Draft Screening Assessment

Trimellitates Group

Chemical Abstract Service Registry Numbers
3319-31-1
70225-05-7
94109-09-8

Environment and Climate Change Canada
Health Canada

January 2018

Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment on three out of five substances referred to collectively under the Chemicals Management Plan as the Trimellitates Group. These three substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA. Two of the five substances were subsequently determined to be of low concern through other approaches, and proposed decisions for these substances are provided in a separate report.[1] Accordingly, this screening assessment addresses the three substances listed in the table below.

Substances in the Trimellitates Group

CAS RN[2]	***DSL* name**	**Common name (abbreviation)**
3319-31-1	1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester	Tris(2-ethylhexyl) trimellitate (TEHT)
70225-05-7	1,2,4-Benzenetricarboxylic acid, mixed branched tridecyl and isodecyl esters	Branched tridecyl and isodecyl trimellitate (BTIT)
94109-09-8	1,2,4-Benzenetricarboxylic acid, tritridecyl ester	Tristridecyl trimellitate (TTDT)

The trimellitates do not occur naturally in the environment. According to information reported in surveys under section 71 of CEPA, more than 10 million kg of TEHT was manufactured in Canada and between 1 000 000 and 10 000 000 kg was imported into Canada in 2011. In the same year, no Canadian manufacturing or importing activities were reported for BTIT above the reporting threshold of 100 kg. TTDT was imported into Canada in 2009 in quantities ranging from 1 000 to 10 000 kg but was not manufactured above the reporting threshold.

TEHT is used as a plasticizer in floor coverings, building and construction materials, plastic and rubber materials, and medical devices. It is also used as a fuel additive, in adhesives and sealants used in the transportation sector, as a lubricant and lubricant additive, and in cosmetics.

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[1] Proposed conclusions for CAS RNs 53894-23-8 and 68515-60-6 are provided in the Substances Identified as Being of Low Concern based on on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Draft Screening Assessment.

[2] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

BTIT is used in cosmetics in Canada. TTDT is primarily used in cosmetics but is also present as a non-medicinal ingredient in drugs, including natural health products. In addition to the uses listed above, TEHT and BTIT have been identified as ingredients of some incidental additives for use in food processing establishments in Canada.

The ecological risks of the substances in the Trimellitates Group were characterized using the ecological risk classification of organic substances (ERC) approach. The ERC is a risk-based approach that employs multiple metrics for both hazard and exposure with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are established primarily on the basis of metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. The ERC identified the three substances in Trimellitates Group as having low potential to cause ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from TEHT, BTIT and TTDT. It is proposed to conclude that TEHT, BTIT and TTDT do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

TEHT has been reviewed by the Organisation for Economic Cooperation and Development and the Cosmetic Ingredient Review Expert Panel. These reviews were used to inform the health effects characterization in this screening assessment. TEHT is not genotoxic and is not expected to be carcinogenic. The available health effects information on TEHT indicates potential effects on the male reproductive system.

A read-across approach was used in the absence of substance-specific data to inform the assessment of human health effects for BTIT and TTDT on the basis of structural, functional, and/or physical chemical similarity. TEHT and two other trimellitates were identified as analogues for this read-across analysis. As a conservative approach, the critical effect levels from TEHT, which has a shorter alkyl chain, are used for the risk characterization of the longer chain BTIT and TTDT.

The general population of Canada may be exposed to one or more of the trimellitates from dust and from use of products available to consumers, including cosmetics. A comparison of estimated levels of exposure to the trimellitates and critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that TEHT, BTIT and TTDT do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that TEHT, BTIT and TTDT do not meet any of the criteria set out in section 64 of CEPA.

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1. Introduction

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of three of five substances, referred to collectively under the Chemicals Management Plan as the Trimellitates Group, to determine whether they present or may present a risk to the environment or to human health. These three substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]). The three trimellitates in this group belong to a category of tri-esters of trimellitic acid, which share the same basic structure of 1,2,4-benzenetricarboxylic acid, but vary in side chain length or branched structure.

The other two substances (CAS RNs[3] 53894-23-8, 1,2,4-benzenetricarboxylic acid, triisononyl ester; 68515-60-6, 1,2,4-benzenetricarboxylic acid, tri-C7-9-branched and linear alkyl esters) were considered in the Ecological Risk Classification of Organic Substances (ERC) and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances science approach documents (ECCC 2016a; Health Canada 2016a) and were identified as being of low concern to both human health and the environment. As such, they are not further addressed in this report. Proposed conclusions for these two substances are provided in the Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Draft Screening Assessment Report (ECCC, HC 2017b). The 3 substances addressed in this screening assessment will hereinafter be referred to as the Trimellitates Group.

The ecological risks of the three substances in Trimellitates Group were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics, including mode of action, chemical reactivity, food-web derived internal toxicity threshold, bioavailability, and chemical and biological activity, and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of such factors as potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

[3] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

Tris(2-ethylexyl)benzene-1,2,4-tricarboxylate (CAS RN 3319-31-1, TEHT), one substance in the trimellitate group currently being evaluated, has been reviewed internationally through the Organisation for Economic Cooperation and Development (OECD) Cooperative Chemicals Assessment Programme, and an OECD Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) is available. These assessments undergo rigorous review (including peer-review) and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in this process and consider these assessments reliable. The OECD SIAR on TEHT is used to inform the health effects characterization in this screening assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to June 2017. Targeted literature searches were conducted up to May 2017. Empirical data from key studies as well as some results from models and read-across approaches were used to reach proposed conclusions.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external review and/or consultation. Comments on the technical portions relevant to human health were received from TetraTech Inc. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was peer-reviewed and subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

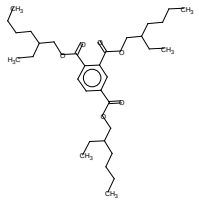
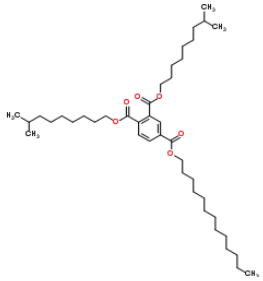
This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight–of-evidence approach and precaution.[4] This draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

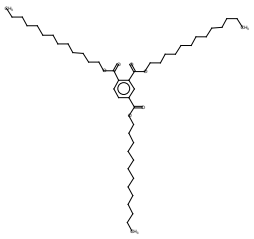
[4]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations* ~~and the *Controlled Products Regulations*~~, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

2. Identity of Substances

The CAS RN, *Domestic Substances List* (DSL) names, common names and/or abbreviations for the individual substances in the Trimellitates Group are presented in Table 2-1. There is some uncertainty regarding the use of common names and the associated CAS RNs. TEHT (CAS RN 3319-31-1) is often referred to as trioctyl trimellitate or TOTM, which is also a common name for CAS RN 89-04-3. CAS RN 89-04-3 is one of the analogues being used in this assessment. BTIT (CAS RN 70225-05-7) is often referred to as tridecyl trimellitate, which has also been linked to TTDT (CAS RN 94109-09-8). In this assessment, the common names and abbreviations listed in Table 2-1 will be used. A list of additional chemical names (e.g., trade names) is available from the National Chemical Inventories (NCI 2015).

Table 2-1. Substance identities

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
3319-31-1 (TEHT)	1,2,4-Benzenetricarboxylic acid, tris(2-ethylhexyl) ester (tris-(2-ethylhexyl)-trimellitate; triethylhexyl trimellitate)	 $C_{33}H_{54}O_6$	546.79
70225-05-7 (BTIT)	1,2,4-Benzenetricarboxylic acid, mixed branched tridecyl and isodecyl esters (Branched tridecyl and isodecyl trimellitate; Triisodecyl tridecyl trimellitic ester)	 (UVCB, representative structure)	673.02

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
94109-09-8 (TTDT)	1,2,4-Benzenetricarboxylic acid, tritridecyl ester (Tristridecyl trimellitate)	 $C_{48}H_{84}O_6$	757.19

Abbreviations: UVCB, unknown or variable composition, complex reaction products and biological materials

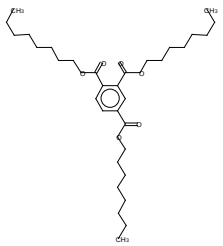
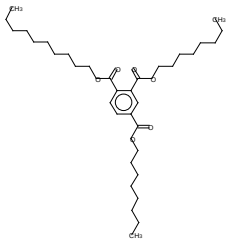
2.1 Selection of Analogues and Use of (Q)SAR Models

The trimellitates are structurally related and belong to a category of tri-esters of trimellitic acid, which share the same basic structure of 1,2,4-benzenetricarboxylic acid, but vary in side chain length or branched structure. Among the three trimellitates, TEHT has been evaluated by two organizations (OECD 2002a; CIR 2015), and sufficient empirical data are available for hazard characterization. However, limited empirical hazard data are available for the other two chemicals and their physical-chemical properties were obtained from appropriate (Q)SAR models.

A read-across approach using data from analogues, where appropriate, has been used to inform the human health hazard assessments of BTIT and TTDT. Analogues are selected in terms of structural and/or functional similarity and hazard data availability. TEHT, one member of the group of trimellitates in this assessment, was identified as the primary analogue for the hazard evaluation of the other two trimellitates (BTIT and TTDT) through a category read-across approach (SRC 2016). This primary analogue (TEHT) has branched side chains with 8 carbons, whereas one target chemical, BTIT, has mixed branched side chains with 10 or 13 carbons, and the other, TTDT, has linear and longer side chains with 13 carbons. Because of the difference in side chain length and linearity, two other analogues, 1,2,4-benzenetricarboxylic acid, 1,2,4-trioctyl ester (CAS RN 89-04-3, TOTM) and 1,2,4-benzenetricarboxylic acid, mixed decyl and octyl triesters (CAS RN 90218-76-1, MDOT), were also selected and included to inform this read-across. More details of the read-across approach are discussed in section 6.2. Information on the identities and chemical structures of the two additional analogues is presented in Table 2-2.

Table 2-2. Analogue identities[1] for hazard assessment

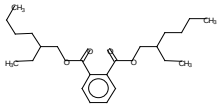
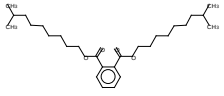
CAS RN (abbreviation)	DSL or other name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)

89-04-3 (TOTM)	1,2,4-Benzene-tricarboxylic acid, 1,2,4-trioctyl ester (Trioctyl trimellitate)	 $C_{33}H_{54}O_6$	546.87
90218-76-1 (MDOT)	1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters	 (UVCB, representative structure)	602.9

[1] TEHT is identified as the primary analogue, and its identity is shown in Table 2-1.

With respect to the exposure assessment, as limited data on dermal absorption was available for the trimellitates and no data were available from the analogues in Table 2-2, dermal absorption data for certain phthalates (DEHP, DIDP) were used.

Table 2-3. Analogue identities for exposure assessment

CAS RN (abbreviation)	DSL or other name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
117-81-7 (DEHP)	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester	 $C_{24}H_{38}O_4$	390.6
26761-40-0 (DIDP)	1,2-Benzenedicarboxylic acid, diisodecyl ester	 $C_{28}H_{46}O_4$	446.7

3. Physical and Chemical Properties

A summary of physical and chemical properties of the substances in the Trimellitates Group is presented in Table 3-1. Measured data were only available for TEHT; therefore modelling using EPI Suite (c2000-2012) was also used to estimate the physical and chemical properties for these substances. The trimellitates are large, hydrophobic compounds that can form emulsions or micelles in water similar to DEHP and other phthalates (Environment Canada, Health Canada 1994; Environment Canada 2004/2005; Jonker 2016). This complicates the experimental determination of water solubility and octanol-water partition coefficients and results in a wide range of measured values as well as a large discrepancy between measured and estimated parameters, as seen in Table 3-1 (Letinski et al. 2002; Staples et al. 1997; Jonker 2016). Most of the measured water solubilities and octanol-water partition coefficients for TEHT were derived using the shake-flask method, which is now considered inappropriate for hydrophobic compounds (Jonker 2016; Staples et al. 1997; Letinski et al. 2002). Therefore, the estimated values for water solubility and octanol-water partition coefficient or values derived using the slow-stir method will be used in determining the fate and exposure to these substances. Additional physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Physical and chemical property values (at standard temperature) for the trimellitates

Property	TEHT	BTIT	TTDT	Key reference(s)
Physical state	liquid	liquid	liquid	US EPA 2009, AGDH 2013
Vapour pressure (Pa)	5.25E-09 – 5.9E-08	7.36E-13	1.08E-15	PhysProp c2013, US EPA 2009, EPI Suite c2000-2012
Henry's law constant ($Pa \cdot m^3/mol$)	0.045 – 0.056	7.08E-6	3.88E-5	PhysProp c2013, OECD 2002, US EPA 2009, EPI Suite c2000-2012

Property	TEHT	BTIT	TTDT	Key reference(s)
Water solubility (mg/L) [measured data]	**0.003 [3.9E-04 - 100][a]**	NA	NA	OECD 2002, US EPA 2009, ECHA c2007-2017a, PhysProp c2013,
Water solubility (mg/L) [estimated]	4.5E-8	9.73E-13	6.09E-16	EPI Suite c2000-2012
Log K_{ow} (dimensionless) [measured]	**8 [4.35 – 5.94][a]**	NA	NA	ECHA c2007-2017a, OECD 2002, US EPA 2009
Log K_{ow} (dimensionless) [estimated]	8.81 – 12.25	> 10	> 10	OECD 2002, US EPA 2009, EPI Suite c2000-2012, Sakuratani et al. 2007
Log K_{oc} (dimensionless) [estimated]	7.20 – 7.83	9.69 – 10.17	11.40 – 11.84	EPI Suite c2000-2012

Measured data in bold text. Abbreviations: NA, not available; K_{ow}, octanol–water partition coefficient; K_{oc}, octanol-carbon partition coefficient (soil adsorption coefficient).
[a] Measured using shake-flask method.

4. Sources and Uses

The trimellitates do not occur naturally but are commercially produced.

The substances in the Trimellitates Group have been included in surveys issued pursuant to CEPA section 71 surveys (Canada 2009, 2013). Table 4-1 presents a summary of information on the total manufacture and total import quantities for the trimellitates.

Table 4-1. Summary of information on Canadian manufacturing and imports of the trimellitates submitted pursuant to CEPA section 71 surveys

Abbreviation	Total manufacture (kg)	Total imports[a] (kg)	Reporting year	Survey reference
TEHT	Over 10 million	1 000 000 – 10 000 000	2011	Environment Canada 2013
BTIT	< 100 kg	< 100 kg	2011	Environment Canada 2013
TTDT	< 100 kg	1 000 – 10 000	2008	Environment Canada 2009

[a] Values reflect quantities reported in response to the surveys conducted under section 71 of CEPA (Canada 2009, 2013). See surveys for specific inclusions and exclusions (schedules 2 and 3).

TEHT is manufactured in Canada and is used as a plasticizer in floor coverings, building and construction materials, plastic and rubber materials, and medical devices. This substance is also imported into Canada as a fuel additive in fuels and related products, in adhesives and sealants used in the transportation sector, as a lubricant and lubricant additive in lubricants and greases, and as a plasticizer (Environment Canada 2013). Globally, TEHT is primarily manufactured as a plasticizer for polyvinyl chloride (PVC) products, especially for flexible applications such as heat resistant wires and cabling (OECD 2002). It is also used in automotive parts, heat-resistant hoses and tubes, insulation tape, and medical devices, including blood bags, infusion sets, catheters, and hemodialysis tubing (OECD 2002; CIR 2015). TEHT can also be used in PVC articles including toys and floor/wall coverings (Biedermann-Brem et al. 2008; Bui et al. 2016).

BTIT is not manufactured or imported into Canada above the reporting threshold (Environment Canada 2013). In Europe, BTIT is manufactured and/or imported in quantities ranging from 100 to 1000 tonnes per year, and is reportedly used in adhesives and sealants, heat transfer fluids, hydraulic fluids, lubricants and greases, and polishes and waxes, as well as in the manufacture of other chemicals (ECHA c2007-2017c). BTIT is used in industrial processing of lubricant and lubricant additives, commercial/consumer personal care products, and lubricants and greases (US CDR 2012).

TTDT is imported into Canada and used as a skin conditioning agent, a solvent and a viscosity adjustor in the cosmetics sector (Environment Canada 2009). TTDT does not appear to be manufactured or imported in the United States or Europe according to the US Chemical Data Reporting database (CDR 2012) and ECHA's registration dossiers (ECHA c2007-2017a).

Table 4-2 presents a summary of additional Canadian uses. In Canada, only TEHT and BTIT have been identified as an ingredient of some incidental additives for use in food processing establishments but only where there is no direct contact with food. None of the trimellitates in this grouping, including TEHT, have been identified for use in food packaging applications (personal communication, email from Food Directorate, Health

Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated September 26, 2016; unreferenced). In 2016, the US Food and Drug Administration (FDA) approved TEHT for use as a plasticizer in repeated-use food contact vinyl chloride polymers at a concentration up to 30% by weight, except for use with infant formula and breast milk (US FDA 2016).

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, TEHT, BTIT[5] and TTDT are used in certain cosmetic products in Canada, such as face and body moisturizers, 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 (personal communication, email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated October 5, 2016; unreferenced).

TTDT is a non-medicinal ingredient in natural and non-prescription health products, such as face moisturizers, make-up and lipsticks associated with a sun protection factor (SPF), acne treatment products, and pain relief creams (personal communication, email from Therapeutic Products Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated September 28, 2016; unreferenced).

[5] The CAS RN associated with BTIT (70225-05-7) has no specific International Nomenclature of Cosmetic Ingredients (INCI) name. However, based on a comparison of chemical names and structures, the following INCI names could be linked to BTIT: triisodecyl trimellitate (CAS RN 36631-30-8) and triisotridecyl trimellitate (CAS RN 72361-35-4). In this assessment, it is assumed that cosmetics that were listed under these two INCI names could be BTIT (personal communication, email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated December 1, 2016; unreferenced). In addition, CAS RN 70225-05-7 is often associated with the common name tridecyl trimellitate which is linked to several cosmetic products in the Skin Deep Database (EWG c2007-2017) as well as the Household Products Database (2016).

Table 4-2. Additional uses in Canada for each of the substances in the Trimellitates Group

Use	TEHT	BTIT	TTDT
Food additive[a]	N	N	N
Food packaging materials[b]	N	N	N
Incidental additives[b]	Y	Y	
Internal Drug Product Database as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products in Canada[c]	N	N	Y, as non-medicinal ingredient in topical products
Natural Health Products Ingredients Database[d]	N	N	Y, with a non-medicinal ingredient role for topical use as skin-conditioning agent
Licensed Natural Health Products Database as medicinal or non-medicinal ingredients in natural health products in Canada[e]	N	N	Y, as non-medicinal ingredient in topical products
List of Prohibited and Restricted Cosmetic Ingredients[f]	N	N	N
Notified to be present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* to Health Canada[g]	Y	Y	Y
Formulant in pest control products registered in Canada[h]	N[i]	N	N[i]

Abbreviations: Y, yes; N, no

[a] Personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced

[b] Personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced

[c] DPD [modified 2016]

[d] NHPID [modified 2017]

[e] LNHPD [modified 2016]

[f] Health Canada [modified 2015]

[g] Personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016, 2017; unreferenced

[h] Personal communications, emails from Pest Management Regulatory Agency, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016; unreferenced

[i] TEHT and TTDT can be used as formulants in pest control products in Canada; however, they are currently not registered in any products (personal communication, e-mail from Pest Management Regulatory Agency to Existing Substances Risk Assessment Bureau, Health Canada, dated September 23, 2016; unreferenced).

BTIT was previously used in two stainless steel cleaners in the United States. However, according to a product survey conducted by the American Cleaning Institute (ACI) in 2016, none of the 1060 cleaning products examined contained BTIT (tridecyl

trimellitate). To determine the availability of this substance in the Canadian market for this product class, information was sought from the Canadian Consumer Specialty Products Association (CCSPA). CCSPA surveyed its members and reported back that none of the trimellitates in this assessment are present in CCSPA member household cleaning products in Canada (personal communication, emails from the Canadian Consumer Specialty Products Association to Existing Substances Risk Assessment Bureau, Health Canada, dated April-May 2017; unreferenced). Therefore, exposure of the Canadian general public to TEHT, BTIT and TTDT from use of household cleaning products is not expected.

5. Potential to Cause Ecological Harm

5.1 Characterization of Ecological Risk

The ecological risks of substances in the Trimellitates Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that employs multiple metrics for both hazard and exposure with weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., LC_{50}) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and from responses to surveys conducted under section 71 of CEPA, or they were generated using selected quantitative structure-activity relationship (QSAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were established primarily on the basis of metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also based on multiple metrics, including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate, or high classification of potential risk for each substance on the basis of its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances that had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios, designed to be protective of the environment, in order to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over- and under-classification of hazard, exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016a. The following describes two of the more substantial areas of uncertainty. Error in empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from QSAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue used for critical body residue (CBR) analysis. Error in underestimation of acute toxicity will be mitigated through the use of other hazard metrics, such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada considering what is believed to be the current use quantity and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the three substances in the Trimellitates Group and the hazard, exposure and risk classification results are presented in ECCC (2016b).

The hazard and exposure classifications for the three substances in the Trimellitates Group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the three substances in the Trimellitates Group

Common Name	ERC hazard classification	ERC exposure classification	ERC risk classification
TEHT	low	low	low
BTIT	low	low	low
TTDT	low	low	low

On the basis of low hazard and low exposure classifications according to ERC for TEHT, BTIT and TTDT, these substances were classified as having a low potential for ecological risk. It is unlikely that these substances result in concerns for organisms or the broader integrity of the environment in Canada.

6. Potential to Cause Harm to Human Health

6.1 Exposure Assessment

Environmental media and food

These substances do not occur in nature. Only empirical data on the presence of TEHT in dust was identified. However, given the very low water solubility, very low vapour

pressure and high log K_{ow}, these substances are not expected to be found in air or water. Considering the high estimated log K_{oc}, these substances are expected to adsorb to suspended solids and sediments in water and would have low mobility in soil (US EPA 2009; HSDB 1983-).

TEHT was identified in 14 household dust samples from a Quebec City field study conducted in homes of children with asthma. The concentrations of TEHT ranged from 2.61 to 553.54 mg/kg [µg/g], with a geometric mean of 21.43±3.70 mg/kg [µg/g] (Won and Lusztyk 2011). The geometric mean concentrations of TEHT in house dust from three separate studies conducted in Germany between 2001 and 2009 ranged from 1.6 to 2.1 mg/kg, with maximum concentrations ranging from 22 to 120 mg/kg (Nagorka et al. 2011). In 2011 and 2012, TEHT was detected in 63 dust samples from daycare centres located in Germany, with concentrations ranging from less than the limit of quantification (13 mg/kg) to 107 mg/kg (Fromme et al. 2016). TEHT was not detected (limit of detection of 5 to 10 ng/m^3) in any of the 43 indoor air samples that were collected from these daycare centres (Fromme et al. 2016). The maximum concentration of TEHT in household dust from the study conducted in Quebec City was used to estimate exposures to the general population. Given current use patterns and quantities in Canada, TTDT and BTIT are not expected to be found in dust or other environmental media.

Stuer-Lauridsen et al. (2001) conducted an environmental and health assessment of various alternative plasticizers used in Denmark, including TEHT. Estimated regional concentrations of TEHT in water (4E-5 mg/L), air (8E-6 mg/m^3), soil (1E-9 to 5E-7 mg/kg) and sediment (5.4E-3 mg/kg) were based on worst-case releases into the Danish environment using the European Union System for the Evaluation of Substances (EUSES) model. This “worst-case” scenario assumed that 100% of all phthalates would be replaced by TEHT in PVC production in Denmark, resulting in an input of 10,700 tonnes (10,700,000 kg) of TEHT being used in the EUSES model (Stuer-Lauridsen et al. 2001). Estimated “worst-case” concentrations of TEHT were also derived for fish (0.037 mg/kg), meat (9E-7 mg/kg wet weight), and milk (3E-7 mg/kg wet weight), using estimated values for partitioning and degradation.

A study conducted in Spain on the use of plasticizers in printing inks in certain food packaging detected TEHT in the packaging of chocolate bars, dried fruits, biscuits, confectionery, and snacks. However, the study did not examine the potential migration of TEHT into these pre-packaged foods (Nerín et al. 1993). Hamdani and Feigenbaum (1996) investigated the use of isooctane and ethanol as potential fatty simulants in food packaging migration tests compared to the use of sunflower oil. The potential migration of TEHT from polyvinyl chloride (PVC) packaging to food simulants was measured in all three simulants and ranged from 450 mg/dm^2 for ethanol to 1400 mg/dm^2 for isooctane at 40°C after 3 days, which translates to 49% to 94% of the TEHT found in the PVC (27.5%) (Hamdani and Feigenbaum 1996). In Canada, none of the trimellitates in this group are used in food packaging applications (personal communication, e-mail from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated September 26, 2016; unreferenced).

No occurrence data for trimellitates in food were identified in Canada or elsewhere. For the purposes of this assessment, worst-case dietary intakes of TEHT for the general population of Canada were estimated on the basis of modelled concentrations in some food categories identified in the Danish report (Stuer-Lauridsen et al. 2001). This dietary exposure assessment is considered to be very conservative and is not expected to be representative of actual exposures of Canadians.

Exposure estimates for TEHT for the general population of Canada from environmental media and food using information from Won and Lusztyk (2011) and Stuer-Lauridsen et al. (2001), respectively, ranged from 0.06 µg/kg-bw per day for adults older than 60 years old to 2.8 µg/kg-bw per day for infants 0 to 6 months of age (see Appendix A).

No information or data on levels of TTDT and BTIT in environmental media and food were identified. A comparison of physical and chemical properties and current use patterns suggests that exposure of the general population of Canada to TTDT and BTIT is likely less than that estimated for TEHT. Therefore, exposure to TTDT and BTIT in environmental media and food is not considered further.

Products available to consumers

Cosmetics and drugs including natural health products

All three trimellitates in this group are present in cosmetics, primarily as emollients and skin conditioning agents. TTDT is also a non-medicinal ingredient in natural and non-prescription health products (personal communication, email from Natural and Non-Prescription Health Products Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated September 26, 2016; unreferenced).

Dermal and oral exposure estimates were only derived for the sentinel scenarios (lip products, body and face moisturizers, facial make-up, manicure preparation creams and massage oil) and are presented in Table 6-1 (daily use products) and Table 6-2 (per event estimates for products used less than once a day). These estimates are also considered to account for any exposures from non-prescription drugs and natural health products since these are very similar to the cosmetics (e.g., facial cleansers, make-up, and moisturizers). Only exposure estimates for adults and toddlers are shown; however, they represent the range of potential exposures for all age groups. Exposures via inhalation were not considered, given the very low vapour pressures for these three substances (5.9E-8 to 7.36E-13 Pa, see Table 3-1). Details on the method and parameters used to estimate dermal and oral exposures to cosmetics are available in Appendix B.

Table 6-1. Daily exposure estimates from use of cosmetics for adults and toddlers for the trimellitates

Substance	Exposure scenario	Concentration range	Adult exposure estimate (mg/kg-bw/day)	Toddler exposure estimate (mg/kg-bw/day)
TEHT, TTDT, or BTIT	Lip products[a]	0.1 – 74% [0.1 – 30% for toddlers]	0.00034 – 0.25	0.00038 – 0.11
TTDT or BTIT	Body moisturizer[b]	0.1 – 10%	0.00068 – 0.068	0.0015 – 0.15
TEHT, TTDT, or BTIT	Face moisturizer[b]	0.1 – 30%	0.0003 – 0.091	N/A
TEHT, TTDT, or BTIT	Facial make-up[b]	0.1 – 60%	9.4E-05 – 0.057	N/A

Abbreviations: bw, body weight; N/A, not applicable.
[a] Oral exposure estimates for lip products assuming all of the product is ingested.
[b] Dermal exposure estimates assuming 1% of chemical applied to the skin is absorbed.

Table 6-2. Per event exposure estimates from use of cosmetics for adults for the trimellitates

Substance	Exposure scenario	Concentration range	Adult exposure estimate (mg/kg-bw/event)
TTDT or BTIT	Manicure preparation creams[a,b]	3 – 30%	0.0072 – 0.072
TTDT or BTIT	Massage oil[a,b]	3 – 35%	0.014 – 0.16

Abbreviations: bw, body weight.
[a] Dermal exposure estimates assuming 1% of chemical applied to the skin is absorbed.

For the dermal exposure estimates, a dermal absorption of 1%, based on several lines of evidence, was used. Limited data were available on the potential dermal absorption for the three substances in the Trimellitates Group. Only two in vitro skin absorption studies were identified for TEHT (Pan et al., 2014; Mielke et al. 2015 [abstract only]). Pan et al. (2014) conducted an in vitro skin absorption study of TEHT using full-thickness excised skin from nude mice and pigs, analyzed using Franz diffusion cells. No flux was demonstrated after 12 hours for both the nude mice and pig skins (Pan et al. 2014). Mielke et al. (2015) conducted an in vitro skin penetration study using Franz diffusion cells and various skin models including pig, human, and artificial skin. The authors examined the penetration of TEHT using Fourier transform infrared spectroscopy (FTIR) and showed that TEHT was capable of penetrating the porcine

skin after 24 hours. However, no further information was provided (Mielke et al. 2015 [abstract only]). These two studies show that TEHT can penetrate the skin but did not provide sufficient information to derive a dermal absorption value. Therefore, given that the trimellitates are structurally similar to the phthalates and have similar uses, dermal absorption data from certain phthalates was considered to read across to the trimellitates.

Two studies on dermal absorption of phthalates were used to estimate dermal absorption for the trimellitates. Wester et al. (1998) reported that 1.8 ± 0.5% DEHP was dermally absorbed after 24 hours in an in vivo human study conducted on 6 adult participants. In an in vivo study in rats, the dermal absorption of DIDP, a larger phthalate, was determined to be 1% (Elsisi et al. 1989), and it has been shown that human skin is less permeable than other mammals, including rats (Mint and Hotchkiss 1993; Mint et al. 1994; Wester et al. 1998). Since the trimellitates are larger and more lipophilic than DEHP and DIDP (higher molecular weights and log K_{ow}, lower water solubility), it is unlikely that the dermal absorption of TEHT, BTIT and TTDT would exceed 1%.

The exposure estimates in Table 6-1 and Table 6-2 were used to characterize risk for all three trimellitates in this group.

Children's products

No information was identified on TTDT and BTIT in any children's products in Canada or elsewhere. However, TEHT has been measured in children's products found in Europe. One study examined the presence of TEHT and other phthalate alternative plasticizers in 172 toys and childcare articles, including sandals (252 samples) purchased in Germany, Switzerland and Austria in 2008 (Biedermann-Brem et al. 2008). TEHT was observed in 3 of the samples (2 dolls and 1 toy), with concentrations ranging from 13% to 30% w/w with a mean of 20% w/w (Biedermann-Brem et al. 2008). In Canada, the Product Safety Laboratory of Health Canada analyzed 118 samples of plastic consumer products intended for children for phthalates in 2014 using FTIR and gas chromatography mass spectrometry. All samples were also analyzed in scan mode to identify any non-phthalate plasticizers (no quantification), including TEHT. None of the samples contained TEHT (personal communication, email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated March 3, 2016; unreferenced). Considering this Canadian information, exposure to TEHT from mouthing of plastic toys is not expected

TTDT and BTIT have not been identified in any children's toys in Canada or elsewhere and are not used as plasticizers. Therefore, exposure to TTDT and BTIT from children's toys is not expected.

6.2 Health Effects Assessment

6.2.1 TEHT

TEHT has been reviewed by OECD (2002a) and CIR (2015). Those reviews provide a basis for the health effect characterization in this draft screening assessment. A literature search was conducted from one year prior to the OECD publication up to April 2017 and significant new information is included in this health effects assessment.

Toxicokinetics

The toxicokinetics of TEHT is summarized in OECD (2002a) and CIR (2015). In male Sprague Dawley (SD) rats administered a single dose of 100 mg/kg bw TEHT (^{14}C-labeled) by oral gavage after 144 hours, about 75% of the dose was excreted in the feces, 16% in the urine as metabolites and 1.9% as expired $^{14}CO_2$. In the feces, the radioactivity was excreted as unchanged TEHT (85%), di-(2-ethylhexyl)trimellitate (7%), mono-(2-ethylhexyl)trimellitate (1%) and unidentified polar metabolites. Less than 0.6% of the radioactivity remained in the tissues, which suggests that the accumulation of this substance is low (Eastman Kodak 1984; reviewed in OECD 2002a; CIR 2015).

Carcinogenicity and genotoxicity

In a report of one study in a strain of mice with a propensity to form pulmonary adenomas, there were no increases in the incidence of tumours in animals exposed to TEHT, but no further details were provided (OECD 2002a). Although structural alerts for carcinogenicity were identified in QSAR modelling (Derek Nexus), this alert was associated with peroxisome proliferation, which has been observed in rats. However, given the low relevance of this mode of action for tumour development in humans, TEHT should be considered negative for carcinogenicity in humans (ECHA c2007-2017a). In addition, molecular modelling (SYBYL V6.9.1) indicated that TEHT was not able to bind to human peroxisome proliferator-activated receptors (PPARs) (Kambia et al. 2008).

TEHT was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537, with or without S9 metabolic activation. In mammalian cells, TEHT did not cause gene mutation in either a mouse lymphoma L5178Y tk+/- assay or a Chinese hamster ovary/hprt assay, with or without metabolic activation. TEHT did not cause chromosomal aberrations in human lymphocytes or Chinese hamster lung fibroblast cells (V79). Likewise, it did not cause an increase in unscheduled DNA synthesis in primary rat hepatocytes (OECD 2002a; CIR 2015; AGDH 2017).

TEHT was not mutagenic in an *in vivo* rodent dominant lethal assay in male Swiss mice (AGDH 2017). In addition, urine from rats dosed with TEHT was not mutagenic in the Ames test, suggesting that no significant mutagenic metabolites were excreted in the urine by rats (Divincenzo et al. 1985; reviewed in CIR 2015 and AGDH 2017).

On the basis of the available *in vitro* and *in vivo* genotoxicity studies, TEHT is not considered to be genotoxic.

Repeated dose toxicity

Several subchronic oral toxicity studies were conducted and no-observed-adverse-effect levels (NOAELs) were derived. No repeated dose toxicity study was available for TEHT by either dermal or inhalation exposure.

In a 28-day oral study with SD rats (5 animals/sex/dose) administered TEHT by gavage at 0, 100, 300, or 1000 mg/kg-bw/day, no chemical-related changes were observed in terms of clinical signs, or hematological, biochemical and histopathological effects (OECD 2002a).

In a 28-day oral study with Fischer 344 rats (5 animals/sex/dose) administered TEHT via diet at 0%, 0.2%, 0.67% or 2% (equivalent to 0, 184, 650 and 1826 mg/kg- bw/day), no chemical-related mortalities were observed at any dose level. At 650 mg/kg-bw/day and above, there were statistically significant decreases in hemoglobin and increases in leucocyte counts, serum cholesterol and liver weight. The observed increases of liver palmitoyl CoA oxidation and catalase activity suggest the induction of peroxisome proliferation at high doses. No dose-related histopathological changes were seen in any treated group. The NOAEL for repeated dose oral toxicity is considered to be 184 mg/kg-bw/day, on the basis of effects on hematological parameters and liver weight at 650 mg/kg-bw/day (OECD 2002a).

In a subchronic oral study conducted in accordance with OECD test guideline 408, SD rats (10 animals/sex/dose) were administered TEHT in the diet at doses equivalent to 0, 50, 225 or 1000 mg/kg-bw/day for 90 days. There were no significant changes in clinical signs, mortality, body weight, or food consumption. At the highest dose, statistically significant changes in hematological parameters (increases in platelet counts and neutrophils or decreases in erythrocytes, haemoglobin and haematocrit) were reported in male or female rats. Significant increases (>10%) in liver weights (absolute and relative) were observed in both male and female rats, even at the end of recovery; decreases in spleen weights (absolute and relative) were also seen in male rats at the highest dose. The histopathological examination revealed diffused hepatocytic hypertrophy in liver and an increased incidence of extramedullary haematopoiesis in spleen. No treatment-related effects were seen in estrous cycle or spermatogenic cycle. Some changes in clinical chemistry, including alkaline phosphatase (ALT), γ-glutamyl transferase and cholesterol, were also observed at the middle dose but they returned to levels similar to controls during the recovery phase. Overall, the NOAEL was determined to be 225 mg/kg-bw/day on the basis of hematological changes and increases in liver weight (ECHA c-2007-2017a).

The results of the 28-day and 90-day studies in rats via the diet are considered collectively in selection of the critical effect level for repeated dose toxicity given the similar nature of the effects identified in both studies (i.e., hematological changes and increases in liver weights). Although a NOAEL of 184 mg/kg-bw/day was established in the 28-day study, the higher NOAEL (225 mg/kg-bw/day) from the 90-day study is selected as the critical effect level for hazard characterization of the repeated dose toxicity, as it is based on a more comprehensive study protocol (OECD test guideline protocol) of longer duration and is identified as the highest dose without observed

adverse effects in this database, but still below the LOAEL of 650 mg/kg-bw/day from the 28-day study.

Reproductive and developmental toxicity

A reproductive/developmental toxicity screening test on TEHT was performed according to OECD TG 421. A group of SD rats (12/sex/dose) were dosed with TEHT at 0, 100, 300 or 1000 mg/kg-bw/day by gavage. Male rats were treated 14 days before mating (total 46 days), while female rats were also dosed from 14 days before mating through day 3 of lactation. There were no mortalities, clinical signs of toxicity, or effects on body weight, food consumption, organ weights or gross pathology. There were also no effects on male or female fertility or fetal development following treatment with TEHT at all doses. No histological changes in the ovaries of treated females were detected. Thus, reproductive toxicity in females and developmental toxicity was not seen at the doses up to 1000 mg/kg-bw/day. In male rats, histopathological examination of testes revealed slight decreases in numbers of spermatids at stage I-VI of the spermatozoa formative cycle at 300 mg/kg-bw/day and decreases in numbers of spermatocytes and spermatids and/or other parameters at all stages at 1000 mg/kg/day. On the basis of the testicular toxicity, a NOAEL for reproductive toxicity in males was considered to be 100 mg/kg-bw/day (OECD 2002a; CIR 2015). However, it should be noted that no effects on reproductive performance was observed and that the original study authors considered 100 mg/kg-bw/day to be a no-observed effect level (NOEL) (OECD 2002b).

In another study, pregnant SD rats were treated with TEHT at 0, 100, 500 or 1050 mg/kg-bw/day by gavage on gestation days (GD) 6 to 19 (prenatal development) (20/group) or on GD 6 through lactation day 20 (post-natal development) (15/group). No significant effects were seen on body weight, gravid uterus weight, number of implantations, post-implantation loss, gestation length and index, or live litter size. No significant differences were observed in fetal body weights, variations or malformations of external appearance, viscera, skeletal system or anogenital distance of pups. A higher incidence of displaced testes in fetuses was reported in the high dose group; however, the value was within the range of historical control (ECHA c2007-2017a; AGDH 2017). Thus, maternal and developmental toxicity was not seen at the tested doses of up to 1050 mg/kg-bw/day.

In a short-term in vivo screening test, pregnant rats were dosed up to 1000 mg/kg-bw/day from GD 14 to 18, and fetal testis testosterone production (T Prod, a key event in the phthalate adverse outcome pathway) was measured. TEHT exposure did not affect fetal testis testosterone production (Furr et al. 2014).

6.2.2 BTIT and TTDT

There are limited empirical hazard data available for TTDT and no empirical data available for BTIT. The only acute toxicity study for TTDT indicated an oral LD_{50} of greater than 5000 mg/kg-bw in Wistar-derived albino mice (AGDH 2013). In light of the paucity of data on TTDT and BTIT, a read-across approach was used to characterize

the health effects of these substances, incorporating data from two other analogues, namely TOTM and MDOT.

A combined repeated dose and reproductive/developmental toxicity screening test on TOTM was performed according to OECD TG 422. Groups of SD rats (13/sex/dose) were dosed with TOTM at 0, 30, 125 or 500 mg/kg-bw/day by gavage. Male rats were treated 14 days before mating (total 42 days), while female rats were exposed from 14 days before mating through day 4 of lactation. One female rat died at 500 mg/kg-bw/day on GD 23. Increased liver weight and reduced red blood cell count were observed in female rats at 125 and 500 mg/kg-bw/day; decreased testes weight was also observed at 125 mg/kg-bw/day in male rats but not at 500 mg/kg-bw/day. The NOAEL for parental toxicity (repeated oral) is considered to be 30 mg/kg-bw/day. In the F1 generation, no adverse effects were observed on pup weight, sex ratio, survival index or viability index at doses up to 500 mg/kg-bw/day (ECHA 2007-2017c; SRC 2016).

In a 28-day oral study with SD rats (5 male/5 female animals), administered MDOT by gavage at doses of 0, 100, 300 or 1000 mg/kg- bw/day), a statistically significant increase in leucocytosis and a significant increase in absolute and relative liver weights were observed in male and female rats at the highest dose. Increased ALT, γ-glutamyl transferase and decreased bilirubin, protein and sodium were also noted in males and females dosed with 1000 mg/kg- bw/day. The observed effects were reversible over a 2-week recovery period in the highest-dose animals. A NO(A)EL of 300 mg/kg- bw/day was derived on the basis of the effects on hematology, clinical chemistry and organ weights (ECHA c2007-2017d; SRC 2016).

A prenatal developmental toxicity study on MDOT was performed according to OECD test guideline (TG 414). Groups of mated female SD rats (24/dose) were dosed with MDOT at 0, 100, 300 or 1000 mg/kg/day by gavage over GD 6 to 19. Maternal effects such as decreased body weight, body weight gain and absolute weight gain as well as decreased gravid uterus weight and food consumption were observed at the highest dose. A NOAEL of 300 mg/kg/day is considered for maternal toxicity. Decreased fetal weight and litter weight, delayed ossification and visceral malformations were observed in mid- and high-dose fetuses; however, the incidence of the malformations was low and not dose-related. The developmental toxicity was not seen at the doses up to 1000 mg/kg/day (ECHA c2007-2017d; SRC 2016).

Both analogues TOTM and MDOT were not genotoxic. The available critical physical-chemical and toxicological data of the analogues are summarized in Appendix C.

Read-across for hazard characterization

A category-based read-across approach is used to identify critical effects and critical effect levels for risk characterization for TTDT and BTIT from the available data of the three analogues (SRC 2016)**.**

The trimellitate esters are a structurally homogenous group of chemicals. All chemicals in this group are tri-esters of 1,2,4-benzenetricarboxylic acid and aliphatic alcohols containing eight or more carbon atoms. All of the chemicals are hydrophobic and non-volatile, and the concurrence of their physicochemical properties supports the expectation that they will have the same relatively low bioavailability, absorption, and rates of metabolism and elimination. No differences in structure, functionality, or electronic influences are present, which suggests deviations in their primary metabolic pathways are unlikely. There are no steric or electronic differences in their chemical structures to suggest significant differences in the chemical reactivity or biological activity of these esters relative to the toxicological endpoints.

Given their similarities in chemical structure, physical-chemical properties, potential metabolism and mechanism of action, the group of trimellitates may share similar biological activities. TEHT is identified as the primary analogue for BTIT and TTDT to fill the data gaps on repeated dose toxicity, reproductive/developmental toxicity, genotoxicity and carcinogenicity. TOTM and MDOT are also identified as analogues to support the read-across analysis. BTIT and TTDT have higher molecular weight and bulky side chains, higher log K_{ow} and lower water solubility (from model predictions) than the three analogues and are thus expected to have less bioavailability and lower toxicity. It is therefore considered conservative to use the toxicity data from TEHT to represent the potential hazard of other members in this group.

Male reproductive toxicity is identified as the critical effect of trimellitates. A NO(A)EL of 100 mg/kg-bw/day is derived from the primary analogue TEHT, on the basis of the slight effects on sperm parameters in the absence of effect on reproductive performance observed in male rats at 300 mg/kg-bw/day. The testes were also a target for toxicity in male rats exposed to TOTM, as decreased testes weight was observed at 125 mg/kg-bw/day but not at 500 mg/kg-bw/day (ECHA c2007-2017c). Thus the NO(A)EL of 100 mg/kg-bw/day is used as a critical effect level for TTDT and BTIT by a category read across for the risk characterization of reproductive concerns.

Regarding read-across of repeated dose toxicity, the NOAEL for TEHT was 225 mg/kg-bw/day, with effects on hematological parameters and liver weight at 1000 mg/kg-bw/day, whereas the analogue TOTM had a lower NOAEL of 30 mg/kg-bw/day, and MDOT had a higher NO(A)EL of 300 mg/kg-bw/day for similar toxicological effects. Considering the trend of decreasing toxicity with increasing side chain length, TTDT and BTIT are expected to be less toxic than MDOT because of their longer alkyl side chain and larger molecular weight. In addition, BTIT contains mixed branched side chains, similar to TEHT. Theoretically, BTIT and TTDT should have higher NOAELs than MDOT. Thus, it is protective to select the NOAEL of 225 mg/kg-bw/day from TEHT for the risk characterization of repeated dose toxicity for both BTIT and TTDT (see Appendix C).

6.3 Characterization of Risk to Human Health

The available empirical toxicological data from TEHT and a category read-across analysis indicate that trimellitates have low acute toxicity. They are not genotoxic and are not expected to be carcinogenic.

In an OECD SIAR, a NOAEL of 100 mg/kg-bw/day was identified for reproductive toxicity, on the basis of the observed slight decreases in the numbers of spermatocytes and/or spermatids only at early stages of the spermatogenesis cycle in male rats at higher doses (OECD 2002a). This critical effect level is adopted for the risk characterization of TEHT. In the same screening test (by gavage), no adverse effects on reproductive performance of male or female rats or on fetal development were observed, up to the highest dose tested. In the original study report, authors also considered this level to be a NOEL rather than a NOAEL (OECD 2002b). In addition, in an OECD test guideline compliant 90-day repeated dose study in rats (via diet), no treatment-related effects were seen in the estrous cycle or spermatogenic cycle (ECHA c2007-2017a). These lines of evidence indicate that the effect of TEHT on reproductive toxicity should be considered minimal. It is therefore considered to be protective to use the NO(A)EL of 100 mg/kg-bw/day, based on the minimal reproductive effects (of questionable toxicological significance), for the risk characterization of all three trimellitates in this group.

No critical effect level is available for the dermal route of exposure. The dermal exposure estimates were derived using a dermal absorption of 1% and are thus considered systemic exposures. The critical effect level from the oral exposure route is therefore adjusted to a systemic dose in order to derive margins of exposure (MOEs). The critical effect level (administered dose) is adjusted to a systemic dose by using an oral absorption rate of 36% based on an oral absorption, distribution, metabolism, and excretion (ADME) study, which indicated that 75% of the oral dose of ^{14}C-labeled TEHT was excreted in the feces and that 85% of the radioactivity in feces was unchanged TEHT. Assuming unchanged TEHT did not enter the blood circulation, the oral absorption rate is estimated to be 100%-(75%*85%) = 36%. It should be noted that the extent of biliary excretion and enterohepatic circulation is not considered in this estimation because of a lack of information. No adjustment is needed in the derivation of MOEs for oral exposure scenarios.

Estimated exposures of the general population to TEHT through environmental media and food ranged from 6.0E-5 mg/kg-bw per day for adults 60 years of age and older to 2.8E-03 mg/kg-bw per day for infants 0 to 6 months old. Exposures are estimated to be primarily from indoor dust and from food (fish). The use of the NO(A)EL of 100 mg/kg-bw per day for reproductive toxicity results in MOEs greater than 35,000. No information or data on levels of TTDT and BTIT in environmental media and food were identified. In Canada, BTIT may be used as an ingredient of some incidental additives for use in food processing establishments, but exposure from this use is not expected. Exposure of the general population of Canada to TTDT and BTIT is likely less than that estimated for TEHT given their larger chemical structure and mass and their current use patterns.

TEHT, BTIT and TTDT were all identified in various but similar cosmetics. TTDT was present in the greatest number and variety of products with the highest concentrations, and it is considered to result in the highest exposures from cosmetics used on a daily basis in this group. BTIT exposure estimates were highest for cosmetics used less frequently, including massage oil and manicure preparation creams. Table 6-3 summarizes the daily sentinel exposure estimates for TEHT, BTIT or TTDT and the associated MOEs and Table 6-4 summarizes the per event sentinel exposure estimates and associated MOEs. An adjusted NO(A)EL of 36 mg/kg-bw per day is used to derive MOEs for the dermal exposure estimates, while the unadjusted NO(A)EL is compared to the oral exposure estimates.

Table 6-3. Sentinel daily exposures to trimellitates for adults and toddlers and MOEs, for determination of risk

Substance	Exposure scenario	Adult systemic exposure (mg/kg bw per day)	MOEs for adults	Toddler systemic exposure (mg/kg bw per day)	MOEs for toddlers
TEHT, TTDT, or BTIT	Lip products (100% oral absorption)	0.00034 – 0.25	400 – 294 118[a]	0.00038 – 0.11	909 – 263 158[a]
TTDT or BTIT	Body moisturizer[b]	0.00068 – 0.068	529 – 52 941[c]	0.0015 – 0.15	240 – 24 000[c]
TEHT, TTDT, or BTIT	Face moisturizer[b]	0.0003 – 0.091	396 – 120 000[c]	N/A	N/A
TEHT, TTDT, or BTIT	Facial make-up[b]	9.4E-05 – 0.057	632 – 382 979[c]	N/A	N/A

Abbreviations: N/A, not applicable
[a] Using a NO(A)EL = 100 mg/kg bw per day
[b] Used a dermal absorption of 1%
[c] Using a NO(A)EL = 36 mg/kg bw per day based on adjusting the NO(A)EL of 100 mg/kg bw per day to account for oral absorption of 36 % [100%-(75%*85%)] considering the excretion rates in feces from oral administration.

Table 6-4. Sentinel per event exposures to trimellitates for adults and toddlers and MOEs, for determination of risk

Substance	Exposure scenario	Adult systemic exposure (mg/kg bw per day)	MOEs for adults	Toddler systemic exposure (mg/kg bw per day)	MOEs for toddlers
BTIT or TTDT	Massage oil[a]	0.014 – 0.16	225 – 2 571[b]	N/A	N/A
BTIT or TTDT	Manicure preparation creams[a]	0.0072 – 0.072	500 – 5 000[b]	N/A	N/A

Abbreviations: N/A, not applicable
[a] Used a dermal absorption of 1%
[b] Using a NO(A)EL = 36 mg/kg bw per day based on adjusting the NO(A)EL of 100 mg/kg bw per day to account for oral absorption of 36 % [100%-(75%*85%)] considering the excretion rates in feces from oral administration.
[c] Using a NO(A)EL = 100 mg/kg bw

On the basis of the parameters used to generate conservative estimates of exposure to environmental media, food and products available to consumers (e.g., use of maximum and/or modelled concentrations in dust, food and products) and the use of a critical effect level associated with minimal effects of uncertain toxicological significance, the calculated MOEs presented above are considered adequate to address uncertainties in the health effects and exposure databases. Even if multiple cosmetics containing these substances are used on the same day (i.e., aggregate exposure), the MOEs would be considered adequate.

6.4 Uncertainties in Evaluation of Risk to Human Health

The key sources of uncertainty are presented in the table below.

Table 6-5. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Exposure	
Although there is a lack of data for TEHT in foods in Canada or elsewhere, modelled values from a Danish assessment report and other assumptions were used to derive estimates of dietary exposure to TEHT, which likely overestimate actual exposures.	+
There is some literature to suggest that TEHT may be present in inks used for certain food packaging. However, TEHT has not been identified for use in food packaging in Canada and approved uses in the United States do not include printing inks. While there is uncertainty regarding exposure to TEHT from its possible use in materials to package food, it is considered to be accounted for in the conservative estimates derived for environmental media and food.	+/-
Maximum concentrations were used to estimate cosmetic exposures, which likely result in overestimates.	+

Key source of uncertainty	Impact
In the absence of dermal absorption data for TEHT, 1% was used on the basis of information on phthalates. No information on dermal absorption was available for TTDT or BTIT.	+
Hazard	
There is uncertainty regarding the adversity of the effects observed in the screening reproductive study on TEHT; it is recognized that the estimates of risk presented here are conservative.	+
There are no subchronic or chronic animal studies for TEHT for dermal exposure.	+/-
Limited empirical toxicity data were available for BTIT and TTDT; a conservative read-across approach was therefore used to identify critical effects and critical effect levels.	+
Uncertainty in extent of gastrointestinal absorption and adjustment of critical effect level	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

There is uncertainty in the estimates of exposure to trimellitates in products available to consumers, with respect to types of products available to Canadians, the range of concentrations in the various products, as well as the prevalence in Canada of these products. Confidence is high that maximum exposure estimates from use of cosmetics actually overestimate exposures. Similarly, no information is available on the presence of TEHT in food packaging materials in Canada. However, exposure to TEHT from such uses would be expected to be in the range of what was estimated for environmental media and food. Therefore, confidence is high that the MOEs from such uses would still be considered adequate.

Limited toxicity data are available for BTIT and TTDT, and a category read-across approach is applied for risk characterization. Overall, it is considered to be conservative to use the critical effect level for reproductive toxicity in males and to apply the category read-across approach for the risk characterization of trimellitates, since the toxicity of BTIT and TTDT is expected to be lower than the toxicity of TEHT given their longer side chains.

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from TEHT, BTIT and TTDT. It is proposed to conclude that TEHT, BTIT and TTDT do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an

immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that TEHT, BTIT and TTDT do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that TEHT, BTIT and TTDT do not meet any of the criteria set out in section 64 of CEPA.

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Appendices

Appendix A. Deterministic estimates of daily human exposure to TEHT in dust and food

Table A-1. Estimated intakes of TEHT from dust and food

Route of exposure	breast fed (0–6 months[1])	formula fed (0–6 months[1])	not formula fed (0–6 months[1])	0.5–4 years[2]	5–11 years[3]	12–19 years[4]	20–59 years[5]	60+ years[6]
Food and beverages[7]	0.00	0.00	0.00	0.13	0.11	0.06	0.06	0.04
Dust[8]	2.8	2.8	2.8	1.5	0.6	0.02	0.02	0.02
Total intake[9]	2.8	2.8	2.8	1.6	0.7	0.08	0.08	0.06

Note: estimated intakes are expressed in µg/kg-bw per day of TEHT

[1] Assumed to weigh 7.5 kg (Health Canada 1998) and to ingest 38 mg of soil per day (Wilson et al. 2013).

[2] Assumed to weigh 15.5 kg (Health Canada 1998) and to ingest 41 mg of soil per day (Wilson et al. 2013).

[3] Assumed to weigh 31.0 kg (Health Canada 1998) and to ingest 31 mg of soil per day (Wilson et al. 2013).

[4] Assumed to weigh 59.4 kg (Health Canada 1998) and to ingest 2.2 mg of soil per day (Wilson et al. 2013).

[5] Assumed to weigh 70.9 kg (Health Canada 1998) and to ingest 2.5 mg of soil per day (Wilson et al. 2013).

[6] Assumed to weigh 72.0 kg (Health Canada 1998) and to ingest 2.5 mg of soil per day (Wilson et al. 2013).

[7] No measured data of TEHT in food was identified in Canada or elsewhere. Estimates of intake from food are based upon the maximum "worst-case" modelled concentrations in fish, milk and meat (Stuer-Lauridsen et al. 2001). These data were broadly applied to the twelve food groups and their corresponding food consumption rate value specified by Health Canada (1998):

Dairy products: maximum estimated concentration of 3.0×10^{-4} (µg/kg) of TEHT in dairy products.

Meat and poultry: maximum estimated concentration of 9.0×10^{-4} (µg/kg) of TEHT in meat.

Fish: maximum estimated concentration of 37 (µg/kg) of TEHT in fish.

[8] Maximum concentration of 553,540 (µg/kg) of TEHT in indoor dust, from 14 samples measured in Quebec City (Won and Lusztyk 2011). TEHT was also measured in dust in German homes and daycares (Fromme et al. 2016, Nagorka et al. 2011).

[9] TEHT is not volatile and insoluble and therefore not expected to occur in air and water. No measured data on levels of TEHT in soil were identified. Estimated maximum soil concentrations from Stuer-Lauridsen et al. (2001) resulted in exposure estimates below 2.5 ng/kg-bw/day and are therefore considered negligible.

Appendix B. Estimated human exposures to trimellitates from products available to consumers

Cosmetic exposures were estimated using ConsExpo Web (2016). Exposure estimates were derived based on default body weights of 70.9 kg for adults (20 years and older), and 15.5 kg toddlers (6 months to 4 years old) (Health Canada 1998). The estimated dermal and oral exposure parameters for cosmetics are described in Table B-1 and Table B-2, respectively. Dermal absorption is conservatively assumed to be 1%.

Table B-1. Exposure parameter assumptions for dermal scenarios[a]

Substance - Product	Assumptions[a]
Body moisturizer (TTDT, or BTIT)	Concentration:[b] 0.1 – 10% Adults: Product amount (g/use): 4.4 (Loretz et al. 2005) Frequency (use/day): 1.1 (Loretz et al. 2005) Surface area: whole body – head = 16 925 cm^2 (Health Canada 1995) Toddlers: Product amount (g/use): 1.4 (Wormuth et al. 2006) Frequency (use/day): 1.7 (Wormuth et al. 2006) Surface area: whole body – head = 4910 cm^2 (Health Canada 1995)
Face moisturizer (TEHT, TTDT, or BTIT)	Concentration:[b] 0.1 – 30% Adults: Product amount (g/use): 1.2 (Loretz et al. 2005) Frequency (use/day): 1.8 (Loretz et al. 2005) Surface area: Half area of head = 637.5 cm^2 (Health Canada 1995)
Facial make-up (TEHT, TTDT, or BTIT)	Concentration:[b] 0.1 – 60% Adults: Product amount (g/use): 0.54 (Loretz et al. 2006) Frequency (use/day): 1.2 (Loretz et al. 2006) Surface area: Half area of head = 637.5 cm^2 (Health Canada 1995)
Massage oil (TTDT or BTIT)	Concentration:[b] 3 – 35% Adults: Product amount (g/use): 3.2 (Ficheux et al. 2016)

	Frequency is less than once a day, exposure estimates are per event Surface area: Total body surface area - half area of head – half area of trunk = 14 380 cm^2 (Health Canada 1995)
Manicure preparation creams (TTDT or BTIT)	In the absence of specific data for this exposure scenario, assumed exposure was similar to hand cream but occurred less frequently Concentration:[b] 3 – 30% Adults: Product amount (g/use): 1.7 (Bremmer et al. 2006) Frequency is less than once a day, exposure estimates are per event Surface area: Hands = 910 cm^2 (Health Canada 1995)

[a] Unless specified, a retention factor of 1 was used.
[b] Personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016-2017; unreferenced.

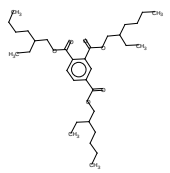
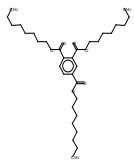
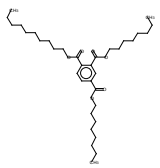
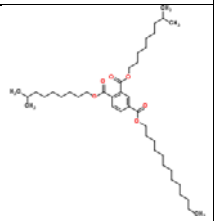
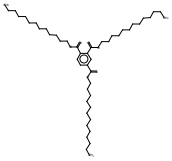
Table B-2. Oral exposure parameter assumptions for other cosmetics

Substance - Product	**Assumptions[a]**
Lip products (TEHT, TTDT, or BTIT)	Concentration:[b] 0.1 – 74% Adults: Product amount (g/use): 0.01 (Loretz et al. 2005) Frequency (use/day): 2.4 (Loretz et al. 2005) Toddler: Product amount (g/use): 0.01 (assumed to be the same as adults) Frequency is less than once a day, exposure estimates are per event

[a] Assume amount applied is completely ingested, no dermal exposure.
[b] Personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated 2016-2017; unreferenced.

Appendix C. Read across table

Table C-1. Read across by a chemical category approach using TEHT, TOMT and MDOT as analogues

Chemical name	TEHT[a]	TOTM[b]	MDOT[c]	BTIT[d]	TTDT[e]
Role	Target chemical and used as an analogue for BTIT and TTDT	Analogue	Analogue	Target chemical	Target chemical
CAS RN#	3319-31-1	89-04-3	90218-76-1	70225-05-7	94109-09-8
Chemical structure			 (UVCB, representative structure)	 (UVCB, representative structure)	
Carbon number of side chains	8	8	8-10	10-13	13
Physical-chemical data					
Molecular weight (g/mol)	546.78	546.78	602.9	673.04	757.18
Partition coefficient (log K_{ow})	8 (US EPA)	9.3 (ECHA c2007-2017c, HPLC method)	10.6 (ECHA c2007-2017d, HPLC method)	>10 (modeled by EPI Suite)	>10 (modeled by EPI Suite)
Water solubility (mg/L)	3.9 x 10^{-4}; insoluble (<0.1)	4.1 x 10^{-6} to <1	<1x10^{-8}	<1 x 10^{-8} (modeled by EPI Suite)	<1 x 10^{-8} (modeled by EPI Suite)
Toxicological data					
Toxicokinetics and metabolism	Limited amount was absorbed and subsequently metabolized	N/A	N/A	Low potential to be absorbed and metabolized (read across)	Low potential to be absorbed and metabolized (read across)
Acute toxicity	LD50 >1970 mg/kg-bw (oral)	LD50 > 2000 mg/kg-bw	LD50 > 3000 mg/kg-bw (oral); LD50 > 2000 mg/kg-bw (dermal)	Low (read across)	LD50 > 5000 mg/kg-bw (oral)
Repeated dose toxicity	NOAEL=225 mg/kg-bw/day (hematological changes and increases of liver weight)	NOAEL= 30 mg/kg-bw/day (female) (increased liver weight and reduced red blood cell count);	NO(A)EL= 300 mg/kg-bw/day (increased liver weight, increased leucocytosis and decreased globulin)	NOAEL=225 mg/kg-bw/day (read-across)	NOAEL=225 mg/kg-bw/day (read-across)

		LOAEL= 125 mg/kg-bw/day			
Reproductive/ developmental toxicity	NO(A)EL=100 mg/kg-bw/day (decreases in spermatocytes and spermatids);	NOEL= 500 mg/kg-bw/day (no changes in sex ratio, body weight, viability or morphology of pups (F1)	NOAEL= 300 mg/kg-bw/day (maternal toxicity: decreased body weight, body weight gain, decrease in gravid uterine weight); NOAEL= 1000 mg/kg-bw/day (developmental toxicity)	NO(A)EL=100 mg/kg-bw/day (read- across)	NO(A)EL=100 mg/kg-bw/day (read- across)
Genetic toxicity	Not genotoxic (negative in Ames, tk+/- assay in mouse L5178Y cells or CHO/hprt assay; negative chromosomal aberration in human lymphocytes or V79); negative in rodent dominant lethal assay)	Not genotoxic (negative in Ames, tk+/- assay in mouse L5178Y cells or chromosomal aberration in Chinese hamster lung cells)	Not genotoxic (negative in Ames, tk+/- assay in mouse L5178Y cells or chromosomal aberrations in human lymphocytes)	Not genotoxic (read across)	Not genotoxic (read across)
Carcinogenicity	Not expected to be carcinogenic	N/A	N/A	Not expected to be carcinogenic (read across)	Not expected to be carcinogenic (read across)
Endocrine modulation	Potential is considered to be low	N/A	N/A	Potential is considered to be low (read-across)	Potential is considered to be low (read-across)

Abbreviations: N/A, not available.
[a] Data details in section 6.2.1.
[b,c] Data from ECHA (c2007-2017c,d) registration dossier.
[d,e] Data mainly from category read across approaches.