Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Trimellitates (high molecular weight)

Evaluation statement

30 May 2022

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AICIS evaluation statement

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Reason for the evaluation

An evaluation is needed to provide information on human health risks.

Parameters of evaluation

Chemicals in this evaluation are esters of trimellitic acid (1,2,4-benzene tricarboxylic acid) with shortest linear carbon side chain lengths of C7 or above. These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of chemicals in this group. These chemicals have been assessed as a group due to their similarities in structure, metabolic pathways and breakdown products, physicochemical properties and uses.

In the absence of toxicological data, endpoint information for identified analogues together with trend analysis for the structurally related phthalate esters are used to predict the toxicity of these chemicals in this evaluation.

Summary of evaluation

Summary of introduction, use and end use

No specific Australian industrial use information are available. Non-industrial uses in Australia are indicated for triisodecyl trimellitate in topical medicines for dermal application.

Based on international use information, chemicals in this evaluation are commonly used as alternatives for phthalate plasticisers in high temperature and/or low migration applications. Some are used as skin conditioners and emollients in a range of rinse off and leave on cosmetics (concentrations up to 74%) and domestic products. Chemicals in this group also have reported commercial, site limited, and non-industrial applications.

Human health

Summary of health hazards

Limited toxicological data are available specifically for these chemicals. Chemicals listed in this evaluation are higher molecular weight trimellitate esters, related to the long chain phthalate esters, which do not have the same level of systemic toxicity as diethylhexyl phthalate (DEHP).

Like the structurally similar phthalate esters, chemicals in this evaluation are expected to be largely inert, without significant acute or local toxicity. Due to their higher molecular weights and partition coefficients compared with those of phthalates, dermal absorption of the trimellitates is expected to be low.

The primary question for trimellitate esters is whether the relationship with phthalate esters extends to having the same level of reproductive toxicity of phthalate esters. There are limited data to evaluate the reproductive toxicity of any group of trimellitate esters. Available information for chemicals in this evaluation do not indicate reproductive toxicity. The majority of the data are for the analogue, triethylhexyl trimellitate (TOTM), which is related to the potent reproductively toxic phthalate, DEHP. TOTM also has, as a metabolite, the alcohol 2-ethylhexanol (2-EH) which has developmental toxicity effects. Therefore, TOTM must be considered worst case for reproductive toxicity of trimellitate esters. TOTM was considered to show, at worst, very limited reproductive toxicity.

Like the long chain phthalate esters, chemicals in this evaluation do not have the same level of reproductive toxicity as the “intermediate chain” (C4–6) phthalates. The limited data available indicate that chemicals in this group may interfere with endocrine function. However, based on the combined weight of evidence and analogue read across approach, chemicals in this evaluation are unlikely to cause adverse reproductive effects, with any effects only occurring at high doses.

The most common systemic target organ observed in the available repeated dose studies with trimellitates is the liver, although the severity of effects and the doses at which effects were seen varied for different trimellitates. Effects were not sufficient to warrant classification. There is not sufficient evidence to conclude that effects are related to peroxisome proliferation. Based on the available data (see **Supporting information**), chemicals in this group may be slightly irritating to the skin (particularly after prolonged or repeated contact), and slightly irritating to the eye, nose, throat, and upper respiratory tract (when mist, fume or vapour are generated or at high levels of exposure).

Chemicals in this evaluation:

- have low acute oral and dermal toxicity
- are not skin sensitisers
- do not have genotoxic potential.

Health hazard classification

These chemicals do not satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety. This evaluation does not consider classification of physical hazards and environmental hazards.

Summary of health risk

Public

Based on the available use information, the public may be exposed to chemicals in this evaluation by:

- direct application to the skin, lips, and hair
- skin contact during use of domestic products
- incidental skin and eye contact during use
- incidental ingestion and/or inhalation from spray, aerosolised or loose powder products.

Although these chemicals are slight skin and eye irritants, application of these chemicals in formulated products is not predicted to cause local irritant effects. A quantitative risk assessment of cosmetic products containing some of the trimellitates concluded that these chemicals are of low concern or do not pose any risk to human health (Government of Canada 2019). The margins of exposure (MOE) calculated were based on conservative scenarios and a No Observed Adverse Effect Level (NOAEL) value for reproductive effects of TOTM. The MOE was large enough to account for any uncertainties or inter- and intra-species extrapolation.

Given that migration of trimellitates from soft polyvinyl chloride (PVC) or food contact materials do not exceed 5 mg/kg food, the European Food Safety Authority (EFSA 2019) concluded that TOTM (which is expected to have higher toxicity than chemicals in this evaluation) does not raise safety concerns for the consumer.

Considering the wide range of potential domestic articles and products containing chemicals in this group, there is a possibility of public exposure to these chemicals through secondary exposure via the environment (e.g. incidental inhalation or ingestion of dust, or eye exposure). However, this indirect human exposure is expected to be at very low levels; hence, it is not comparable to direct exposure.

Overall, there are no identified risks to the public that require management.

Workers

During product formulation and manufacture, dermal, ocular and inhalation exposure of workers to chemicals in this group might occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis,

cleaning, and maintenance of equipment. Worker exposure to these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

While chemicals in this group are not recommended for classification as hazardous chemicals, these chemicals could pose a risk to workers. Control measures to minimise repeated exposure to high concentrations or inhalation of mists are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Workers

Information relating to safe introduction and use

The information in this statement should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate control under the relevant jurisdictions and Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal, ocular and inhalation exposure to chemicals in this group include, but are not limited to:

- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with chemicals in this group.

Measures required to eliminate or to manage risk arising from storing, handling, and using potential hazardous chemicals depend on the physical form and the manner in which chemicals are used.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare safety data sheets (SDS) and label containers of hazardous chemicals. Your Work Health and Safety Regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace

health and safety, and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

Grouping rationale

Chemicals in this evaluation belong to a group of esters of trimellitic acid (1,2,4-benzene tricarboxylic acid) with shortest linear carbon side chain lengths of C7 or above. They are produced by esterification of trimellitic anhydride with a range of aliphatic alcohols (C7–C13, linear, branched or mixed) (Maag et al. 2010; Polynt 2016). Chemicals in this evaluation are expected to share similar metabolic pathways, e.g. hydrolysis breakdown. Monoesters are the main metabolites while oxidative metabolic products are present at low levels, if any (CIR 2015; Hollerer et al. 2018).

There are two chemicals in this evaluation that may have components with linear carbon chain lengths less than C7:

- 1,2,4-benzenetricarboxylic acid, mixed decyl and hexyl and octyl esters (CAS No. 68130-50-7), which is described as C8-C10 rich and commonly known as 810TM (BASF 2021); and
- 1,2,4-benzenetricarboxylic acid, tri-C_{7-9}-branched and linear alkyl esters (CAS No. 68515-60-6) in which the branched components may also contain linear carbon side chain lengths less than C7.

The majority of chemicals in this group are triesters. One chemical (decyl trimellitate) may contain monoester and diester components. As monoesters are hydrolysed metabolites of the triesters, it is considered that the systemic toxicity of this chemical will be related to that of the triesters.

Due to the limited availability of toxicological data for chemicals in this evaluation, this evaluation is principally based on the analogue approach for read across (OECD 2017).

The available data are mostly for triethylhexyl trimellitate (CAS No. 3319-31-1; TOTM – a trimellitate with a linear carbon side chain of C6). Chemicals in this evaluation are expected to demonstrate a lower order of toxicity than TOTM. This is based on the structure-activity relationship observed with the structurally related phthalate esters that indicates the higher molecular weight phthalates with linear carbon side chain lengths of C7 or above are less active than the transitional phthalates of C4–C6 (US EPA 2007 cited in OECD 2017).

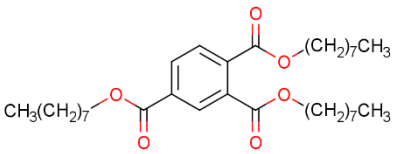
For the purposes of this evaluation, the following chemicals are also identified as acceptable analogues in a data matrix for read across where appropriate:

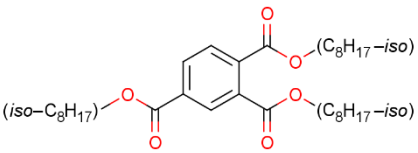
- decyl octyl trimellitate (DOTM; CAS No. 67989-23-5; unlisted)
- triisononyl trimellitate (CAS No. 53894-23-8; unlisted)
- tristridecyl trimellitate (CAS No. 94109-09-8; INCI name as tridecyl trimellitate): previously assessed under a limited certificate as LTD1654 under NICNAS (2013).

The chemical DOTM and tricaprylyl/capryl trimellitate (TM8-10; CAS No 90218-76-1; listed) are 2 separate entities in the CAS Registry, although the latter has been frequently claimed to replace the former. They can be named interchangeably as DOTM. Tricaprylyl/capryl trimellitate is an UVCB while DOTM contains linear side chains of C8 and C10, with a specified molecular formula (C10H22O.xC9H6O6.xC8H18O). The synonym 810TM can also be used interchangeably for tricaprylyl/capryl trimellitate and DOTM (Sasol 2019).

Based on their physicochemical similarities (e.g. liquids of low vapour pressure, low water solubility and high partition coefficient), trimellitates are commonly used as alternatives for phthalate plasticisers in applications where higher temperature, lower volatility and/or lower water extractability are required (Stuer-Lauridsen et al. 2001; SCENIHR 2016; BASF 2021). Some trimellitates also have reported cosmetic uses as skin conditioners and/or as plasticisers (CIR 2015; Government of Canada 2019; CosIng) (see **Introduction and use** section).

Chemical identity

Chemical Name	1,2,4-Benzenetricarboxylic acid, trioctyl ester
CAS registry number	89-04-3
Synonyms	tri-n-octyl trimellitate trioctyl trimellitate TM8 trioctyl benzene-1,2,4-tricarboxylate
Structural formula	
Molecular formula	C33H54O6
Molecular weight (g/mol)	546.78
SMILES	O=C(OCCCCCCCC)C1=CC=C(C(=O)OCCCCCCCC)C(=C1)C(=O)OCCCCCCCC
Chemical description	-

Chemical Name	1,2,4-Benzenetricarboxylic acid, triisooctyl ester
CAS registry number	27251-75-8
Synonyms	triisooctyl trimellitate IOTM triisooctyl benzene-1,2,4-tricarboxylate
Structural formula	
Molecular formula	C33H54O6
Molecular weight (g/mol)	546.78
SMILES	CC(C)CCCCCOC(=O)C1=CC(C(=O)OCCCCCC(C)C)=C(C=C1)C(=O)OCCCCCC(C)C

Chemical description	Not specified

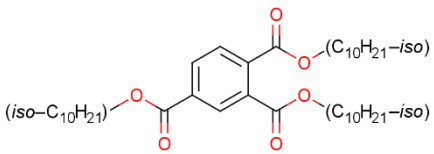
Chemical Name	1,2,4-Benzenetricarboxylic acid, tri-C_{7-9}-branched and linear alkyl esters
CAS registry number	68515-60-6
Synonyms	tri-(C_{7-9})-alkyl trimellitate TM7-9 trimellitic acid, C7-9-trialkyl ester
Structural formula	Not specified
Molecular formula	Not specified
Molecular weight (g/mol)	504.70
SMILES	O=C(c1ccc(cc1C(=O)OCC(CCC)CC)C(=O)OCC(CCC)CC)OCC(C(C)CC)C
Chemical description	UVCB

Chemical Name	1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters
CAS registry number	90218-76-1
Synonyms	tricaprylyl/capryl trimellitate (INCI) TM8-10 trimellitic acid, C8-10-alkyl triesters
Structural formula	Unspecified
Molecular formula	C33H51O6 to C39H66O6
Molecular weight (g/mol)	661.01
SMILES	Not specified
Chemical description	UVCB

Chemical Name	1,2,4-Benzenetricarboxylic acid, mixed decyl and hexyl and octyl esters
CAS registry number	68130-50-7
Synonyms	mixed decyl and hexyl and octyl trimellitates 810TM 1-hexanol, 1-octanol, 1-decanol, trimellitic anhydride mixed esters

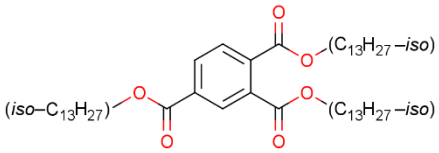
Structural formula	Not specified
Molecular formula	Not specified
Molecular weight (g/mol)	591
SMILES	O=C(c1ccc(cc1C(=O)OCCCCCC)C(=O)OCCCCCCCC)OCCCCCCCCCC
Chemical description	UVCB

Chemical Name	1,2,4-Benzenetricarboxylic acid, decyl ester
CAS registry number	51281-36-8
Synonyms	decyl trimellitate
Structural formula	Not specified
Molecular formula	C10H22O.xC9H6O6
Molecular weight (g/mol)	546.78–630.94
SMILES	Not specified
Chemical description	Not specified

Chemical Name	1,2,4-Benzenetricarboxylic acid, triisodecyl ester
CAS registry number	36631-30-8
Synonyms	triisodecyl trimellitate (INCI) IDTM triisodecyl benzene-1,2,4-tricarboxylate
Structural formula	
Molecular formula	C39H66O6
Molecular weight (g/mol)	630.94
SMILES	CC(C)CCCCCCCOC(=O)C1=CC(C(=O)OCCCCCCCC(C)C)=C(C=C1)C(=O)OCCCCCCCC(C)C
Chemical description	Not specified

Chemical Name	1,2,4-Benzenetricarboxylic acid, branched tridecyl isodecyl esters
CAS registry number	70225-05-7
Synonyms	tri(isodecyl, tridecyl) trimellitate tridecyl trimellitate triisodecyl tridecyl trimellitic ester
Structural formula	Not specified
Molecular formula	C39H64O6 to C48H76O6
Molecular weight (g/mol)	Not specified
SMILES	Not specified
Chemical description	UVCB

Chemical Name	1,2,4-Benzenetricarboxylic acid, tri-C_{9-11}-alkyl esters
CAS registry number	94279-36-4
Synonyms	tri-(C_{9-11})-alkyl trimellitate TM9-11
Structural formula	Not specified
Molecular formula	C36H60O6 to C42H72O6
Molecular weight (g/mol)	588.86–673.02
SMILES	Not specified
Chemical description	UVCB

Chemical Name	1,2,4-Benzenetricarboxylic acid, triisotridecyl ester
CAS registry number	72361-35-4
Synonyms	Triisotridecyl trimellitate (INCI) Tris(isotridecyl)trimellitate triisotridecyl benzene-1,2,4-tricarboxylate
Structural formula	
Molecular formula	C48H84O6
Molecular weight (g/mol)	757.18
SMILES	CC(C)CCCCCCCCCCOC(=O)C1=CC(C(=O)OCCCCCCCCCCC(C)C)=C(C=C1)C(=O)OCCCCCCCCCCC(C)C
Chemical description	n/a

Relevant physical and chemical properties

Chemicals in this group are oily liquids. They are large, hydrophobic compounds that can form emulsions or micelles in water like DEHP and other phthalates. They are estimated to have negligible vapour pressures (Government of Canada 2019).

Introduction and use

Australia

No specific Australian industrial use, import, or manufacturing information has been identified for chemicals in this evaluation.

Non-industrial uses in Australia are indicated for triisodecyl trimellitate in topical medicines for dermal application (TGA 2021).

International

The following international uses have been identified through the:

- European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers
- the European Commission Cosmetic Ingredients and Substances (CosIng) database
- Substances in Preparations in Nordic Countries (SPIN) database
- international reviews (CIR 2015; US CPSC 2018; Government of Canada 2019)
- technical product information (BASF 2021; Polynt 2016).

The following chemicals have reported cosmetic uses:

- tricaprylyl/capryl trimellitate: skin conditioning, emollient.
- triisodecyl trimellitate: skin conditioning, emollient.
- tri(isodecyl, tridecyl) trimellitate: skin conditioning.
- triisotridecyl trimellitate: skin conditioning.

These chemicals are reported to be used in a variety of leave on and rinse off products (face and body moisturisers, lipsticks and other lip care products, eye and face make-up, face and body cleansers, hair products, massage oil, nail polish and manicure preparation creams, and shaving products) at a range of concentrations (4–74%) (CIR 2015; Government of Canada 2019).

Commercial or professional uses including as lubricants, adhesives, functional fluids, paints and coatings, fuel additives and fertilisers have been reported for one or more of the following chemicals:

- tri-n-octyl trimellitate
- tri-(C_{7-9})-alkyl trimellitate
- tricaprylyl/capryl trimellitate
- triisodecyl trimellitate
- tri(isodecyl, tridecyl) trimellitate
- tri-(C_{9-11})-alkyl trimellitate and triisotridecyl trimellitate.

Some of these commercial uses may also be used in domestic applications.

The following chemicals have reported site limited uses:

- tri-n-octyl trimellitate: in manufacture and formulation of compounds and plastisol (pellets and dry blend), plastic and polymer products, lubricants and additives in high kinetic energy conditions, in metal working operations.
- tricaprylyl/capryl trimellitate: in manufacture and formulation of compounds and plastic products, lubricants, metal working fluids, coatings, inks, adhesives and sealants.
- triisodecyl trimellitate: in manufacture and formulation of plastic and rubber products, lubricants in high energy processes, metal working fluids, inks and toners, adhesives and sealants, polishes and wax blends.
- tri(isodecyl, tridecyl) trimellitate: in manufacture and formulation of lubricants, functional and metal working fluids, in some incidental additives for use in food processing establishments without direct food contact.
- tri-(C_{9-11})-alkyl trimellitate and triisotridecyl trimellitate: in manufacture and formulation of articles, resins, auxiliary chemicals, lubricants, functional fluids, metal treatment, textile coating, leather finishing.

The following chemicals have reported non-industrial uses:

- tri-n-octyl trimellitate: in medical devices, pesticides (inert ingredient).
- triisodecyl trimellitate: in medical devices.
- tri-(C_{9-11})-alkyl trimellitate and triisotridecyl trimellitate: in insecticides.

Trimellitates may be released from plastic, rubber or PVC articles with domestic uses, including in:

- building materials, car interiors, automotive components
- electrical articles, wire and cable insulation, electrical batteries and accumulators
- computer, electronic and optical products
- refrigerator gaskets
- textile articles
- food packaging.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

Triisodecyl trimellitate has reported non-industrial uses as excipients (permissible ingredients other than active ingredients) only for use in topical medicines for dermal application and must not be included in medicines intended for use in the eye. The concentration in the medicine must be no more than 5% (TGA 2021).

Workers

These chemicals are not listed in the Hazardous Chemicals Information System (HCIS) and no exposure standards are available in Australia (Safe Work Australia).

International regulatory status

Exposure standards

No specific exposure standards were identified.

OECD

Guidance on grouping of chemicals by Organisation for Economic Co-operation and Development (OECD 2017) includes the trimellitate category as an example of read across. Triethylhexyl phthalate (TOTM; CAS No. 3319-31-1) is considered the category representative on the basis that:

> *Due to their higher molecular weight and bulky side chains, the remaining members of this category are expected to demonstrate a lower order of toxicity than TOTM. This is supported by a similar structural-activity relationship observed with phthalate ester compounds, i.e. the higher molecular weight phthalates (ester side chains >C7) are less active than the transitional phthalates (ester side chains C4–C6). Thus, the use of TOTM to represent the potential hazards of the other category members is a conservative position (US EPA 2007).*

Canada

Canada Government considered the following 5 trimellitates as a group:

- triethylhexyl phthalate (CAS No. 3319-31-1)
- tri(isodecyl, tridecyl) trimellitate (CAS No. 70225-05-7)
- tristridecyl trimellitate (CAS No. 94109-09-8)
- triisononyl trimellitate (CAS No. 53894-23-8)
- tri-(C_{7-9})-alkyl trimellitate (CAS No. 68515-60-6).

Government of Canada (2018) identified the last 2 above trimellitates 'as being of low concern' to human health, based on the threshold of toxicological concern (TTC) approach.

Government of Canada (2019) concluded that the other 3 trimellitates do not present a risk to human health in its screening assessment.

European Union

ECHA has evaluated the dossiers of several trimellitates in this group and requested submission of additional information, such as:

1. Extended one-generation reproductive toxicity study for tri-n-octyl trimellitate (ECHA 2018*).*

2. In vitro gene mutation study in bacteria for:
    - tricaprylyl/capryl trimellitate (ECHA 2020a)
    - triisodecyl trimellitate (ECHA 2020b)
    - tri-(C_{9-11})-alkyl trimellitate (ECHA 2020c)
    - triisotridecyl trimellitate (ECHA 2020d).

The European Food Safety Authority (EFSA 2019) concluded that TOTM does not raise safety concerns for the consumer when used in the manufacture of soft PVC or food contact materials, providing that its migration does not exceed 5 mg/kg food. The NOAEL was 225 mg/kg bw/day, derived from a 90-day oral toxicity study in rats.

United States of America

The Cosmetic Ingredient Review (CIR 2015) review determined that the following trimellitates are safe at the current use and concentration in cosmetics when formulated to be non-irritating. However, irritant effects to the skin, eye, nose, throat, and upper respiratory tract from incidental contact and/or inhalation (from spray, aerosolised or loose powder products) cannot be ruled out for some known use concentrations.

- tristridecyl trimellitate (CAS No. 94109-09-8; INCI name as tridecyl trimellitate)
- triethylhexyl phthalate (CAS No. 3319-31-1)
- tricaprylyl/capryl trimellitate (CAS No. 90218-76-1)
- triisodecyl trimellitate (CAS No. 36631-30-8)
- triisotridecyl trimellitate (CAS No. 72361-35-4).

Health hazard information

Toxicokinetics

No data are available for the trimellitates in this group.

Based on the rat and human kinetic studies for TOTM, chemicals in this evaluation (linear, branched or mixed) are expected to be rapidly absorbed and distributed to the tissues after oral exposure. Metabolism and elimination can be slow and biphasic with minimal accumulation in the body. Although the majority of administered doses were excreted unchanged in the faeces, oral bioavailability of trimellitates could be high based on repeated dose toxicity.

Due to chemicals in this group having higher molecular weights and partition coefficients compared with those of phthalates, dermal absorption of these chemicals is expected to be low.

In a rat single dose study, TOTM at 100 mg/kg bw was administered by gavage to 4 fasted male Sprague Dawley (SD) rats. About 75% of the dose was excreted in the faeces, 16% in the urine as metabolites and 1.9% as expired $^{14}CO_2$. Less than 0.6% of the radioactivity remained and this was concentrated mainly in the liver and adipose tissues. In the faeces, 85% of the radioactivity excreted was unchanged TOTM, and the remaining attributed to di(2-ethylhexyl) trimellitate (DEHTM; 7%), mono(2-ethylhexyl) trimellitate (MEHTM; 1%), and other polar metabolites. In the urine, MEHTM, 2-EH, 2-ethylhexanoic acid and 2-heptanone were identified. Elimination in the urine and in CO_2 was biphasic with half lives of 3.1 and 42 hours and 4.3 and 31 hours, respectively (CIR 2015; EFSA 2019; Enriquez et al. 1984).

Following intravenous administration of radiolabelled TOTM at 10.5 mg/kg bw in 5 male SD rats, a biphasic pattern composed of a rapid initial distribution and slow plasma clearance was observed with half lives of 46.2 minutes and 5.34 days, respectively. The distribution volume was apparently large at 7.49 L/kg. Excretion was 16.9% in the faeces and 3.3% in the urine after 14 days. To study tissue distribution as a function of time, TOTM at 15.6 mg/kg bw was administered intravenously in 28 rats (4/group/time) and recovery of the dose in various tissues was measured at 1, 6, 24, 48, 72, 168, and 336h. Distribution peaked in the lungs (18.6%) at 1h, and in the liver (71.6%) and the spleen (5.3%) at 24h. After 14 days, radioactivity declined in the liver (44.8%), but remained constant in the spleen (4.7%) (Martis et al. 1987; CIR 2015; EFSA 2019).

In a human study, after oral administration of TOTM at 1.12 mg/kg bw in 4 healthy volunteers (2 males and 2 females), TOTM was found to be regioselectively hydrolysed to its diesters (1,2-DEHTM, 2,4-DEHTM) and monoester isomers (1-MEHTM, 2-MEHTM) with blood concentrations peaking at 3 and 5h, respectively. Approximately 5.8% of the dose was recovered in urine (3.3% as 2-MEHTM) over 72h. Urinary elimination of TOTM and all measured hydrolysis and oxidative metabolites was biphasic with half lives of 4–6h (1st phase) and 10–33h (2nd phase). TOTM had the longest elimination half life of 27h, compared with its hydrolysis metabolites. It was concluded that TOTM was mainly excreted unmetabolised via faeces on the basis of its slow metabolic rate as well as its low bioaccumulation potential (Hollerer et al. 2018; EFSA 2019).

The dermal absorption of TOTM was investigated using Franz cells (full thickness skin samples excised from female nude mice and specific pathogen-free pigs). The receptor medium contained 40% ethanol and the donor medium had 5.4 mM chemical in 40% ethanol

and pH 7.4 buffer. This chemical was not found in the receptor medium after 12hrs, indicating that there was no dermal absorption of this chemical (CIR 2015).

Acute toxicity

Oral

Based on the available data, chemicals in this group are expected to have low acute oral toxicity.

Tri-n-octyl trimellitate: median lethal dose LD50 (rats) >2000 mg/kg bw (JECDB; REACHa)

Tricaprylyl/capryl trimellitate: LD50 (rats) >3000 mg/kg bw (CIR 2015; REACHb)

Triisodecyl trimellitate: LD50 (rats 2M/2F; non-guideline) >9590 mg/kg bw (10 mL/kg) (CIR 2015; REACHc)

Analogue(s):

TOTM: LD50 (rats) >2000 mg/kg bw (NICNAS 2016)

DOTM: LD50 (rats) >3000 mg/kg bw (REACHa)

Tristridecyl trimellitate: LD50 (rats) >5000 mg/kg bw (CIR 2015; NICNAS 2013)

Dermal

Based on the weight of evidence from available data, chemicals in this group are expected to have low acute dermal toxicity.

Tricaprylyl/capryl trimellitate: LD50 (rats) >2000 mg/kg bw/day (CIR 2015; REACHb)

Analogue(s):

TOTM (OECD 2002, NICNAS 2016):

- LD50 (3 rabbits of either sexes, 2 controls) >2 mL/kg bw (~2000 mg/kg bw; density 0.987–0.990 kg/m^3 at 20 °C)
- LD50 (rabbits 3M/3F) >1970 mg/kg bw.

Inhalation

No data are available for the trimellitates in this group. Based on the analogue data, these chemicals are expected to have low acute inhalation toxicity.

TOTM (NICNAS 2016; US CPSC 2018; REACHd):

- LC50 (OECD TG 403; rats 5M/5F) >2.6 mg/L/4 hours (aerosol).
  Reddened patches on the lung were observed in 5/5 male and 3/5 female animals on day 14 post exposure.
- LC50 (non-guideline; 3 rats, sex not specified): 100% mortality at ≥2.64 mg/L/6h (vapour).

Corrosion/Irritation

Skin irritation

Based on the weight of evidence from available data, chemicals in this group may be slightly irritating to the skin. Prolonged or repeated contact with these chemicals may cause defatting and making the skin more susceptible to damage by other substances.

Tricaprylyl/capryl trimellitate: not to slightly irritating to rabbit skin (CIR 2015; REACHb).

Triisodecyl trimellitate: slightly irritating in New Zealand White (NZW) rabbits (mean scores of 24 hours and 72 hours only for erythema 0.33 and oedema 0.5). At 24h, slight to well defined erythema at 3/6 intact and 4/6 abraded sites; very slight to slight oedema at 5/6 intact and 5/6 abraded sites. At 72h, very slight oedema at 3/6 intact and abraded sites. All effects were resolved after 6 days (CIR 2015; REACHc).

Tri-(C_{9-11})-alkyl trimellitate: slightly irritating in NZW rabbits (mean scores for erythema 1.22 and oedema 1.11). At 24h, slight to well defined erythema and slight oedema in all rabbits. Reactions were reversible in 2/3 animals after 7 days and in 1/3 after 14 days (REACHe).

Analogue(s):

TOTM: slightly irritating to rabbit and guinea pig skin (OECD 2002; CIR 2015; NICNAS, 2016; REACHf):

- a reversible dermal irritant in Californian rabbits (4 hour occlusive patch)
- a slight irritant in NZW rabbits (24 hour occlusive patch)
- a reversible dermal irritant in guinea pigs (24 hour occlusive exposure caused moderate erythema and moderate to severe oedema; all reactions appeared normal after 7 days).

DOTM: slightly irritating in Russian white rabbits (mean scores for erythema 1.56 and oedema 0.11). At 24 hours, slight to well defined erythema in 3/3 rabbits and slight oedema in 2/3 rabbits. All reactions were reversible after 6–8 days (REACHa; REACHb).

Tristridecyl trimellitate: slightly irritating at 10% to rabbit skin (CIR 2015; NICNAS 2013).

Observation in humans

Analogue(s):

TOTM: slightly irritating at 1% to human skin. In a human repeated insult patch test (HRIPT), slight erythema was observed in 4/203 subjects, 2 of which resolved within 96h; and one had delayed skin reaction occurring after 96h (David et al. 2003; CIR 2015) (see **Skin Sensitisation** section).

It was reported that prolonged or repeated skin contact with TOTM may cause defatting, making the skin more susceptible to damage by other substances (OECD 2002).

Tristridecyl trimellitate: not irritating at 57.1% (in lipstick formulation) and at 100% to human skin, as observed in HRIPTs in 53 and 51 subjects, respectively (CIR 2015; NICNAS 2013) (see **Skin Sensitisation** section).

Eye irritation

Based on the weight of evidence from available data, chemicals in this group may be slightly irritating to the eye.

Tricaprylyl/capryl trimellitate: slightly irritating to rabbit eyes. At 1 hour, slight to moderate conjunctival irritation in 3/3, and moderate iritis in 1/3 rabbits. Reactions decreased by 48 hours and all animals appeared normal at 72 hours (REACHb).

Triisodecyl trimellitate: not irritating to rabbit eyes. At 1–24 hours, very slight conjunctival redness in 2/3 rinsed and 3/3 unrinsed eyes was resolved, except for 2/3 unrinsed eyes. At 48 hours, all eyes were normal (CIR 2015; REACHc).

Analogue(s):

TOTM: slightly irritating in NZW rabbits with mean scores of 2.3 (day 1), 1.7 (day 2), and 0 (day 3, 4, 7) (CIR 2015; NICNAS 2016; OECD 2002).

DOTM: slightly irritating in white Russian rabbits (severe transient conjunctival redness with mean score 2.67 at 1 hour and resolved by 24 hours (REACHb).

Triisononyl trimellitate: slightly irritating in NZW rabbits (severe conjunctival effects with mean score 3.66 at 1 hour and decreased to 1.33 and 0.33 at 24 hours and 48 hours, respectively) (REACHf).

Tristridecyl trimellitate: slightly irritating in NZW rabbits (severe conjunctival effects at 1 hour, diminished in severity by 24 hours, and were resolved by 72 hours (CIR 2015; NICNAS 2013).

Respiratory irritation

Based on the limited data, chemicals in this group may cause respiratory irritation.

Analogue(s):

TOTM: respiratory irritation was reported in rat studies (Stuer-Lauridsen et al. 2001; US CPSC 2018).

- slight irritation at 0.23 mg/L/6h
- moderate irritation at 16 ppm/6h
- severe irritation at ≥2.64 mg/L/6h (vapour) (see **Acute toxicity – Inhalation**).

Observation in humans

Analogue(s):

TOTM: mist and fumes from hot processing may cause irritation to mucous membranes (eye, nose, throat, and upper respiratory tract), nausea and vomiting (OECD 2002; Stuer-Lauridsen et al. 2001).

Sensitisation

Skin sensitisation

Based on the weight of evidence of available data, chemicals in this group are not expected to be skin sensitisers.

Tricaprylyl/capryl trimellitate: a local lymph node assay (LLNA) result was negative with Stimulation Index (SI) <3 at 100% (REACHb).

Analogue(s):

TOTM: not sensitising to guinea pig skin, based on negative test results in:

- a modified Buehler test in albino guinea pigs (only 10M; 24 hours occlusive; induction 100% x 10 patches on alternate days / challenge 100%) (CIR 2015; REACHc)
- a maximisation test in guinea pigs (20M; induction intradermal 30% and dermal 100% / challenge 10% and 30%) (REACHe).

DOTM: not sensitising in a maximisation test in Dunkin-Hartley guinea pigs (20F; induction intradermal 10% and dermal 100% / challenge 100%) (REACHa; REACHb).

Tristridecyl trimellitate: mixed results in local lymph node assays (LLNA) with stimulation Index (SI) >3 at 10% and 100% in experiment 1, but not in experiment 2) (CIR 2015).

Observation in humans

Analogue(s):

TOTM: not sensitising at 1% in a HRIPT (203 subjects; 24 hours semi-occlusive; induction 1% × 9 patches for 3 weeks / challenge 1%) (David et al. 2003; CIR 2015).

Tristridecyl trimellitate: not sensitising at 57.1% (in lipstick formulation) and at 100% in HRIPTs in 53 and 51 subjects, respectively (NICNAS 2013; CIR 2015).

Repeated dose toxicity

The most common systemic target organ observed in the available repeated dose studies with trimellitates is the liver, although the severity of effects and the doses at which effects were seen varied for different trimellitates.

Tri-n-octyl trimellitate (JECDB; REACHa):

- In a rat 90 day gavage study (OECD TG 408; 4-week recovery; SD rats 10/sex/dose) with 0, 50, 200, 800 mg/kg bw/day: NOAEL of 800 mg/kg bw/day was reported in the study. However, absolute and relative liver weight increases were dose dependent (7–3%, 10–6%, 18–19% and 4–5%, 8–11%, 25–26% (male–female), respectively, (compared with the control), as well as statistically significant at the mid/high dose. Changes in blood biochemistry were also observed.

- In a rat combined repeated dose toxicity and reproduction/developmental toxicity screening study (OECD TG 422; SD rats 13/sex/dose) with 0, 30, 125, 500 mg/kg bw/day

(gavage for approximately 42–63 days male–female): the NOAEL was established at 30 mg/kg bw/day for female animals, based on reduced red blood cell count and increased liver weight at higher doses. The NOAEL was 125 mg/kg bw/day for male animals, based on decreased protein, increased alkaline phosphatase (ALP – a biomarker of hepatobiliary injury), and centrilobular hypertrophy of hepatocytes at 500 mg/kg bw/day.

Tricaprylyl/capryl trimellitate (REACHb):

- In a rat 28 day gavage study (OECD TG 407; 2-week recovery; SD rats 5/sex/dose) with 0, 100, 300, 1000 mg/kg bw/day: NOAEL of 1000 mg/kg bw/day was reported in the study although all effects were considered treatment related and some were dose dependent and statistically significant without being fully reversible. They included decreases in food consumption and body weight gain (19.9% and 32.5% in males at high dose, and 17.4% and 26.2% in females at mid dose, respectively). Body weights were decreased by 11–6.4% (male–female) at the end of the recovery period. At 1000 mg/kg bw/day, while increases in blood biochemistry and liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and ALP) were reversible in both sexes, organ weight alterations (thymus, spleen, liver, and adrenals) did not resolve at the end of the recovery period. Hepatocellular hypertrophy was correlated with increased liver weights in males at 300 mg/kg bw/day and above, and females at 1000 mg/kg bw/day. Adrenal enlargement was observed in male animals at 1000 mg/kg bw/day and in female animals at 300 mg/kg bw/day and above. In addition, erythrophagocytosis (ingestion of red blood cells by white blood cells) in the medullary sinus of the mesenteric lymph node was observed in male animals (1/5, 3/5, 4/5 at low, mid, high doses, respectively), and in female animals (5/5 at high dose).

Analogue(s):

TOTM (CIR 2015; OECD 2002; REACHd; US CPSC 2018):

- In a rat 90 day feeding study (OECD TG 408; 4-week recovery; SD rats 10/sex/dose) with 0, 50, 225, 1000 mg/kg bw/day: NOAEL was 225 mg/kg bw/day, based on adverse changes in blood and clinical biochemistry, histopathology, and organ weights (kidney, spleen, liver, and adrenals) at the high dose. Absolute and relative liver weight increases were dose dependent and statistically significant in high dose female animals (increases of 9% and 10%, respectively, at the end of recovery). Relative liver weight increases (20%) were also statistically significant in high dose male animals. Absolute and relative spleen weight decreases (22% and 14%, respectively) were observed in high dose male animals. Histopathological changes were found in the liver of high dose animals of both sexes, and in spleens of the female animals. It was noted that at 225 and 1000 mg/kg bw/day, increases of ALP (15% and 28%, respectively) and cholesterol (21% and 41%, respectively) in male rats, and decreases of both ALT and AST (18% to 29%) in female rats were reported.

- In a rat 28 day feeding study (Phase I non-guideline; Fischer F344 rats 5/sex/dose) with 0, 0.2, 0.67, 2% (0, 184, 650, 1826 mg/kg bw/day): NOAEL was 184 mg/kg bw/day, based on changes in blood and clinical biochemistry, and liver enlargement in both sexes at mid and high doses. A slight reduction in cytoplasmic basophilia (2/5 females) and a slight increase in liver peroxisomes were reported at 2%. Although showing the same spectrum of effects, TOTM at 2% was less potent in causing enzyme induction and peroxisome proliferation in the rat liver, compared with DEHP at 0.67% (Hodgson 1987).

- In a rat 21 day gavage study (Phase II non-guideline; Fischer F344 rats 5/sex/dose) with 0, 200, 700, 2000 mg/kg bw/day: statistically significant non-dose related increases in relative liver weight were observed in female rats at all doses. Histopathology of livers of all treated animals showed a reduction in the quantity of neutral lipid. TOTM at 2000 mg/kg bw/day caused less peroxisome induction in rats, compared with a metabolically equivalent dose of DEHP at 700 mg/kg bw/day (Hodgson 1987).

- In a rat 28 day gavage study (non-guideline; 4-week recovery; albino rats 6M/group): DEHP at 300 mg/kg bw/day caused severe irreversible damages to the rat liver, including loss of lobular architecture, marked periportal cellular and fatty infiltrations, and hepatocytes with shrunken nuclei, peroxisomes and lipid globules, which were still observed at the end of recovery. TOTM at 300 mg/kg bw/day gave preserved lobular architecture, and some reversible effects on shrunken hepatocytes and hepatic vascular dilatation and congestion (e.g. prominent Kupffer cells in congested blood sinusoids) (EFSA 2019; Shehata et al. 2013).

- In a rat 28 day gavage study (OECD TG 407; 2-week recovery; SD rats 5/sex/dose) with 0, 100, 300, 1000 mg/kg bw/day: NOEL was 1000 mg/kq/day for both males and female rats. No treatment related changes were noted in clinical signs, body weights, food consumption, haematology, clinical biochemistry, urinalysis or pathological findings (JECDB).

- In a rat 28 day feeding study (OECD TG 407; 2 week recovery; SD rats 5/sex/dose) with 0, 100, 300, 1000 mg/kg bw/day: NOAEL of 1000 mg/kq/day was reported in the study. Increased absolute and relative adrenal weights in female rats, hypertrophy of the kidney and parathyroid, and coloured patches in the lungs of male rats (1/5, 2/5, and 3/5 at increasing doses) were considered non-adverse and/or non-treatment related (OECD 2002; REACHg).

DOTM (CIR 2015; REACHa; REACHe; REACHg):

- In a rat 90 day gavage study (OECD TG 408; 4-week recovery; SD rats 10/sex/dose) with 0, 50, 200, 500 mg/kg bw/day: NOEL/NOAEL of 50/500 mg/kg bw/day were reported in the study. At the mid and high doses, absolute and relative liver weight increases (9–9%, 8–19% and 6–9%, 9–22% (male–female), respectively), together with biochemical and microscopic changes were fully reversible at the end of recovery.

- In a rat 28 day gavage study (OECD TG 407; 2-week recovery; SD rats 5/sex/dose) with 0, 100, 300, 1000 mg/kg bw/day: NOEL/NOAEL was 100/300 mg/kq/day. At 1000 mg/kg bw/day, reduced body weights (9% in males), hair loss (6/10 females), increased leucocytosis (27% in females), increased absolute and relative liver weights (16–33% and 29–34% (male–female), respectively), and increased absolute and relative adrenal weights (8% and 20% in males with microscopic changes, respectively) were observed. At 300 mg/kg bw/day, slight effects were observed in male rats only.

Genotoxicity

Based on the weight of evidence from available data, chemicals in this group are not expected to have genotoxic potential.

Tri-n-octyl trimellitate (JECDB; REACHa): the test results were reported to be negative in:

- a bacterial reverse mutation test using *Salmonella typhimurium* TA1535, TA1537, TA98, TA100, and *Escherichia coli* WP2 *uvrA*, with or without metabolic activation

- an in vitro chromosomal aberration test in Chinese hamster lung (CHL/IU) cells, with or without metabolic activation
- an in vitro gene mutation test at the thymidine kinase gene in mouse lymphoma L5178Y cells, with or without metabolic activation.

Analogue(s):

TOTM (CIR 2015; JECDB; OECD 2002; REACHc; REACHf): the test results were reported to be negative in:

- two bacterial reverse mutation tests: one using 5 strains (*S. typhimurium* TA1535, TA1537, TA98, TA100, and *E. coli* WP2 *uvrA*) and the other using 4 strains (*S. typhimurium* TA1535, TA97, TA98, TA100), with or without metabolic activation
- two in vitro chromosomal aberration tests: in human lymphocytes and in CHL/IU V79 fibroblasts, with or without metabolic activation
- two in vitro gene mutation tests: one in mouse lymphoma L5178Y tk+/-3.7.2C cells and the other in Chinese hamster ovary (CHO/HGPRT) cells, with or without metabolic activation
- an unscheduled DNA synthesis test in primary rat hepatocytes
- an in vivo dominant lethal test in male Swiss mice (details not provided).

DOTM (REACHa; REACHb): the test results were reported to be negative in:

- a bacterial reverse mutation test using 3 strains *S. typhimurium* TA97, TA98, TA100 only. No results were available for the other required strains TA1535 or TA1537 and either TA102 or *E. coli* WP2 *uvrA* or *E. coli* WP2 *uvrA* (pKM101) (ECHA 2020a; 2020c)
- an in vitro chromosomal aberration test in human lymphocytes, with or without metabolic activation
- an in vitro gene mutation test at the thymidine kinase gene in mouse lymphoma L5178Y cells, with or without metabolic activation.

Carcinogenicity

No carcinogenicity studies are available for the trimellitates. Based on the combined weight of evidence and analogue read across approach, the trimellitates in this group are expected to have lower carcinogenic potential than DEHP.

Limited data are available for the structurally related long chain phthalates. Data for diisononyl phthalate (DINP) do not indicate a carcinogenic potential in humans (NICNAS 2012). There is not sufficient evidence to conclude that chemicals in this evaluation cause peroxisome proliferation.

The ability of TOTM to induce peroxisome proliferation was investigated in a rat 28 day feeding study. TOTM at 2% caused less peroxisome proliferation than DEHP at 0.67 % (Hodgson 1987). Peroxisome proliferation is reported to cause an increase in liver weights and is also believed to induce non-genotoxic hepatocarcinogenesis in rodents. Liver effects, when related to peroxisome proliferator-activated receptor alpha (PPARα), which is a rodent specific mode of action, are unlikely to be relevant to humans.

In addition, TOTM was reported to cause less pronounced hepatocellular changes and minor immunohistochemical abnormalities, compared with DEHP (Hodgson 1987; Shehata et al. 2013; see **Repeated Dose Toxicity** section). TOTM at 300 mg/kg bw/day produced a

narrow area of immunohistochemical abnormalities around the central veins in the rat liver, compared with a wide area induced by DEHP at 300 mg/kg bw/day. This was based on microscopic analyses of an immunoperoxidase reaction of hepatocyte mitochondrial membrane antigen with hepatocyte paraffin-1 (Hep Par-1) antibody (a marker for hepatocellular carcinoma) (Shehata et al. 2013).

Reproductive and developmental toxicity

Limited data are available. Available information for chemicals in this evaluation do not indicate reproductive toxicity. The majority of the data are for the analogue TOTM, which was reported to cause a slight reduction in the number of spermatocytes & spermatids in male rats (NOAEL 100 mg/kg bw/day). However, TOTM is related to the potent reproductively toxic phthalate, DEHP, and which also has, as a metabolite, the alcohol 2-ethylhexanol(2-EH) which has developmental toxicity effects. Studies generally indicated that high molecular weight phthalates (≥C7) are not potent male reproductive toxins. Of these phthalates, only DINP produced some minor effects on male reproductive tract development at high levels of exposure (NICNAS 2012).

Based on the combined weight of evidence and analogue read across approach, chemicals in this evaluation are unlikely to cause reproductive (testicular) toxicants, with any effects only occurring at high doses.

Tri-n-octyl trimellitate (JECDB; REACHa):

- In a rat 90 day gavage study (OECD TG 408; 4-week recovery; SD rats 10/sex/dose) with 0, 50, 200, 800 mg/kg bw/day (see **Repeated Dose Toxicity**): NOAEL of 800 mg/kg bw/day was reported for both sexes in the study. However, absolute uterus weights were decreased in females at all doses (47%, 27%, 45%), with a statistical significance at low and high doses.

- In a rat combined repeated dose toxicity and reproduction/developmental toxicity screening study (OECD TG 422; SD rats 13/sex/dose) with 0, 30, 125, 500 mg/kg bw/day (gavage for approximately 42–63 days male–female): the maternal NOAEL was 30 mg/kg bw/day (see **Repeated Dose Toxicity**). The reproductive/developmental NOAEL was 500 mg/kg bw/day. No adverse effects on oestrous cycle, copulation, fertility, deliver, gestation, or numbers of corpora lutea, implantation sites or implantation index were found. There were no effects on pup weight, sex ratio, live birth or viability index. No data on sperm parameters were available.

- In a rat prenatal developmental toxicity study (OECD TG 414; SD rats 24F/dose) with 0, 100, 300, 1000 mg/kg bw/day (gavage) on gestation days (GD) 6–19: the NOAEL was 300 mg/kg bw/day for maternal effects. The NOAEL was 1000 mg/kg bw/day for developmental effects. At 1000 mg/kg bw/day, dams showed decreases in food consumption and body weight gain (from day 9), body weight (from day 12), terminal body weight, and absolute weight gain. No foetal effects were reported in this study.

- In a rabbit prenatal developmental toxicity study (OECD TG 414; NZW rabbits 20F/dose) with 0, 100, 300, 1000 mg/kg bw/day (gavage) on GD 6–28: NOAELs were 1000 mg/kg bw/day for both maternal and developmental effects. At 300 mg/kg bw/day and above, decreases in food consumption and body weight gain were reported on GD 9–21, but not apparent by the end of treatment. Foetal weight reductions observed at these doses did not follow a dose related pattern, and hence they were considered secondary to the early stage of maternal effects.

Analogue(s):

TOTM (CIR 2015; REACHd; REACHf):

- In a rat 90 day feeding study (OECD TG 408; 4-week recovery; SD rats 10/sex/dose) with 0, 50, 225, 1000 mg/kg bw/day (see **Repeated Dose Toxicity**): no adverse effects were observed on oestrus cycle, spermatogenic cycle or morphology of testes.

- In a rat reproduction/developmental toxicity screening study (OECD TG 421; SD rats 12/sex/dose) with 0, 100, 300, 1000 mg/kg bw/day (gavage for approximately 46–63 days male–female): the reproductive/developmental NOAELs were 100 mg/kg bw/day for male rats and 1000 mg/kg bw/day for female rats and offspring. Spermatocytes and spermatids were decreased at 300 mg/kg bw/day and above. No other adverse effects were detected on fertility; reproductive organ weights of both sexes; body weights or autopsy findings of offspring (JECDB).

- In a rat prenatal developmental toxicity study (OECD TG 414; SD rats 20F or 15F/dose) with 0, 100, 500, 1050 mg/kg/day (gavage) on GD 6–19 or GD 6 to postnatal day (PND) 20: the maternal NOAEL was 1050 mg/kg bw/day. The developmental NOAEL was 500 mg/kg bw/day, based on a statistically significant transient increase in the number of male offspring with retained areolar regions on PND 13 at the high dose.

- In a study of foetal testosterone production (non-guideline; SD rats 3F/dose) with 0, 250, 500, 1000 mg/kg bw/day (gavage) on GD 14–18: TOTM at 1000 mg/kg bw/day did not reduce foetal testosterone production or maternal weight gain, compared with positive effects of DEHP at 100 mg/kg bw/day. Neither was reported to affect chemical foetal viability on GD 18 (Furr et al. 2014).

- In a study of transcriptional profiling to assess the potential of the chemical to induce foetal testicular maldevelopment (TMD) (non-guideline; Han Wistar rats 24F/dose) with 0, 500 mg/kg bw/day (gavage) on GD 12–19: TOTM at 500 mg/kg bw/day did not cause a significant repression of genes in the rat foetal testes associated with TMD (i.e. genes involved in cholesterol synthesis and transport, steroidogenesis and testes development). DEHP and mono(2-ethylhexyl) phthalate (MEHP) at 500 mg/kg bw/day induced testicular dysgenesis while 2-EH showed minor but statistically significant regression of some of the genes in the TMD pathway (Elcombe et al. 2012; EFSA 2019).

DOTM (CIR 2015; REACHb; REACHg):

- In a rat gavage prenatal developmental toxicity study (OECD TG 414; SD rats 24F/dose) with 0, 100, 300, 1000 mg/kg bw/day on gestation days (GD) 6–19: NOAELs were 300 mg/kg bw/day for maternal effects and 1000 mg/kg bw/day for developmental effects. At 1000 mg/kg bw/day, marked maternal toxicity was observed, including statistically significant decreases in food consumption, body weight gain (34–54% on GD 9–20), body weight (4–17% on GD 12–20), absolute weight gain (67%), and uterus weight (16%). Foetal toxicity included 12% decreases in foetal and litter weights, and a delay in skeletal ossification although these were considered secondary to the maternal toxicity.

Endocrine effects

Tri-n-octyl trimellitate: ECHA (2018) suggested that there are indications of an endocrine disrupting mode of action (MOA) from the 90 day repeated toxicity study. The evaluation noted that the terminal body weight decrease of 3% cannot alone explain the decreases in

the absolute weight of a hormone sensitive organ (uterus) at all doses (see **Reproductive/Developmental Toxicity** section).

Limited data are available for the structurally related long chain phthalates. Data on the oestrogenic or antiandrogenic potency of DINP are limited and equivocal. The exact mechanism of DINP effects on the male reproductive system cannot be determined, although DINP does appear to interfere with endocrine function. DINP was considered to be less potent than DEHP (NICNAS 2012).

Analogue(s):

TOTM: ECHA (2002a) indicated that while DEHP caused bias in the genes involved in the steroidogenesis and steroid metabolism pathways, TOTM caused bias in the genes involved in glucocorticoid signalling and androgen signalling under the conditions of the study (Elcombe et al. 2012). The authors of the study concluded that there are indications of one or more MOA related to endocrine disruption because such changes in genes expression have been reported in rats.

The CIR (2015) discussed the fact that TOTM exhibited estrogenic activity in both ERα (alpha) and ERβ (beta) indicated gene cell lines (ter Veld et al. 2006). However, the Panel considered that trialkyl trimellitates are not significantly absorbed through the skin and; hence, was not concerned with potential endocrine effects.

Human health risk characterisation

Public risk

- triethylhexyl phthalate (CAS No. 3319-31-1)
- tri(isodecyl, tridecyl) trimellitate (CAS No. 70225-05-7)
- tristridecyl trimellitate (CAS No. 94109-09-8)

In the Government of Canada (2019) screening assessment, margins of exposure (MOEs) for use of cosmetic products were derived by comparing estimated levels of general public exposure to these trimellitates with critical reproductive effect levels:

- the NOAEL of 100 mg/kg bw/day (assuming 100% oral absorption for lip products)
- an adjusted NOAEL of 36 mg/kg bw/day (assuming [100% − (75% × 85%)] = 36% oral absorption based on excretion data of TOTM, and 1% dermal absorption for other make-up and skin care cosmetics).

For a variety of products, MOEs were calculated in the range of 396–382979 for adults and 240–263158 for toddlers.

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