ and $p<0.01$. The latter was not defined, however, and no reason was given for having two different significance levels.

5.6 Genotoxicity

The available data suggest that TOTM is not genotoxic. TOTM did not induce reverse mutation in various strains of *Salmonella typhimurium* (U.S. EPA, 1983; Japan Ministry of Health and Welfare, 1996; Zeiger et al., 1988; as cited by Versar, 2010) or *Escherichia coli* strain WP2 (Japan Ministry of Health and Welfare, 1996, as cited by OECD, 2002), or forward mutation at the HGPRT locus of Chinese hamster ovary (CHO) cells (CMA, 1985a). TOTM also did not induce chromosomal aberrations in cultured Chinese hamster lung cells in the presence or absence of metabolic activation *in vitro* or cause unscheduled DNA synthesis (UDS) in primary rat hepatocytes (CMA, 1985b),

TOTM was also negative for dominant lethal mutations *in vivo* in white Swiss mice (CMA, 1983). Urine from rats fed TOTM in the diet at 2000 mg/kg-day for 15 days did not induce mutagenic activity with or without metabolic activation in various strains of *S. typhimurium* (Divincenzo et al., 1985).

Overall, TOTM has been thoroughly tested *in vitro* and did not cause gene mutations or chromosomal damage. TOTM has not been evaluated in standard *in vivo* tests for chromosome damage, but there was no evidence of genetic damage to sperm in a dominant lethal assay, or of the production of mutagenic forms in excreta.

5.7 Mechanistic Studies

In a molecular modeling study using SYBYL software, Kambia et al. (2008) found that TOTM was not able to dock with either the alpha or gamma isozymes of PPAR, due to the large volume of TOTM. This finding is consistent with the lower PPAR activity seen with TOTM compared to DEHP (CMA, 1986; Hodgson, 1987).

5.8 Mode of Action

Hepatic Peroxisome Proliferation

TOTM has not been evaluated in a chronic study, but several studies have shown that TOTM is a weak inducer of peroxisome proliferation in rats (CMA, 1986, 1987; Hodgson, 1987). This MOA suggests that TOTM could have the potential to induce hepatocellular tumors in rodents. However, peroxisome proliferation potency is also important in determining whether a chemical causes hepatocellular tumors in rodents, and TOTM is a less potent peroxisome proliferator than DEHP.

In rodents, peroxisome proliferation is a well-studied MOA for effects on the liver, and for the formation of liver tumors. Peroxisome proliferators, such as DEHP, cause liver-related changes that include increased liver to body weight ratios due to hepatocellular hypertrophy and proliferation, increased replicative DNA synthesis, increased number and size of peroxisomes (ultrastructural effects) and induction of peroxisomal and microsomal fatty acid-oxidizing

enzymes, among other changes. Overall, the weight of evidence from a large number of studies supports the existence of a PPARα-dependent MOA for liver effects and for liver tumor formation in rodent models (Corton et al., 2014; Felter et al., 2018). As described by Felter et al. (2018), the key events for this MOA are: 1) activation of PPARα, 2) alteration of cell growth pathways, 3) alteration in hepatocyte fate including increased cell proliferation and decreases in apoptosis, and 4) clonal expansion leading to tumors. In humans, activation of PPARα does not lead to increased liver to body weight ratios, oxidative enzyme induction or other responses typically associated with sustained PPARα activation observed in wild-type mice (Felter et al., 2018; Ito et al., 2012). The weight of evidence therefore supports the conclusion that a PPARα MOA is either "not relevant" or "unlikely to be relevant" in humans (Felter et al., 2018).

Other MOAs

Some of the liver-related effects of TOTM are related to peroxisome proliferation. However, some of the observed effects may be related to another MOA. Specifically, these include increased cholesterol levels, extramedullary hematopoiesis, and changes in serum enzymes indicative of liver damage. However, these changes appear to be either adaptive (extramedullary hematopoiesis) or of a magnitude below that considered to be adverse. The only potentially adverse liver effect were increased cholesterol in male rats and decreased bile acids in females.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

Key available repeated-dose animal toxicity data for TOTM are presented in Table 2 and include short-term, subchronic, reproductive and developmental toxicity studies, but only from oral studies involving rats. In those studies TOTM only caused minimal signs of toxicity.

The primary effects noted in the systemic toxicity studies were peroxisome proliferation and related effects in the liver (CMA, 1986, 1987; Hodgson, 1987). Males were more sensitive than females to peroxisome proliferation. Increased liver weight and markers of peroxisome proliferation were seen in males exposed to about 200 mg/kg-day for 3-4 weeks. A dose of about 200 mg/kg-day was a NOAEL in the 90-day study, perhaps because only liver weight (rather than peroxisome markers) was evaluated. Females were affected at the next dose up in the 3-4 week studies (about 700 mg/kg-day), but at the same dose as males (about 1000 mg/kg-day) in the 90-day study. Peroxisome proliferation is considered a rodent-specific effect that is not relevant to humans (Felter et al., 2018).

Three studies, all in rats, included a comprehensive assessment of toxicity. There were no effects of any type at doses up to 1000 mg/kg-day in a 28-day gavage study in rats (Japan Ministry of Health and Welfare, 1996, as cited in OECD, 2002; JECDB, 1996). In contrast, a 28-day feeding study in rats (CMA, 1986; Hodgson, 1987) reported a number of statistically significant changes.

Few of these changes were clearly adverse, however. Similarly, a 90-day feeding study in rats at nominal doses up to 1000 mg/kg-day reported several changes unrelated to peroxisome proliferation (increased serum markers of liver damage, increased extramedullary hematopoiesis), but these changes were considered to be of a magnitude that is not adverse, or to be adaptive (Anonymous, 2012, as cited by ECHA, 2018). The only consistent exception was increased serum cholesterol in males, which was observed at 642 mg/kg-day in the 28-day feeding study and at 992 mg/kg-day in the 90-day feeding study. The NOAELs in the respective studies were 184 and 226 mg/kg-day. The higher NOAEL for serum cholesterol in the 90-day study reflects dose spacing, rather than study duration sensitivity. Decreased bile acids were also seen in the females at 1023 mg/kg-day in the 90-day study, but not in the 28-day study at 1641 mg/kg-day.

A single-generation study found no effects on reproductive function, but did report decreased spermatocyte and spermatid counts in males treated by gavage with 300 or 1000 mg/kg-day for 46 days (JECDB, 1998; Japan Ministry of Health and Welfare, 1998, as cited in OECD, 2002). However, there was no effect on spermatogenic cycle or sperm staging in a 90-day rat feeding study at nominal doses up to 1000 mg/kg-day (ECHA, 2018). The reason for the discrepancy between the two studies is not clear, but may be because the 90-day study conducted a qualitative evaluation, while the reproductive study conducted a quantitative analysis. No effect on estrous cycle or organ weight or histopathology of the reproductive organs was seen in the 90-day study. There was no effect on female reproductive parameters in either study.

TOTM did not induce developmental effects in rats following gavage treatment during gestation (Huntington Life Sciences, 2002; Renaut and Whitley, 2017).

TOTM is not genotoxic in *in vitro* and *in vivo* testing. Results were negative in tests for mutagenicity in bacteria and mammalian cells, unscheduled DNA synthesis in rat hepatocytes, chromosomal aberrations in Chinese hamster lung cells, and dominant lethal mutations *in vivo* in white Swiss mice (U.S. EPA, 1983; Japan Ministry of Health and Welfare, 1996, as cited in OECD, 2002; Zeiger et al., 1988; CMA, 1983, 1985a,b).

Limited data in a screening study conducted with strain A mice suggests that TOTM is not carcinogenic (CMA, 1983).

5.10 Uncertainties and Data Gaps

Several uncertainties of varying importance were identified in this assessment.

Database:

The overall database on TOTM is fairly complete, including many of the key studies. Acute, subacute, and subchronic studies are available, as well as reproductive and developmental toxicity studies. Neurological endpoints were evaluated in the subchronic study (Anonymous, 2012, as cited by ECHA, 2018), and estrous cycling and seminiferous tubule staging were evaluated in both the subchronic and reproductive studies (Japan Ministry of Health and Welfare, 1996). Except for the acute studies, all studies were conducted in rats.

There is no chronic study, and no systemic or developmental toxicity study in a second species. In addition, the reproductive toxicity study did not include premating exposure for the entire spermatogenic cycle, and only included one generation of offspring. For most study types there is only one study (i.e., one subchronic study, one developmental toxicity study, etc.), which limits the evaluation of reproducibility of effects. Many of the studies have not been peer-reviewed. Instead, they are available either only as unpublished studies, or as summaries in the ECHA (2018) or the U.S. EPA HPV (high production volume) dossiers. Repeated-dose data for the inhalation route are also lacking but it is not clear how much exposure would occur via the inhalation route.

Hazard:

There is uncertainty regarding the acute inhalation lethality of TOTM, in light of the marked differences in lethality reported in the Nuodex (1983b) aerosol study and in the Eastman Kodak Co. (1983a,b) study of apparently mixed exposure to vapor and aerosol.

Liver: Although many of the observed liver effects (increased liver weight, hypertrophy) are related to peroxisome proliferation, there is some uncertainty about interpretation of other potentially related effects. Increased cholesterol in males was reported in the 28-day feeding study (CMA, 1986; Hodgson, 1987) and the 90-day feeding study (Anonymous, 2012, as cited by ECHA, 2018), but the toxicological significance has not been fully characterized. It is not known whether these changes reflected liver dysfunction, or some other change in lipid homeostasis. Decreased bile salts were noted in females in the 90-day study, and the significance of this change is also unknown. Finally, the etiology and significance of extramedullary hematopoiesis in the liver and spleen of the 90-day study are uncharacterized.

Reproductive toxicity: Apparent inconsistencies about the potential effect of TOTM on spermatogenesis are also a source of uncertainty. A single-generation study decreased spermatocyte and spermatid counts in a quantitative evaluation (JECDB, 1998; Japan Ministry of Health and Welfare, 1998, as cited in OECD, 2002), but there was no effect on spermatogenic cycle or sperm staging in a 90-day rat study at similar doses (Anonymous, 2012, as cited by ECHA, 2018).

Carcinogenicity: TOTM has not been tested in a standard carcinogenicity assay so the long term effects on cancer are unknown.

Table 2. Summary of NOAELs/LOAELs Identified for TOTM by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[11]	Toxicological Basis	Comments
Repeat Dose Toxicity					
Sprague-Dawley rat (M&F) (5/sex/dose) **Japanese testing guidelines** **Japan Ministry of Health and Welfare, 1996, as cited by OECD, 2002; JECDB, 1996**	28 days Gavage in corn oil 0, 100, 300 or 1000 mg/kg-day	Systemic	NOAEL = 1000 No LOAEL	No adverse effects	No treatment-related effects were observed based on clinical signs, body weights, food and water consumption, hematology, clinical chemistry, urinalysis, organ weights or gross or histological pathology
		Liver	NOAEL = 1000 No LOAEL	No adverse effects	
Fischer-344 rat (M) (5/dose) **Nuodex, 1983f, as cited**	4 weeks Gavage in corn oil 0 or 1000 mg/kg-day	Systemic	NOAEL = 1000 No LOAEL	No adverse effects	Only endpoints evaluated were body weight, weights of selected organs (liver, kidney, brain, spleen, testes), and triglyceride levels. Triglyceride levels were significantly reduced, but the toxicological significance of this finding is unclear.
		Liver	NOAEL = 1000 No LOAEL	No adverse effects	

[11] All effect levels as identified by the authors of this assessment. Effect levels identified by previous assessments are in the comments column

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[11]	Toxicological Basis	Comments
by Versar, 2010					
Fischer-344 rat (M&F) (5/sex/dose) GLP compliant **CMA, 1986; Hodgson, 1987**	28 days Feed 0, 0.2, 0.67 or 2% M: 0, 184, 642, 1826 mg/kg-day; F: 0, 182, 666 or 1641 mg/kg-day	Systemic	NOAEL = 1000 No LOAEL	No adverse effects	Doses reported by the researchers. No effect on triglycerides, although cholesterol was significantly increased in males. Changes in liver considered related to peroxisome proliferation and not relevant to humans. Changes in hematology were slight and not clearly related to dose
		Serum lipids	NOAEL = 184 (M) LOAEL = 642 (M) NOAEL = 1641 (F) No LOAEL (F)	Increased cholesterol, which is unrelated to peroxisome proliferation	
		Liver	No NOAEL (M) LOAEL = 184 (M) NOAEL = 182 (F) LOAEL = 666 (F)	Statistically significant increases in liver weight and peroxisome proliferation, but the effects are not relevant to humans	
		Hematology	NOAEL = 1826 (M) NOAEL = 1641 (F) No LOAEL	No adverse effects	
Fischer-344 rat (M&F) (5/sex/dose) **CMA, 1987; Hodgson, 1987**	21 days Gavage in corn oil 0, 200, 700 or 2000 mg/kg-day	Systemic	NOAEL = 2000 No LOAEL		Serum triglyceride and cholesterol levels did not differ significantly from controls. Changes in relative liver weight of females were not dose-dependent.
		Liver	No NOAEL (M) LOAEL = 200 (M) NOAEL = 700 (F) LOAEL = 2000 (F)	Markers of peroxisomes, indicating peroxisome proliferation, an endpoint not relevant to humans.	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[11]	Toxicological Basis	Comments
Sprague-Dawley rat (M&F) (10/sex/dose) Satellite groups of 10/sex for post-exposure recovery for 4 weeks **GLP compliant OECD guideline 408** **Anonymous, 2012, as cited by ECHA, 2018**	90 days Feed (concentrations not provided) M: 0, 52, 226, 992 mg/kg-day F: 0, 52, 233, 1023 mg/kg-day	Systemic	NOAEL = 992 (M) NOAEL = 1023 (F) No LOAEL (M, F)	No effect on body weight or other general targets	Mean daily dosages calculated by study authors based on body weight and food intake. "Slight decrease" in mean grip strength and increase in landing foot splay in high-dose females not considered toxicologically significant, because of their low magnitude and high individual variability. Reproductive evaluation included detailed evaluation of seminiferous tubule staging, spermatogenic cycle, estrous cycle, and reproductive organ weight and histopathology.
		Liver	NOAEL = 226 (M), 233 (F) LOAEL = 992 (M), 1023 (F)	Increased liver weight, hypertrophy	
		Serum lipids	NOAEL = 226 (M), 233 (F) LOAEL = 992 (M), 1023 (F)	Increased cholesterol (M), decreased bile acids (F)	
		Hematology	NOAEL = 992 (M) NOAEL = 1023 (F) No LOAEL (M, F)	Slight decreases not considered toxicologically significant	
		Neurological	NOAEL = 992 (M) NOAEL = 1023 (F) No LOAEL (M, F)	No adverse effect in FOB or neurobehavioral exam	
		Reproductive	NOAEL = 992 (M) NOAEL = 1023 (F) No LOAEL (M, F)	No effects	
Reproductive/Developmental Toxicity					
Sprague-Dawley rat (M&F) (12/sex/dose)	14 days prior to mating for both sexes, through mating for males (total of 46 days),	Reproductive - Male	NOAEL = 100 LOAEL = 300	Decreased spermatocytes and spermatids in the testes	No effect on reproductive function
		Reproductive - Female	NOAEL = 1000 LOAEL = None	No effect	
		Developmental	NOAEL = 1000 LOAEL = None	No effect	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[11]	Toxicological Basis	Comments
OECD guideline 421 **Japan Ministry of Health and Welfare, 1998; JECDB, 1998**	and through LD 3 for females Gavage 0, 100, 300 or 1000 mg/kg-day				
Sprague-Dawley rat (F) **(35/dose)** **OECD Guideline 414 and GLP compliant** **Renaut and Whitley, 2017; Huntingdon Life Sciences, 2002**	GD 6-19 (20/dose) Or GD 6-19 *and* LD 0-20 (15 dams/ dose); no direct treatment of F1 after weaning Gavage in corn oil 0, 100, 500, or 1050 mg/kg-day	Developmental	F1 pups NOAEL = 1050 LOAEL = None	No biologically meaningful developmental toxicity	Pups were exposed *in utero* or via milk; there was no direct treatment of the offspring. There were several statistically significant differences in the offspring that were not considered treatment-related or biologically significant: Increased number of litters with testis displaced and in the number of litters with 13/14 or 14/14 ribs. Decreased male offspring body weight at age 4 weeks at the mid and high doses. Significantly increased number of litters with the areolar region visible at PND 13/14 at 1050 mg/kg-day, but the retained areolar regions were no longer present by PND 18.
		Maternal	NOAEL = 1050 LOAEL = None	None	
Sprague-Dawley rat (F)	GD 14-18 Gavage	Developmental	NOAEL = 1000 LOAEL = None	None	Screening assay; only fetal testosterone and fetal viability were assessed

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[11]	Toxicological Basis	Comments
(2-3/dose) **Furr et al., 2014**	0, 200, 500, 750, or 1000 mg/kg-day				

6 Exposure

The use of TOTM in consumer products has been described in Section 3 of this report.

The general population may be exposed to TOTM via dermal contact or ingestion following chemical migration out of a plasticized consumer product.

Bui et al. (2016) reported that TOTM has been measured in PVC toys and children's products (mean concentration of 20% w/w) (Biedermann-Brem et al., 2008; as cited by Bui et al., 2016). An estimated daily intake rate for TOTM of 1.62×10^{-13} µg/kg-day (based on exposure via the inhalation, oral, and dermal routes) was reported by Bui et al. (2016). The authors noted that this was the lowest intake rate for the 20 plasticizers and alternatives covered in their review (Stuer-Lauridsen et al., 2001; as cited by Bui et al., 2016).

TOTM is considered to be resistant to migration based on its relatively high molecular weight and bulky structure. In a study by Kambia et al. (2001, as cited by Versar, 2010), less TOTM and less DEHP (combined, by weight) were released from hemodialysis tubing plasticized with a TOTM-DEHP combination, than DEHP released from the same tubing plasticized with DEHP only. In a similar study by Flaminio et al. (1988, as cited by Versar, 2010), two groups of patients on chronic hemodialysis treatment were treated with TOTM plasticized tubing in place of the common PVC-DEHP tubing. Results showed less TOTM leached from the TOTM tubing than DEHP leached from DEHP plasticized tubing. The low migration rate indicates that leaching (and resulting non-occupational exposure) of TOTM residues from a PVC-based consumer product or medical device would be expected to be lower than to those products if they used DEHP. In addition, the very low vapor pressure of TOTM (3.9×10^{-11} mm Hg), would indicate low potential for non-occupational inhalation exposure.

Occupational exposure to TOTM is primarily through dermal contact and breathing mists in the plastics industry (HSDB, 2018). However, TOTM is produced and used in closed systems, and occupational exposure time is reported to be very short, and limited to sampling and maintenance at the production facilities (SCENIHR, 2016). U.S. EPA estimates that 1000 or more workers are likely to be exposed in the U.S. in industrial manufacturing or processing facilities, but indicates that this number may be greatly underestimated (as cited by HSDB, 2018). NIOSH estimated that 1023 workers were exposed to TOTM based on a survey in the early 1980s (HSDB, 2018). Total daily intake of a worker in a Japanese production site was 1.77×10^{-3} mg/kg-day (calculated based on 70 kg body weight, 1.25 m^3/hour respiratory volume) (HSDB, 2018).

<u>Biomonitoring</u>

No publications on biomonitoring for TOTM or its metabolites were located. However, Hollerer et al. (2017) developed a method for measuring TOTM and its mellitate ester metabolites in blood. The authors noted that their method had been used to analyze blood from patients for whom TOTM-containing tubing was used in a heart-lung machine during an operation. A publication was in preparation, but no record of the study was located.

7 Discussion

7.1 Toxicity Under FHSA

Animal data were sufficient to support the conclusion that **TOTM does not fit the designation of "acutely toxic" under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single oral or dermal exposures. The oral LD_{50} is >5000 in rats (Nuodex, 1983a, as cited by OECD, 2002). The dermal LD_{50} of TOTM in rabbits is >2000 mg/kg (Nuodex, 1983c, as cited by OECD, 2002). It is unclear whether TOTM is "acutely toxic" under the FHSA via the inhalation route for two reasons. First, no study has tested TOTM up to 200 mg/L. Second, substantially different results were obtained in the two available acute lethality studies (Nuodex, 1983b, as cited by OECD, 2002; ECHA, 2018) and Eastman Kodak Co. (1971, as cited by U.S. EPA, undated; ECHA, 2018).

No data were available on the effects of TOTM in humans, except for one study that demonstrated that TOTM is not irritating and non-sensitizing to human skin (David et al., 2003). TOTM was only slightly irritating to rabbit and guinea pig skin, and not sensitizing to guinea pig skin (Ciba-Geigy, 1984b; Nuodex, 1981, 1983d; Eastman Kodak Co., 1983a,b). Studies in rabbits reported only slight eye irritation from TOTM instillation (Nuodex, 1983e; Eastman Kodak Co., 1983a,b). Irritation was reported in one acute inhalation study (Eastman Kodak Co., 1983a,b).

The systemic toxicity of TOTM is low. Even so, sufficient animal data exist to support the conclusion that TOTM can be considered "toxic" under the FHSA due to its toxicity following short-term and subchronic exposures. Adverse effects are limited to peroxisome proliferation and related increased liver weight (effects that are not considered relevant to humans), increased serum cholesterol in males, and decreased bile acids in females.
TOTM has been tested for developmental effects in rats. No developmental toxicity was seen at doses up to 1000 mg/kg-day (Renaut and Whitley, 2017; Huntingdon Life Sciences, 2002). There was also no evidence of neurotoxicity in an FOB and neurobehavioral examination conducted as part of a subchronic study (Anonymous, 2012, as cited by ECHA, 2018).

It is not clear whether TOTM causes reproductive toxicity. A single-generation study determined that TOTM decreased spermatocyte and spermatid counts in a quantitative fashion (JECDB, 1998; Japan Ministry of Health and Welfare, 1998, as cited in OECD, 2002). In contrast, there was no effect on male or female reproductive function or on spermatogenic cycle or sperm staging in a 90-day rat study at similar doses (Anonymous, 2012, as cited by ECHA, 2018).

TOTM has not been tested in a chronic/carcinogenicity study.

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APPENDIX 1

Search Terms Used

Tri-(2-ethylhexyl)trimellitate” OR "Tris(2-ethylhexyl) trimellitate" OR “1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester” OR “Hatcol 200” OR “Kodaflex TOTM” OR “Morflex 510” OR “Staflex TOTM” OR “TOTM” OR "Tri-2-ethylhexyl trimellitate" OR “Trimex T 08” OR “1,2,4-Benzenetricarboxylic acid, 1,2,4-tris(2-ethylhexyl) ester” OR “Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate” OR (3319-31-1) OR “TEHTM”

APPENDIX 2

Explanation of Physico-chemical Parameters

The organic carbon normalized solid-water partition coefficient (K_{oc}), also known as the organic carbon adsorption coefficient, is defined as the ratio of the chemical's concentration in a state of sorption (i.e. adhered to soil particles) and the solution phase (i.e. dissolved in the soil water). K_{oc} is crucial for estimating a chemical compound's mobility in soil and the prevalence of its leaching from soil. For a given amount of chemical, the smaller the K_{oc} value, the greater the concentration of the chemical in solution. Thus, chemicals with a small K_{oc} value are more likely to leach into groundwater than those with a large K_{oc} value (http://www.acdlabs.com/products/phys_chem_lab/logd/koc.html).

Henry's law, one of the gas laws formulated by William Henry, states that "at a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid (http://en.wikipedia.org/wiki/Henry's_law)." Henry's Law Constants characterize the equilibrium distribution of dilute concentrations of volatile, soluble chemicals between gas and liquid phases (http://www.epa.gov/athens/learn2model/part-two/onsite/esthenry.htm).

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. In recent years, this coefficient has become a key parameter in studies of the environmental fate of organic chemicals. It has been found to be related to water solubility, soil/sediment adsorption coefficients, and bioconcentration factors for aquatic life. Because of its increasing use in the estimation of these other properties, K_{ow} is considered a required property in studies of new or problematic chemicals (http://www.pirika.com/chem/TCPEE/LOGKOW/ourlogKow.htm).

The bioconcentration factor (BCF) is the concentration of a particular chemical in a tissue per concentration of chemical in water (reported as L/kg). This property characterizes the accumulation of pollutants through chemical partitioning from the aqueous phase into an organic phase, such as the gill of a fish. The scale used to determine if a BCF value is high, moderate or low will depend on the organism under investigation. The U.S. EPA generally defines a high potential BCF as being greater than 5,000; a BCF of moderate potential as between 5,000 and 100; a low potential BCF as less than 100 (http://en.wikipedia.org/wiki/Bioconcentration_factor; http://sitem.herts.ac.uk/aeru/footprint/en/Quest/ecotox.htm).