Screening assessment

carboxylic acid anhydrides group

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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 of three of the eight substances referred to collectively under the Chemicals Management Plan as the Carboxylic Acid Anhydrides Group. These three substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA. The other five substances were determined to be of low concern through other approaches, and decisions for these substances are provided in separate reports[1]. Accordingly, this screening assessment addresses the three substances listed in the table below. The three substances addressed in this screening assessment will hereinafter be referred to as the Carboxylic Acid Anhydrides Group.

Substances in the Carboxylic Acid Anhydrides Group

CAS RN[a]	Domestic substances list name	Common name
85-44-9	1,3-Isobenzofurandione	Phthalic anhydride
108-31-6	2,5-Furandione	Maleic anhydride
552-30-7	5-Isobenzofurancarboxylicacid, 1,3-dihydro-1,3-dioxo-	Trimellitic anhydride

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In 2011, reported imported quantities of phthalic anhydride and trimellitic anhydride were < 12 550 000 and 1 000 000 – 10 000 000 kg, respectively, based on information submitted pursuant to section 71 of CEPA. The two substances were not reported as being manufactured in Canada above the reporting threshold of 100 kg. Maleic anhydride was not included in surveys pursuant to CEPA section 71; however, information from the Canadian International Merchandise Trade Database reported average annual import volumes of maleic anhydride from 2013-2016 to be approximately 9 000 000 kg.

All of the substances in the Carboxylic Acid Anhydrides Group are primarily used as intermediates in the production of other chemicals. The substances in this group do not naturally occur in the environment, with the exception of phthalic anhydride which may be formed through the photochemical breakdown of other organic substances in air.

[1] Conclusions for CAS RNs 85-42-7, 26544-38-7, 28777-98-2, 32072-96-1, and 68784-12-3 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 Screening Assessment.

Phthalic anhydride and maleic anhydride are present on the list of substances reported to the National Pollutant Release Inventory (NPRI). Phthalic anhydride and maleic anhydride have been reported to be released in quantities of 90 kg and 18 kg, respectively. A report from the National Research Council Canada reported phthalic anhydride to be present in indoor air and dust in homes in Canada.

Phthalic anhydride is primarily used as a chemical intermediate for the synthesis of phthalate esters. It may also be used in the production of polyester resins, alkyd resins, and other chemical substances such as pigments and dyes. In Canada, phthalic anhydride is present in consumer spray paint products, floor polishes, and cosmetic products including nail polishes and eyelash adhesives. It has also been identified for use in the manufacture of food packaging materials.

Based on available information, maleic anhydride is primarily used as a chemical intermediate in the synthesis of unsaturated polyester resins, as well as other chemical substances. In Canada, maleic anhydride was identified as an ingredient in shampoos, temporary tattoos, exfoliants, bubble baths (foam and oil), bath salts, and body cleansers. Through publicly available safety datasheets (SDS's), the substance was also identified as being used in wood blending-sticks designed to repair minor scratches on wood surfaces. Maleic anhydride has been identified in Canada for use in the manufacture of food packaging materials.

Trimellitic anhydride is used in commercial applications including paint and coating applications, and plastic and rubber materials where it functions as an intermediate. The substance was identified for use as a component in resins used in the manufacture of returnable bottles used for milk, water, and juice. Trimellitic anhydride was reported to be present as an ingredient in one product available to consumers (i.e., nail polish) in Canada.

The ecological risks of the substances in the Carboxylic Acid Anhydrides Group were characterized using the ecological risk classification of organic substances (ERC), which is a risk-based approach that employs multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are based principally on 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 based on their hazard and exposure profiles. Based on the outcome of the ERC analysis, the three substances in the Carboxylic Acid Anhydrides Group are considered unlikely to cause ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from phthalic anhydride, maleic anhydride, and trimellitic anhydride. It is concluded that phthalic anhydride, maleic anhydride, and trimellitic anhydride 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.

Based on the available information, the critical effect for characterization of the risk to human health from exposure to phthalic anhydride is respiratory sensitization. A comparison of the estimated exposure levels of phthalic anhydride from its uses in products available to consumers including spray paints, floor polishes, and eyelash adhesives to critical effect levels resulted in margins of exposure that are considered adequate to account for uncertainties in the health and exposure databases. A comparison of estimated exposure to phthalic anhydride from its presence in indoor air to critical effect levels resulted in margins of exposure that are considered adequate to account for uncertainties in the health and exposure databases.

Based on the collective information, the critical effects for characterization of the risk to human health from exposure to maleic anhydride are effects on kidney and bladder. A comparison of estimated exposure levels from its uses in products available to consumers to critical effect levels resulted in margins of exposure that are considered adequate to account for uncertainties in the health and exposure databases.

The estimated exposure to trimellitic anhydride from environmental media or food packaging is expected to be negligible and exposure from the use of nail polish is not expected based on the substance function in the product. The overall exposure of the Canadian general population to trimellitic anhydride is negligible, therefore the risk to human health is considered to be low.

On the basis of the information presented in this screening assessment, it is concluded that phthalic anhydride, maleic anhydride, and trimellitic anhydride 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 concluded that phthalic anhydride, maleic anhydride and trimellitic anhydride 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 eight substances referred to collectively under the Chemicals Management Plan as the Carboxylic Acid Anhydrides Group, to determine whether these substances 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 other five substances (listed in **Table 1-1** below) were considered in the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016a), and in the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Document (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. Conclusions for these five 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 Screening Assessment Report (ECCC, HC 2018). The three substances addressed in this screening assessment will hereinafter be referred to as the Carboxylic Acid Anhydride Group.

Table 1-1. Substances in the Carboxylic Acid Anhydrides Group that were addressed under other approaches

CAS RN[a]	*Domestic substances list* name	Approach under which the substance was addressed	References
85-42-7	1,3-Isobenzofurandione, hexahydro-	ERC/TTC	ECCC, HC 2018
26544-38-7	2,5-Furandione, dihydro-3-(tetrapropenyl)-	ERC/TTC	ECCC, HC 2018
28777-98-2	2,5-Furandione, dihydro-3-(octadecenyl)-	ERC/TTC	ECCC, HC 2018
32072-96-1	2,5-Furandione, 3-(hexadecenyl)dihydro-	ERC/TTC	ECCC, HC 2018
68784-12-3	2,5-Furandione, dihydro-, mono-C15-20-alkenyl derivs.	ERC/TTC	ECCC, HC 2017

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The ecological risks of the three substances in Carboxylic Acid Anhydrides Group were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard

of a substance using key metrics including mode of toxic action, chemical reactivity, food-web derived internal toxicity thresholds, bioavailability, and chemical and biological activity, and it considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of factors including 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.

Substances in the Carboxylic Acid Anhydrides Group which are included in this assessment were reviewed by the Organization for Economic Cooperation and Development (OECD) Cooperative Chemicals Assessment Programme. These assessments undergo rigorous review and endorsement by international governmental authorities. Environment and Climate Change Canada and Health Canada are active participants in this process, and consider these assessments as reliable. The data in these assessments will be used to inform the health effects characterization for the substances in the Carboxylic Acid Anhydrides Group.

This 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 October 2016. Empirical data from key studies as well as some results from models were used to reach conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This 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 portion of this assessment is based on the ERC document (published July 30, 2016), which was subject to an external review as well as a 60-day public comment period. The 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 Lynne Haber (Department of Environmental Health, College of Medicine, University of Cincinnati), Michael Jayjock (Jayjock & Associates LLC), and Raymond York (RG York & Associates LLC). Additionally, the draft of this screening assessment (published December 9, 2017) was 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 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[2]. The

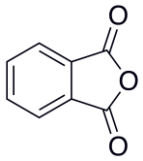
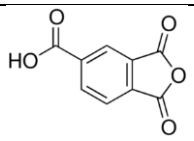
[2]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment.

screening assessment presents the critical information and considerations upon which the conclusions are made.

2. Identity of substances

The CAS RN, *Domestic Substances List* (DSL) names, and common names for the individual substances in the Carboxylic Acid Anhydrides Group are presented in Table 2-1.

Table 2-1. Substance identities for the Carboxylic Acid Anhydrides Group

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
85-44-9	1,3-Isobenzofurandione (Phthalic anhydride)	 C_8H_4O3	148.12
108-31-6	2,5-Furandione (Maleic anhydride)	 $C_4H_2O_3$	98.06
552-30-7	5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo- (Trimellitic anhydride)	 $C_9H_4O_4$	192.13

3. Physical and chemical properties

A summary of physical and chemical properties of the substances in the Carboxylic Acid Anhydrides Group are presented in Table 3-1. Additional physical and chemical properties are presented in ECCC (2016b).

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*, 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.

Table 3-1. Experimental physical and chemical property values for the Carboxylic Acid Anhydrides Group

Property	Phthalic anhydride	Maleic anhydride	Trimellitic anhydride
Physical state	White flakes or needles (Lorz, Towae, and Bhargava 2002, as cited in OECD 2005)	White solid (OECD 2004)	Solid white flakes (OECD 2002)
Molecular Weight (g/mol)	148.12 (OECD 2005)	98.06 (OECD 2004)	192.12 (OECD 2002)
Melting point (°C)	131.6 (Lorz, Towae, and Bhargava 2000, as cited in OECD 2005)	51.2 to 53.1 (Springborn Smithers, as cited in OECD 2004)	163 - 166 (Sigma Aldrich 2015)
Vapour pressure (Pa)	0.06 at 26.6 °C (Crooks and Feetham 1946, as cited in OECD 2005)	15.1 (at 22 °C) 37.7 (at 30 °C) (Springborn Smithers, as cited in OECD 2004)	7.6E-05 at 25°C (Daubert and Danner 1989, as cited in OECD 2002)
Henry's law constant log(Pa·m^3/mol), at 25C	-7.79 (estimated, ChemIDplus 1993- a)	-5.41 (estimated, ChemIDplus 1993- b)	-9.89 (estimated, ChemIDplus 1993- c)
Water solubility (mg/L)	16400 (at 20°C) (Lorz, Towae, and Bhargava 2000, as cited in OECD 2005)	4910 (estimated, ChemIDplus 1993- b)	1036 (estimated, ChemIDplus 1993- c)
Hydrolysis Half-life	30.5 seconds at pH 7.24, 25°C (Andres, Granados and Rossi 2001, as cited in OECD 2005)	22 seconds at 25°C (Bunton et al., as cited in OECD, 2004)	<10 minutes at 27-32 °C (Horan 1962, as referenced in OECD 2002)

4. Sources and uses

4.1 Sources

Information was submitted on two of the substances in the Carboxylic Acid Anhydrides Group pursuant to a CEPA section 71 notice (ECCC 2013). Table 4-1 presents a summary of the total reported import quantities of phthalic anhydride and trimellitic

anhydride. These substances were not reported to be manufactured in Canada above the reporting threshold of 100kg.

Table 4-1. Summary of information on Canadian imports of phthalic anhydride and maleic anhydride submitted pursuant to CEPA section 71

Common name	Total imports[a] (kg)
Phthalic Anhydride	< 12 550 000
Trimellitic Anhydride	1 000 000 – 10 000 000

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

Maleic anhydride was not included in surveys issued pursuant to section 71of CEPA; however, data from the Canadian International Merchandise Trade database (CIMT) indicate that it is expected to be in Canadian commerce. Canadian average annual import volumes of maleic anhydride from 2013 to2016 were approximately 9 000 000 kg (CIMT 2016).

With the exception of phthalic anhydride, which may be formed through the photochemical breakdown of polycyclic aromatic hydrocarbons in the atmosphere, substances in the Carboxylic Acid Anhydrides Group do not naturally occur in the environment (Lee et al. 2012, Jang and McDow 1997, van Tongeren 1989). Anthropogenic sources of substances in the Carboxylic Acid Anhydrides Group include industrial activities and use of products available to consumers.

Production of phthalic anhydride is predominantly carried out by the oxidation of o-xylene and/or naphthalene (OECD 2005). Maleic anhydride is primarily produced from the oxidation of n-butane. Minor sources of maleic anhydride production can include the oxidation of benzene and recovery as a by-product in the oxidative production of phthalic anhydride (OECD 2004). Trimellitic anhydride is produced in a batch process using pseudocumene, air, solvents, and a catalyst in a closed reactor (OECD 2002). This reaction also produces trimellitic acid, a reaction intermediate, which is then dehydrated at high temperatures to form trimellitic anhydride and water (OECD 2002).

All substances in the Carboxylic Acid Anhydrides Group are present on the Organization for Economic Cooperation and Development (OECD) 2004 list of High Production Volume (HPV) substances. In Europe, phthalic anhydride and maleic anhydride are each reported to be manufactured and/or imported in the European Economic Area in quantities ranging from 100 000 to 1 000 000 tonnes (100 000 000 to 1 000 000 000 kg) per year (ECHA 2016a, 2016b). Quantities of trimellitic anhydride are reported to range from 10 000 to 100 000 tonnes (10 000 000 to 100 000 000 kg) per year (ECHA 2016c). In the United States, combined manufacture and import volumes of phthalic, maleic, and trimellitic anhydride in 2012 were reported to be approximately 613 000 000 lbs (278 000 000 kg), 32 000 000 lbs (14 500 000 kg), and 232 000 lbs (105 000 kg), respectively (CDR 2012).

4.2 Uses

There are several reported commercial uses of phthalic anhydride in Canada including uses as a plasticizer, intermediate, and process regulators in applications such as paints and coatings, plastic and rubber materials, and automotive, aircraft, and transportation, among others (ECCC 2013). A majority of phthalic anhydride is produced for use in the manufacture of phthalate esters, and to a lesser extent in the production of unsaturated polyester resins, alkyd resins, and other substances (OECD 2005). Other global uses of phthalic anhydride include uses as an intermediate in the production of pigments and dyes, polyester polyols, and intermediates in the agricultural and pharmaceutical sectors (OECD 2005). During these processes, phthalic anhydride reacts with other chemicals and is thus consumed as a reactant.

Phthalic anhydride was identified in several spray paints and a floor polish product available to consumers in Canada (SDS 2015a-j, SDS 2016). The substance has also been identified as a component in the manufacture of a variety of food packaging materials in Canada including liners, adhesives, coatings, PET-based bottles, paper based materials, lubricants in PVC films and inks (no food contact) (personal communication, emails from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated August 2016; unreferenced). In Canada, it is reported to be used in nail polish products where it is present as a co-polymer as well as an ingredient in eyelash adhesive products (personal communication, emails from Consumer Product Safety Directorate, dated October 2016; unreferenced).

Consumer product surveys conducted by the Danish Environmental Protection Agency (DEPA) have reported phthalic anhydride to be present in a porcelain dye, a fabric dye, a lacquered table top made from a rubber tree, hobby clay/dough, children's toys, and adult sex toys (vibrators) (DEPA 2002, 2005a, 2005b, 2006).

In Washington State, US phthalic anhydride uses in products for children are regulated under the Children's Safe products Act, whereby manufacturers of children's products sold in Washington are required to report products containing phthalic anhydride (Ecology 2016). Data from the Children's Safe Product Act (CSPA) database reported phthalic anhydride to be present in a wide variety of products including arts/crafts/needlework supplies, baby products (bibs and high chair), clothing, cosmetics/fragrances, fabrics/textile furnishings, footwear, jewellery, greeting cards/gift wrap/occasion supplies, skin products, and toys/games. A majority of the data reported was for products in the toys/games and clothing categories (Ecology 2016).

Maleic anhydride was notified to be present in several cosmetic products in Canada including shampoos, temporary tattoos, exfoliants, bubble baths (foam and oil), bath salts, and body cleansers. The substance has been identified in Canada for use in the manufacture of food packaging materials, including non-food contact applications such as casings and laminated films, inks and adhesives, and in coatings (personal communication, emails from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada, dated August 2016; unreferenced). Through publicly available

data, maleic anhydride was identified to be used in blending-sticks designed to repair minor scratches on wood surfaces (SDS 2015k). Globally, maleic anhydride has few, if any, consumer uses as it is primarily used as the starting material for other chemical substances (Felthouse et al. 2001). Maleic anhydride is primarily used in the manufacture of unsaturated polyester resins where it provides the reactivity fundamental to the majority of commercial resins (Felthouse et al. 2001, Nava 2015). Unsaturated polyester resins (UPRs) are generally derived from the polyesterification of unsaturated dibasic acids or anhydrides dissolved in vinyl monomers (Nava, 2015). During these reactions, maleic anhydride is reacted to form the final polyesters (Nava 2015). Other minor industrial uses of maleic anhydride include the production of lube oil additives, agricultural chemicals, and intermediate uses in the synthesis of maleic copolymers such as fumaric acid and maleic acid (Felthouse et al., 2001).

In Canada, trimellitic anhydride has been reported to be used in commercial applications, including paint and coating applications and plastic and rubber materials, where it functions as an intermediate or may be present as a contaminant or impurity during manufacture of other substances (ECCC 2013). Trimellitic anhydride was identified as a component in resins used in the manufacture of returnable bottles for milk, water, and juice (personal communication, emails from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada, dated August 2016; unreferenced). It was also reported to be present in nail polish products in Canada. No other products available to consumers in Canada were identified to contain trimellitic anhydride. A majority of trimellitic anhydride produced is used in the synthesis of plasticizers for polyvinyl chloride (PVC) resins (OECD 2002). Other uses for trimellitic anhydride include as a reactant in wire and cable insulations, polyester resins, coatings, and as a curing agent, binding agent, and cross-linking agent, among others (OECD 2002). In these applications, trimellitic anhydride is fully consumed (OECD 2002).

Information on Canadian uses of the substances in the Carboxylic Acid Anhydrides Group is summarized in Table 4-2 below.

Table 4-2. Information on uses in Canada of substances in the Carboxylic Acid Anhydride Group

Use	Phthalic Anhydride	Maleic Anhydride	Trimellitic Anhydride
Food packaging materials[a]	Y	Y	Y
Present in cosmetics, based on notifications submitted under the *Cosmetic Regulations* [b]	Y	Y	Y

Abbreviations: Y= use was reported for this substance; N= use was not reported for this substance

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

[b] Personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated August 2016; unreferenced

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of substances in the Carboxylic Acid Anhydrides Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure, with weighted considerations 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 in response to surveys under CEPA section 71, 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 based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also composed of 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 based on 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 which 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, 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 and 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 with 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 with 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 based on 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 Carboxylic Acid Anhydrides 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 Carboxylic Acid Anhydrides Group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the three substances in the Carboxylic Acid Anhydrides Group

Common Name	ERC hazard classification	ERC exposure classification	ERC risk classification
Phthalic anhydride	low	low	low
Maleic anhydride	low	high	low
Trimellitic anhydride	low	low	low

According to information considered under ERC, maleic anhydride was classified as having a high exposure based on large use quantities, long half-life in air, and a large margin of exposure. Maleic anhydride has been classified as presenting a low ecological hazard and a low potential for ecological risk. It is unlikely that this substance results in concerns for the environment in Canada.

Based on low hazard and low exposure classifications according to information considered under ERC for phthalic anhydride and trimellitic anhydride, these substances were classified as having a low potential for ecological risk. It is unlikely that these substances result in concerns for the environment in Canada.

6. Potential to cause harm to human health

6.1 Phthalic anhydride

6.1.1 Exposure assessment

Environmental media and food

Phthalic anhydride was not identified in drinking water or soil in Canada. However, considering the physical-chemical properties of the substance, exposure from water or soil is not expected as the substance would rapidly hydrolyze to phthalic acid. Phthalic anhydride was reported as released to air in Canada at 0.090 tons (90kg) in 2015, based on data from the National Pollution Release Inventory (NPRI 1994).

In a 2011 publication, the National Research Council Canada (NRC) examined the presence of 954 organic chemicals which were part of the list of substances identified as priorities for assessment under the Chemicals Management Plan moderate priorities chemical list from four databases on building materials, indoor air, and dust samples. A subset of data from a 2010 NRC study involving indoor air and dust samples from 115 homes with asthmatic children in Quebec City was re-analyzed to identify any moderate priority compounds. Phthalic anhydride was identified during the re-examination of chromatograms from the Quebec field study in both indoor air and dust samples.

As the chromatograms that were re-examined during the NRC study were generated using GC/MS analysis, there is uncertainty in the reported values corresponding to phthalic anhydride. Phthalate esters were also reported to be found in the indoor air and dust samples from this study. The reported concentrations of phthalic anhydride may be due to the dehydration of phthalate esters during GC/MS analysis, and may overestimate reported concentrations of phthalic anhydride (NRC 2011, EPA 1994).

While other available studies reported phthalic anhydride in air (EPA, 1994; Hannigan et al. 1998; Gradel 1978; Sasaki et al. 1997; Ramdhal, Becher, and Bjorseth 1982; Davoli et al. 2003; Machill et al. 1997; Zhu, Zhang, and Shaw 1999; Henriks-Eckerman, Engstroem, and Anaes 1990, as cited in OECD 2005), the NRC Client Report (2011) is considered to be the most relevant to characterize Canadian general population exposure to phthalic anhydride from indoor air and dust as the data from the Quebec field study was the most recent study to identify phthalic anhydride in indoor air and dust in Canada. Concentrations of phthalic anhydride ranged from 0.23 – 2.54 ug/m^3 in indoor air and 0.26 to 112.66 ug/g dust in indoor dust. Considering the rapid rate of hydrolysis of phthalic anhydride in the presence or water or moisture, oral exposure to phthalic anhydride from its presence in household dust is not expected.

Phthalic anhydride has been identified in Canada as a component used in the manufacture of a variety of food packaging applications. However, considering the rapid rate of hydrolysis of the substance to phthalic acid in the presence of water or high humidity, dietary exposure from its use in food packaging materials is expected to be

negligible (personal communication, emails from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated August 2016; unreferenced).

Children's products and other manufactured items

Concentrations of phthalic anhydride in children's products in Canada were not identified. In the U.S. phthalic anhydride has been reported to be present in a variety of children's products. Under the Washington Children's Safe Products Reporting Rule, manufacturers of children's products in Washington, U.S.A. are required to report product data on chemicals listed on the Washington State Chemicals of High Concern to Children list, which includes phthalic anhydride (Ecology 2016). Based on manufacturer information, it is possible that these children's products could be found on the Canadian market as most of the reporting manufacturers are known to operate in Canada.

Phthalic anhydride was reported to be present in a total of 263 children's products from 2012-2016. Children's clothing (including footwear) and toys/games were identified as the major types of products that were reported to contain phthalic anhydride. They accounted for 211 of the 263 records reporting the use of phthalic anhydride in children's products, with toys/games being reported in 120 products. Types of toys reported included dolls/soft toys, costumes, building blocks, drawing boards, ride-on toys, and toy/game variety packs, among others. Types of clothing varied and included articles such as socks, pants, underwear, shirts, stockings, jackets/blazers/cardigans/waistcoats, full-body sportswear, and dresses, among others (Ecology 2012-2017).

Functions of the substance were identified mainly as a plasticizer/softener, coloration/pigment/dye, or as a component of plastic resins or polymer processes, and were accounted for in 94 of the 263 records. The substance was reported to be present as a contaminant with no function in 148 products. A majority of the products listed in the database reported concentrations of phthalic anhydride at less than 500ppm (0.05%); 220 of the 263 identified products reported phthalic anhydride at less than or equal to 1000ppm (0.1%) (Ecology 2012-2017).

Exposure to phthalic anhydride in children's clothing is likely to be short-term, as phthalic anhydride would rapidly hydrolyze in the presence of water such as washing of clothing or textile articles. Hydrolysis of phthalic anhydride is irreversible under normal conditions, with thermal dehydration of the acid to the anhydride requiring temperatures above 180 °C (OECD 2005). In addition, migration of substances through clothing to skin generally occurs through media such as urine, sweat, or saliva, wherein the substance would be expected to hydrolyze during product migration.

Phthalic anhydride was also identified in a limited number of products available to consumers in Denmark that were surveyed by the DEPA (DEPA 2002, 2005a, 2005b, 2006). There is uncertainty associated with these results as the reported concentrations of phthalic anhydride could be due in part to to their formation from the dehydration of

phthalate esters during GC/MS analysis (EPA 1994). Although phthalic anhydride could be present in these types of products if imported to Canada, as mentioned above, migration of a substance occurs through media such as urine, sweat, or saliva, and phthalic anhydride would be expected to hydrolyze during migration from products before it is available for exposure.

Cosmetic products

Based on notifications submitted to Health Canada, phthalic anhydride was reported to be present in nail polish products and eyelash adhesives in Canada. Concentrations of phthalic anhydride in nail polish products were reported at 30%. Based on the function of the substance, phthalic anhydride is expected to react with other ingredients in the nail polish product to form phthalate esters, which impart the necessary flexibility to hardened nail polish. These reactions would take place prior to the user accessing the product. Therefore, exposure to phthalic anhydride from nail polish products is not expected (personal communication, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated June 2016; unreferenced). Dermal exposure estimates, from the use of phthalic anhydride in eyelash adhesives at a maximum concentration of 1%, were 0.0017 and 0.002 mg/kg bw/day for adults and teenagers, respectively, using product amount data from Lim et al, 2014.

Phthalic anhydride was also reported in 7 body wash products at a concentration range of less than or equal to the practical quantification limit of 100 ppm (≤ 0.01%) and 1 lip care product at equal to or greater than 1000 ppm but less than 5000 ppm (0.1% ≤ 0.5%), from information submitted under the CSPA (Ecology 2012-). Considering the rapid rate of hydrolysis for phthalic anhydride in the presence of water or moisture, exposure to the substance from uses in body wash products and lip care products is not expected.

Do-it-yourself products

Phthalic anhydride has been identified in spray paint products and a wood floor polish product available to Canadian consumers. The substance was identified in several automotive primer spray paints, such as filler primers, self-etching primers, primers for engines, and primer sealers (SDS 2015a-j). Phthalic anhydride was reported to be present in rust primer sprays for general purpose applications on metal surfaces where rust is visible. It was also identified in a general purpose primer spray, for use on wood and metal surfaces. These spray paints are recommended for use outdoors or in well-ventilated areas, such as open garages. Exposures to the general population from spray paint products are acute and would only be used on an as-needed basis (i.e. if rust appears on product surfaces, or if painted products begin to wear). The floor polish containing phthalic anhydride is designed for use on naturally oiled and prefinished floors to treat worn surfaces or where scratches are visible. The use of this product is also likely acute and limited to instances where remediation of floor surfaces are necessary.

Estimates of dermal, and inhalation exposure to phthalic anhydride from use in spray paints and floor polishes were modelled using ConsExpo Web and default values were refined based on product specific data (RIVM 2007, 2010). Table 6-1 presents estimated inhalation and dermal exposures to phthalic anhydride from the use of spray paints and floor polishes, and is presented as a peak concentration during the exposure event and a mean air concentration amortized over 8-hours.

Table 6-1: Summary of acute exposure to phthalic anhydride from use in do-it-yourself products.

Product scenario	Estimated dermal exposure per application	Estimated peak concentration during use (mg/m^3)	Estimated 8-hour mean air concentration (mg/m^3)
Floor[a] Polish	0.78 mg/kg bw	0.0048	0.0009
Spray[b,c] Paint	0.00057 mg/kg bw	0.047	0.0013

[a] [SDS] 2016, 2018; the 2018 SDS no longer includes phthalic anhydride in the ingredient list; however, it is assumed to still be present at the previously reported concentration (SDS 2016)
[b] [SDS] 2015a-j
[c] [ECCC] 2016c

6.1.2 Health effects assessment

Phthalic anhydride has been assessed by the OECD (2005), and this assessment was used to inform the health effects characterization of this substance. A literature search was conducted for the period one year before the OECD assessment to October 2016, and no studies that could result in a different health effects characterization from the OECD assessment were identified.

Phthalic anhydride was identified as a skin and respiratory sensitizer by the OECD. Evidence that phthalic anhydride has respiratory sensitization potential has been demonstrated in several epidemiology studies, which has also been supported by animal models. Therefore, respiratory sensitization is identified as the critical endpoint for the risk assessment of phthalic anhydride. A summary of the key studies related to skin and respiratory sensitization and corresponding points of departure (PODs), as well as a summary of other health effects are presented below.

Respiratory tract sensitization

Several epidemiological studies were identified. In one study, phthalic anhydride air levels were measured in two plants producing polyester resins in Sweden and symptoms and antibody levels amongst 60 anhydride-exposed workers (with an average duration of exposure approximately 12 years) were monitored. A control group of 22 workers from a food processing factory, matched for age and smoking habits, was used for comparison throughout the study. The time-weighted average (TWA) air level

during loading of phthalic anhydride at the workplace was 6.6 (1.5 - 17.4) mg/m^3; Loaders were significantly exposed only during loading, which lasted about 30 minutes per day. During the rest of the day workers were exposed to lower levels and the time-weighted average for a full workday was approximately 0.4 mg/m^3. Low amounts of other anhydrides were also used in these plants. Respiratory protection was used irregularly. Symptoms of rhinitis and/or conjunctivitis were frequently reported, mostly by the heavily exposed workers (69 %). Five workers (14 %), all heavily exposed during some periods, exhibited a phthalic anhydride-associated bronchial asthma that was possibly correlated with specific serum IgG antibody levels. The authors reported that the clinical symptoms seemed to appear after repeated peak exposure to phthalic anhydride. More than one third of the workers exposed to such concentrations were found to have increased levels of specific IgG directly against phthalic anhydride and workers with asthma had higher specific IgG than asymptomatic workers, indicating that IgG may have a pathogenic role. However, several subjects without symptoms also had increased IgG (Nielsen et al. 1988).

In an earlier study, among 118 workers occasionally exposed to phthalic anhydride dust for 2 months or more, 28 (24%) suffered from work-related rhinitis, 13 (11 %) from chronic productive bronchitis, and 21 (28 %) from work-associated asthma. Three out of eleven asthmatics had a phthalic anhydride positive skin test, and in two subjects the presence of antibodies was demonstrated. The average concentration of phthalic anhydride dust at the workplaces was reported to be 3–13 mg/m^3, of which 40-46 % was in the inspirable dust fraction (Wernfors et al. 1986).

The respiratory sensitizing potential of phthalic anhydride was also evaluated in a guinea pig model. Animals were exposed to 0.0, 0.5, 1.0 or 5.0 mg/m^3 phthalic anhydride dust, via inhalation, three hours per day for five consecutive days. Two weeks after the last exposure, guinea pigs were challenged either with phthalic anhydride dust (5 mg/m^3) or with a phthalic anhydride/guinea pig serum albumin (PA-GPSA) conjugate dust (2.0 mg/m^3). Inhalation challenge with PA-GPSA conjugate elicited immediate-onset respiratory reactions in animals exposed to all doses of phthalic anhydride dust followed by sustained diaphragmatic contractions that resulted in a significant increase in plethysmograph pressure; however, challenge with phthalic anhydride dust did not elicit an immediate respiratory response. Also, significant levels of IgG antibodies were detected in sera of all exposed animals, and in a dose dependent manner. The animals exposed to and challenged with 5.0 mg/m^3 phthalic anhydride dust had significant numbers of hemorrhagic lung foci; those animals with greatest number of foci had high IgG antibody level. The authors concluded that this experiment showed that phthalic anhydride was immunogenic and allergic in guinea pigs exposed by inhalation to concentrations as low as 0.5 mg/m^3. The author also noted that in an earlier study (Sarlo et al., 1992), exposure of guinea pigs to lower range of phthalic anhydride dust concentrations (0.05 to 0.2 mg/m^3 over 5 days) did not induce detectable antibody, indicating 0.5 mg/m^3 is at or near the minimal concentration to immunize and allergically sensitize guinea pigs (Sarlo et al., 1994).This study presented limitations including a lack of particle irritant control, and concerns with animal restraint (some controls

showed an increased heart pressure response). However, there were strong indications that animals in the high dose group exhibited an allergenic response.

Other effects

The skin sensitization potential of phthalic anhydride was investigated in a guinea pig maximization test. Reactions indicative of the sensitized state were seen in 90 % of treated animals, demonstrating that phthalic anhydride is a skin sensitizer (Basketter and Scholes, 1992, as cited in OECD 2005). A number of murine local lymph node assay (LLNA) were identified. In one LLNA, an EC3 value of 0.357 % (which is the effective concentration of a chemical required to produce 3-fold increase in the proliferation of lymph node cells compared with the vehicle-treated controls) was derived (Van Och et al., 2000, as cited in OECD 2005). Phthalic anhydride was found to cause skin and eye irritation in rabbits. Noted ocular effects following occupational exposure included conjunctivitis, corneal ulceration, necrosis, and photophobia. It is also a primary irritant to mucous membranes and the upper respiratory tract in humans (OECD 2005).

Phthalic anhydride has been shown to have low repeated dose toxicity by the oral route in rats. In a chronic feeding study, rats were administered phthalic anhydride in the diet at 7500 or 15000ppm (approximately 500 or 1000mg/kg bw/day) for 105 weeks. The evidence of toxicity was limited to effects on body-weight gain at the dose level of 1000 mg/kg bw /day, the highest dose tested (NCI 1979, as cited in OECD 2005). As such, a NOAEL of 500 mg/kg-bw/day was identified by OECD (2005).

No evidence of carcinogenicity was found in rats after exposure up to approximately 1000 mg per kg-bw/day of phthalic anhydride, or in male and female mice after exposure up to 4670, and 3430 mg/kg-bw/day, respectively, in a comprehensive two year feeding study (OECD 2005).

Phthalic anhydride was not mutagenic in the Ames test with or without metabolic activation. It did induce chromosomal aberrations in mammalian cell at extremely high cytotoxic concentrations (10 mM). No *in vivo* studies were identified. OECD concluded that phthalic anhydride is genotoxic *in vitro* at extremely high cytotoxic concentrations. This genotoxic effect is not expected to be relevant under *in vivo* conditions, where phthalic anhydride is rapidly hydrolyzed to the non genotoxic phthalic acid (OECD 2005).

No reproductive study with phthalic anhydride was identified. However, the OECD concluded that in the two year carcinogenicity studies in rats and mice, no toxicity to reproductive organs was observed. Also, in the absence of maternal toxicity, phthalic anhydride did not induce developmental effects in experimental animals (OECD 2005).

6.1.3 Characterization of risk to human health

Based on the available information, the critical effect associated with exposure to phthalic anhydride is respiratory sensitization. Based on the collective data from epidemiological and animal studies, taking into account the limitations of the studies, it was considered reasonable to establish an effect level at 6.6 mg/m^3 representative of peak exposure concentration associated with respiratory effects in humans, and 0.4 mg/m^3 as the time-weighted average concentration over one day associated with an effect. Sarlo et al. (1992), showed that exposure of guinea pigs to 0.05 to 0.2 mg/m^3 of phthalic anhydride as dust via inhalation did not induce detectable antibody levels, indicating that a dose of 0.5 mg/m^3, tested on guinea pigs in a later study (Sarlo et al. 1994), could be near the minimal concentration required to cause a sensitization reaction in guinea pigs.

Comparison of the mean event concentration from the use of a spray paint amortized over 8-hours (0.0013 mg/m^3) to the time-weighted average dust concentration of 0.4 mg/m^3 identified from an epidemiology study conducted in an occupational setting resulted in a MOE of 309. Comparison of the peak concentration during the use of a spray paint (0.047 mg/m^3) to the effect level of 6.6 mg/m^3 corresponding to the peak concentration during loading of phthalic anhydride in the epidemiological study resulted in a MOE of 140.

Comparison of an effect level based on chronic exposure to dust in occupational settings with upper bound estimates of acute inhalation exposure to phthalic anhydride applied as a spray is considered to be a conservative approach and these margins are considered adequate to account for the uncertainties in the exposure and health effects databases.

Acute inhalation exposures from the use of a floor polish containing phthalic anhydride were lower than those from the use of a spray paint product, and thus margins of exposure are expected to be adequate for that scenario.

Dermal exposure to phthalic anhydride may arise from the use of eyelash adhesives, spray paints, and floor polish products. Comparison of the NOAEL of 500 mg/kg-bw/day identified from a chronic oral rat study to the acute dermal exposure to floor polishes (0.78 mg/kg-bw) and spray paints (0.00057 mg/kg-bw) resulted in MOEs of 641 and > 877 000, respectively. These margins are considered adequate to account for the uncertainties in the exposure and health effects databases. Additionally, comparison of the NOAEL of 500 mg/kg-bw/day with the estimated chronic dermal exposure from the use of an eyelash adhesive for teenagers (0.002 mg/kg-bw/day) resulted in an MOE of 250 000, which is considered adequate to account for the uncertainties in the exposure and health effects databases.

Phthalic anhydride was reported in indoor air at a mean concentration of 0.00062 mg/m^3. A comparison of the reported concentration of phthalic anhydride in indoor air to the daily time-weighted average dust concentration of 0.4 mg/m^3 from an occupational

study resulted in a MOE of 9677. This margin is considered adequate to account for the uncertainties in the exposure and health effects databases.

Table 6-2 summarizes relevant estimates of exposure, critical endpoints and resulting margins of exposure (MOE) for the characterization of human health risk from exposure to phthalic anhydride.

Table 6-2. Margins of exposure for phthalic anhydride

Exposure scenario	Exposure estimate	Critical level	Critical health effect	MOE
Floor polish (dermal, per event, adult)	0.78 mg/kg-bw	NOAEL = 500 mg/kg-bw/day (chronic (105 weeks) oral study in rats)	Decreased body weight gain at the next dose (1000 mg/kg-bw/day)	641[a]
Spray paint (inhalation, per event (peak concentration), adult).	0.047 mg/m^3	6.6 mg/m^3 (epidemiological study in occupational settings)	Respiratory sensitization effects observed in workers, including increased antibody levels, rhinitis, conjunctivitis and asthma	140
Spray paint (inhalation, 8-hr mean concentration, adult)	0.0013 mg/m^3	0.4 mg/m^3 (epidemiological study conducted in occupational settings)	Respiratory sensitization including increased antibody levels, rhinitis, conjunctivitis and asthma	308
Spray paint (dermal, per event, adult)	0.00057 mg/kg-bw	NOAEL = 500 mg/kg-bw/day (chronic oral in rats)	Decreased body weight gain at the next dose (1000 mg/kg-bw/day)	> 877 000[a]
Eyelash adhesive (dermal, daily, teenagers)	0.002 mg/kg-bw/day	NOAEL = 500 mg/kg-bw/day (chronic (105 weeks) oral study in rats)	Decreased body weight gain at the next dose (1000 mg/kg-bw/day)	250 000[a]
Indoor air (inhalation, adult)	0.00062 mg/m^3	0.4 mg/m^3 (epidemiological study conducted in	Respiratory sensitization including increased	9677

		occupational settings)	antibody levels, rhinitis, conjunctivitis and asthma	

[a] Derived on the basis of the assumption that dermal absorption is equivalent to oral absorption

6.2 Maleic anhydride

6.2.1 Exposure assessment

Environmental media and food

Maleic anhydride was not identified in drinking water, soil, or dust in Canada. However, based on the physical-chemical properties of the substance, exposures from these media are not expected as the substance would rapidly hydrolyze to phthalic acid.

Maleic anhydride was reported to be released to air in Canada at a rate of 0.018 tonnes (18 kg) per year in 2015 (NPRI 1994) by one facility. Upon release, maleic anhydride photodegrades in air through O_3-, OH-, and NO_3- mediated pathways (Grosjean 1990a, 1990b, Grosjean and Williams 1992; as cited in OECD 2004). In a 2004 OECD SIDS Initial Assessment Report (SIAR), the reported half-life in air using experimental data ranged from 4.2 to 18.6 hours, with OH mediated photo-degradation being the most rapid pathway (Grosjean 1990a, 1990b; as cited in OECD 2004). Considering this information, chronic exposure to maleic anhydride based on releases to air is expected to be minimal.

Maleic anhydride has been identified as a component used in the manufacture of a variety of food packaging applications. When considering the rapid rate of hydrolysis of the substance to maleic acid, dietary exposure from such uses are expected to be negligible (personal communication, emails from the Food Directorate, Health Canada, to the RMB, Health Canada, dated September 2016; unreferenced).

Cosmetic products

Maleic anhydride has been identified in several types of products available to consumers based on information submitted to Health Canada. It has been reported to be present in shampoos, temporary tattoos, exfoliants, bubble baths (foam and oil), bath salts, and body cleansers at concentrations ranging from 0.1 to 3 per cent (personal communication, emails from the CPSD, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 2016; unreferenced). These products (with the exception of temporary tattoos and exfoliants) would be diluted in water, wherein maleic anhydride would be expected to rapidly hydrolyze, with a half-life of approximately 22 seconds; thus exposure from uses of cosmetic products containing maleic anhydride, other than temporary tattoos and exfoliants, is not expected (Bunton et al. 1963; as cited in OECD, 2004). Exposure to maleic anhydride from its use in temporary tattoos and an exfoliants was estimated using ConsExpo. The dermal

exposure from use in temporary tattoos at the highest reported concentration of 3% was estimated to be 0.0011 mg/kg-bw. The dermal exposure from the use of exfoliants at the highest reported concentration of 0.3% was estimated to range from 0.0051 to 0.0061 mg/kg-bw/day for adults and teenagers, respectively.

Do-it-yourself products

Maleic anhydride was identified in a blending stick designed to repair minor scratches on wooden surfaces (SDS 2015k). The product is intended to be used by rubbing the blend stick back and forth over the imperfection until filled, and to be used only on finished surfaces where minor imperfections are present. Based on the infrequent use of products of this type, the small amount that would be applied during application, and the physical-chemical properties of maleic anhydride (air half-life of 4-19 hours), appreciable inhalation exposure to maleic anhydride from use of this product is not expected.

As a user may come into direct contact with the blending stick during application, dermal exposure from this product was estimated using ConsExpo Web. Dermal exposure to maleic anhydride at a concentration of 0.25% (assumes 10% reported concentration in product as unreacted maleic anhydride (ECCC 2016d)) in a blending stick product was estimated to be 0.0042 mg/kg-bw.

6.2.2 Health effects assessment

Maleic anhydride has been assessed by OECD (2004). The substance was also on the Community Rolling Action Plan (CoRAP) list under the REACH regulation, and has been evaluated by the Member State Austria, the Environment Agency Austria, in 2013. A Substance Evaluation Report was published in 2014 by the European Chemicals Agency (ECHA, 2014). These assessments were used to inform the health effects characterization of this substance. A literature search was conducted for the period one year before each international assessment to October 2016, and no studies that could result in a different health effects characterization from OECD or ECHA assessments were identified.

Skin and respiratory tract sensitization

The European Commission (EC) classified maleic anhydride as Category 1 for both respiratory and dermal sensitization according to the EC harmonized classification, with the following hazard statements: H317: may cause an allergic skin reaction; and H334: may cause allergy or asthma symptoms or breathing difficulties if inhaled.

The OECD assessment did not conclude on whether the substance was a respiratory or dermal sensitizer based on available information. The report, however, mentioned, that maleic anhydride had been shown to be a skin sensitizer to guinea pigs and a possible respiratory sensitizer to rats. The OECD reports a few published human cases suggesting maleic anhydride provoked asthma in a relatively small proportion of

exposed workers but indicating further that questions were raised about whether the asthma was related to maleic anhydride exposure (OECD 2004).

The Environment Agency Austria evaluated the substance in 2013 under the REACH regulation and concluded that maleic anhydride was considered to be a skin and respiratory sensitizer with high potency. A qualitative risk assessment was carried out, as ECHA determined that it was not possible to derive thresholds for these effects (ECHA 2014).

In addition, Dearman et al (2000, as cited in OECD 2004) conducted an LLNA, and identified an EC3 value of 0.16% for maleic anhydride.

Other effects

The OECD reports the results of several repeated dose studies. In a chronic repeated dose study, male and female rats were administered maleic anhydride in feed at 0, 10, 32 or 100 mg/kg-bw/day, seven days a week for two years. There was slight, but dose-related, decrease in body weights observed in animals in the mid and high dose groups; food consumption was also slightly reduced during limited periods of the study for animals in these groups. Several sub-chronic oral studies were identified. In a 90- day oral study, rats were fed maleic anhydride in diet up to 600 mg/kg-bw/day. Kidney effects were observed at 100 mg/kg-bw/day, the lowest dose tested. In another 90-day fed study in dogs, no adverse effects were observed at 60 mg/kg-bw/day, the highest dose tested (OECD 2004).

In an inhalation study, CD rats, Engle hamster and Rhesus monkeys were exposed (whole body) to maleic anhydride concentrations of 0, 1.1, 3.3 and 9.8 mg/m^3, six hours per day, five days per week for six months. A NOAEC of 3.3 mg/m^3 for rats was considered based on decreased body weights and localized eye and nasal irritation effects; and the NOAECs for hamsters and monkeys were considered to be 9.8 mg/m^3 by the OECD, the highest dose tested based on localized nasal irritation effects only (OECD 2004).

In the above two- year oral study, there was no increase in tumour incidence that was considered to be related to exposure to maleic anhydride (CIIT 1983) and ECHA concluded that there is no indication that maleic anhydride has any carcinogenic potential (ECHA 2014).

Maleic anhydride was negative in bacterial mutation tests. It was found equivocal in *in vitro* chromosomal aberration assays; but negative in the *in vivo* assay (OECD 2004).

With respect to reproductive toxicity, the OECD reported the results of an oral two-generation reproductive toxicity study. Rats were administered 0, 20, 55 and 150 mg/kg/day of maleic anhydride via gavage. No reproductive effects were observed in exposed animals at the highest dose tested. However, adverse effects in kidneys and bladder of parental animals (first generation only) were observed at all doses, and a

LOAEL of 20 mg/kg-bw/day for parental effects, the lowest dose tested, was identified (IRDC 1982; Short et al. 1986, as cited in OECD 2004).

No developmental effects were observed in an oral study in rats at the highest dose tested (Goldenthal et al. 1979b; Short et al. 1986, as cited in OECD 2004).

6.2.3 Characterization of risk to human health

Table 6-3 provides exposure estimates, critical endpoints and resultant margins of exposure for characterization of the human health risk from exposure to maleic anhydride.

Table 6-3: Margins of exposure for maleic anhydride

Exposure scenario	Exposure estimate	Critical effect level	Critical effect	MOE
Blending stick (dermal, per event, adult)	0.0042 mg/kg-bw	LOAEL = 20 mg/kg-bw/day	Histopathological changes in kidneys and bladder	4 700
Temporary tattoo (dermal, per event, children)	0.0011 mg/kg-bw	LOAEL = 20 mg/kg-bw/day	Histopathological changes in kidneys and bladder	18 000
Exfoliants (dermal, per event, adults and teenagers)	0.0051 – 0.0061 mg/kg-bw/day	LOAEL = 20 mg/kg-bw/day	Histopathological changes in kidneys and bladder	3 700 – 3 900[a]

[a] Derived on the basis of the assumption that dermal absorption is equivalent to oral absorption

Acute dermal exposure to maleic anhydride may arise from use of a blending stick to repair minor scratches/imperfections on wooden surfaces, as well as the use of temporary tattoos. Comparison of the estimated dermal exposure from the use of a blending stick (0.0042 mg/kg-bw) and from the use of temporary tattoo products (0.0011 mg/kg-bw) to the LOAEL of 20 mg/kg-bw/day, the lowest dose tested, based on kidney and bladder effects identified in a reproductive study in rats, results in MOEs of approximately 4700 and 18 000, respectively. These margins are considered adequate to account for the uncertainties in the exposure and health effects databases.

Chronic dermal exposure to maleic anhydride may arise from its use as an ingredient in exfoliants. The comparison of the estimated dermal exposure from use in exfoliants for

adults and teenagers (0.0051 – 0.0061 mg/kg-bw/day) to the LOAEL of 20 mg/kg-bw/day results in MOEs of 3 700 to 3 900. These margins are considered adequate to account for the uncertainties in the exposure and health effects databases.

6.3 Trimellitic anhydride

6.3.1 Exposure assessment

Environmental media and food

Concentrations of trimellitic anhydride in the environment were not identified in Canada, or elsewhere. Based on the uses of trimellitic anhydride as a chemical intermediate in the synthesis of other substances, exposures during manufacture and handling of the substance may occur. A number of studies cited in the OECD document (2002) for trimellitic anhydride and trimellitic acid have reported trimellitic anhydride concentrations in air associated with occupational exposures. Trimellitic anhydride concentrations were measured over 14 years in a US production plant. Concentrations were measured almost annually from 1974 to 1989 for two job categories in the facility: operators of the resin manufacturing process and packagers of the completed resin (Grammer et al. 1992). Air concentrations over this period ranged from <0.001 to 2.1 mg/m^3 (Grammer at al. 1992). Trimellitic anhydride is not manufactured in Canada; release quantities of this substance could not be identified. Trimellitic anhydride has a high water solubility, low log K_{ow}, low Henry's law constant, and a low vapor pressure. Based on this information, if releases to the environment occurred, trimellitic anhydride would be expected to partition to the water compartment where it would be rapidly hydrolyzed (OECD 2002).

Trimellitic anhydride has been identified as a component of resins used in the manufacture of some food packaging materials. When considering the rapid rate of hydrolysis of the substance in water or high humidity, dietary exposure from these uses are expected to be negligible (personal communication, emails from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated October 2016; unreferenced).

Cosmetic products

Based on notifications to Health Canada, trimellitic anhydride has been reported to be used as an ingredient in nail polish products at concentrations up to 30% (personal communication, emails from the CPSD, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 2016; unreferenced). Similar to phthalic anhydride, trimellitic anhydride is present in nail polish products as a copolymer. Based on the function of trimellitic anhydride in these products, it is expected to have polymerized and therefore exposure to the monomer from nail polish products is not expected (personal communication, emails from the CPSD, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 2016; unreferenced).

Trimellitic anhydride was not identified in other products available to consumers in Canada, or elsewhere. Exposures to trimellitic anhydride from its use in the synthesis of plasticizers for PVC resins, as well as its use as a reactant in wire and cable insulations, polyester resins, coatings, curing agents, binding agents, and cross-linking agents, among others are not expected as the substance is fully consumed during these uses and therefore not available (OECD 2002).

6.3.2 Health effects assessment

Trimellitic anhydride has been assessed by OECD (2002), and this assessment was used to inform the health effects characterization of this substance. A literature search was conducted for the period one year before OECD assessment to October 2016, and no studies that could result in a different health effects characterization from OECD assessment were identified.

Since the exposure of the Canadian general population to trimellitic anhydride is expected to be negligible, a qualitative risk assessment is conducted for this substance. As such, characterization of the health effects associated with this substance is presented briefly below.

On the basis of available information, OECD (2002) concluded that trimellitic anhydride should be considered a dermal sensitizer. In this report, it was further stated that the principal effects of trimellitic anhydride are on the immune system and the lung. Elevated antibody levels and lung foci were observed in a 13-week inhalation repeat dose study in rats. Elevated antibody levels, asthma, allergic rhinitis, and a late respiratory systemic syndrome (LRSS) were also associated with occupational exposure in some workers. The OECD concluded that the toxicity of trimellitic anhydride following repeated exposure is low, based on NOAELs of approximately 500 mg/kg-day identified for both rats and dogs. In vivo genotoxicity data were not available, however, in vitro assays with trimellitic anhydride were found to be negative. Although reproductive toxicity tests were not identified by the OECD, it was noted that histopathological changes to reproductive tissues have not been observed in rats following subchronic exposures, and trimellitic anhydride has been found to be neither teratogenic nor fetotoxic in developmental toxicity studies (OECD 2002).

6.3.3 Characterization of risk to human health

Exposure to trimellitic anhydride from environmental media or food packaging is expected to be negligible and exposure from nail polish product is not expected based on the substance function in nail polish products. Since the exposure of the general population to trimellitic anhydride is expected to be negligible, the risk to human health is considered to be low.

6.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in Table 6-4 below.

Table 6-4. Sources of uncertainty in the risk characterization.

Key source of Uncertainty	Impact
Reported indoor air and dust concentrations of phthalic anhydride may be overestimated due to the potential degradation of phthalic esters into phthalic anhydride during GC/MS analyses	+
Lack of dermal absorption data for phthalic anhydride and maleic anhydride to inform the route to route extrapolation when using a critical effect level based on oral exposure for risk characterization	+
Uncertainty in the analytical procedures reporting concentrations of phthalic anhydride in children's products, however, there is confidence that if phthalic anhydride was present in low levels in children's product it would be rapidly hydrolyzed upon migration	+/-
There are uncertainties associated with the selection of effect levels for characterization of risk of respiratory sensitization from exposure to phthalic anhydride. There is, however, confidence that the risk assessment approach for the substance is conservative, and the margins of exposure calculated for the risk characterization are adequate to account for this uncertainty although a threshold dose (below which respiratory effects are not observed) was not identified in the literature,.	-
There is also an uncertainty associated with the selection of an effect level from a two generation oral study for risk characterization of an acute dermal exposure scenario for maleic anhydride (wood repair stick and tattoos scenarios).	+

+ = 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.

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from phthalic anhydride, maleic anhydride, and trimellitic anhydride. It is concluded that phthalic anhydride, maleic anhydride, and trimellitic anhydride 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 screening assessment, it is concluded that phthalic anhydride, maleic anhydride, and trimellitic anhydride 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 concluded that phthalic anhydride, maleic anhydride and trimellitic anhydride do not meet any of the criteria set out in section 64 of CEPA.

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Appendices

Appendix A: Estimated exposures to phthalic anhydride

Exposures were estimated based on the assumed weight, 70.9kg, of an adult (Health Canada 1998) and use behaviours of an adult. Exposures were estimated using ConsExpo Web (ConsExpo 2016) or algorithms from the model (RIVM 2007). An inhalation rate of 16.2 m^3/day was assumed for adults (Health Canada 1998). Scenario specific assumptions are provided in Table A-1.

A-1. Estimated exposure from products available to consumers containing phthalic anhydride based on ConsExpo modelling

Exposure Scenario	Assumptions
Exposure to spray paint	Paint scenario using ConsExpo Web(ConsExpo Web 2016, RIVM 2010) Inhalation: Exposure duration of 20 min, room volume of 34m^3, ventilation rate of 1.5/hr Dermal: Contact rate of 100mg/min, release duration of 15 min, absorption fraction of 1
Exposure to floor polish	Floor polish scenario using ConsExpo web (ConsExpo Web 2016, RIVM 2006) Maximum reported weight fraction of 1% (SDS 2016) Inhalation: Exposure and application duration of 90 min, product amount of 550 g, room volume of 58 m^3, ventilation rate of 0.5/h, release area of 22m^2, thibodeaux method for mass transfer rate, molecular weight matrix of 22g/mol Dermal: Exposed area of 430 cm^2, product amount of 5.5g (RIVM 2006)
Use of eyelash adhesive	Concentration: ≤ 1% (email from Consumer Product Safety Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) Age group: Teenager and adult Body Weight: 59.4 kg for teenager and 70.9 kg for adult Product Amount (g): 0.012 (Lim et al. 2014)

	Frequency: 1/day (Lim et al. 2014)

Appendix B: Estimates of exposure to maleic anhydride in products available to consumers

Body weights and age groups are from Health Canada 1998. Scenario-specific assumptions are provided in Table B-1.

B-1. Estimated exposure from products available to consumers containing maleic anhydride based on ConsExpo modelling.

Exposure Scenario	Assumptions
Use of blending stick	Scenario using ConsExpo Web (ConsExpo 2016, RIVM 2007) Dermal: Area exposed: 30cm^2 (1/4 surface area of one hand) Product amount 0.12g (10% of product mass) Concentration: 0.25% (ECCC 2016d)
Use of temporary tattoo	Concentration: ≤ 3% (email from Consumer Product Safety Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) Age group: Child Body Weight: 31.0 kg Product Amount (g): 0.0011 (Scott & Moore 2000)
Use of exfoliant	Concentration: ≤ 0.3% (email from Consumer Product Safety Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) Age group: Teenager and adult Body Weight: 59.4 kg for teenager and 70.9 kg for adult Product Amount (g): 1.2 (Lorets et al. 2005) Retention Factor: 0.1 (EAU 2005; NICNAS 2009)