Screening Assessment

Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

Environment and Climate Change Canada
Health Canada

July 2019

Cat. No.: En14-382/2019E-PDF

ISBN 978-0-660-31521-8

Aussi disponible en français

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 11 of 13 substances referred to collectively under the Chemicals Management Plan as the Musks (macro/poly cyclic) Group. These 11 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA. Two of the 13 substances were determined to be of low concern through other approaches, and decisions for these substances are provided in a separate report[1]. Accordingly, this screening assessment addresses the 11 substances listed in the table below. The 11 substances addressed in this screening assessment report are hereinafter referred to as the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group. The Chemical Abstracts Service Registry Numbers (CAS RN[2]), their *Domestic Substances List* (DSL) names, their common names and their subgroup are listed in the table below.

Substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

CAS RN	DSL name	Common name	Subgroup
106-02-5	Oxacyclohexadecan-2-one	Exaltolide	Macrocyclic lactones and ketones
109-29-5	Oxacycloheptadecan-2-one	Hexadecanolide	Macrocyclic lactones and ketones
502-72-7	Cyclopentadecanone	Exaltone	Macrocyclic lactones and ketones
541-91-3	Cyclopentadecanone, 3-methyl-	Muskone/Muscone	Macrocyclic lactones and ketones
542-46-1	9-Cycloheptadecen-1-one, (Z)-	Civetone	Macrocyclic lactones and ketones

[1] Conclusions for CAS RNs 8001-04-5 and 68140-48-7 are provided in the Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances 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.

7779-50-2	Oxacycloheptadec-7-en-2-one	Hexadecenlactone/ Ambrettolide	Macrocyclic lactones and ketones
28645-51-4	Oxacycloheptadec-10-en-2-one	Isoambrettolide	Macrocyclic lactones and ketones
37609-25-9	5-Cyclohexadecen-1-one	Musk amberol/Ambrettone	Macrocyclic lactones and ketones
1335-94-0	Irone	Irone	Ionones
7779-30-8	1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	1-Methyl-α-ionone	Ionones
108-94-1	Cyclohexanone	Cyclohexanone	Cyclohexanone

Exaltolide, isoambrettolide, 1-methyl-α-ionone, and cyclohexanone were reported to be imported into Canada in total quantities up to 166 810 kg in 2011. In the same year, exaltolide and isoambrettolide were not reported to be manufactured in Canada, whereas 1-methyl-α-ionone and cyclohexanone were manufactured in Canada at quantities up to 950 kg. No quantities were reported for the other substances in this group above the reporting threshold of 100 kg in the 2011 calendar year.

Substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group are used primarily as fragrances or fragrance ingredients. Exaltolide, muskone/muscone, civetone and cyclohexanone occur naturally in the environment. In Canada, substances in this group are used in a variety of applications including cosmetics (including body lotion and eau de toilette), sunscreen, and do-it-yourself products (including wall paint).

The ecological risks of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone 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 upon 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 on the basis of their hazard and exposure profiles. Based on the outcome of the ERC analysis, these substances are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from the 11 substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group. It is concluded that the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and

Cyclohexanone Group 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.

For the human health risk assessment, the 11 substances in this group were separated into the macrocyclic lactones and ketones subgroup, the ionones subgroup and one substance (cyclohexanone). Substances in the macrocyclic lactones and ketones subgroup are considered to have low hazard potential. On the basis of available health effects information for structurally-related substances, the ionones subgroup has adverse effects including kidney changes with repeated oral or dermal exposures. On the basis of this assessment, cyclohexanone demonstrates low potential for adverse effects via the oral and inhalation routes of exposure.

Environmental media and food were not identified as significant sources of exposure to Canadians. For all subgroups, estimates of exposure were derived based upon levels of substances in products available to consumers, such as cosmetics. On the basis of these estimates of exposure compared with critical effect levels identified from laboratory studies, margins of exposure are considered to be adequate to address uncertainties in the health effects and exposure databases.

On the basis of the information presented in this screening assessment, it is concluded that the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group 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 the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group 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 on 11 of 13 substances referred to collectively under the Chemicals Management Plan as the Musks (macro/poly cyclic) Group to determine whether these 11 substances present or may present a risk to the environment or to human health. These 11 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]).

The other two substances (CAS RNs[3] 8001-04-5; musks and 68140-48-7; ethanone, 1-[2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1H-inden-5-yl]-) 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 two substances are provided in the Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment (ECCC, HC 2018).

The 11 substances are addressed in this screening assessment report, and are hereinafter referred to as the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group.

The ecological risks of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone 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 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.

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[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.

The substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group currently being evaluated have been reviewed internationally through the Organisation for Economic Co-operation and Development (OECD) Cooperative Chemicals Assessment Programme, and Screening Information Data Set (SIDS) and Initial Assessment Reports (SIARs) are available (OECD 2012). 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 these processes, and consider these assessments to be reliable. In addition, the health effects of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group have been reviewed by the International Agency for Research on Cancer (IARC) Monographs Programme, United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS) Toxicological Review, Joint Food and Agriculture Organization of the United Nations/World Health Organisation (WHO) Expert Committee on Food Additives (JECFA) and European Food Safety Authority (EFSA), and there are existing assessments available. These assessments were used to inform the health effects characterization in this screening assessment.

This screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure, including additional information submitted by stakeholders. Relevant data were identified up to June 2017. However, more recent studies or information provided via internal and external peer consultation may also be cited. Empirical data from key studies as well as 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 Programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The human health portions of this screening assessment have undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Herman Gibb, Theresa Lopez, Katherine Super, Jennifer Flippin, and Gary Drendel of Tetra Tech. 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. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health 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.[4] The

[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.

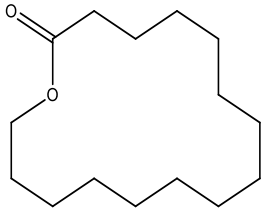
screening assessment presents the critical information and considerations upon which the conclusions are based.

2. Identity of substances

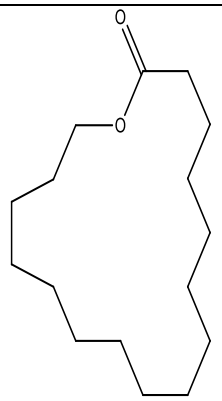
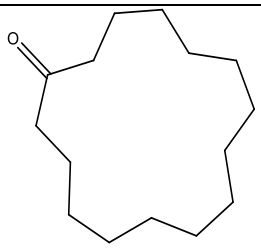
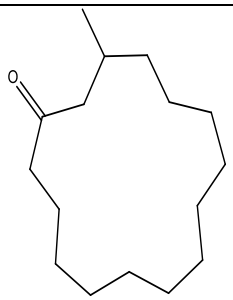
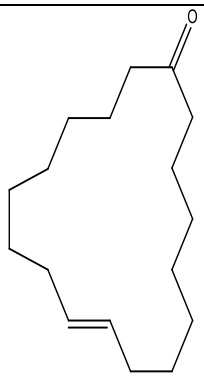
The CAS RN, Domestic Substances List (DSL) names and common names for the individual substances in Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group are presented in Table 2-1, 2-2 and 2-3. A list of additional chemical names (e.g., trade names) is available from the National Chemical Inventories (NCI 2014).

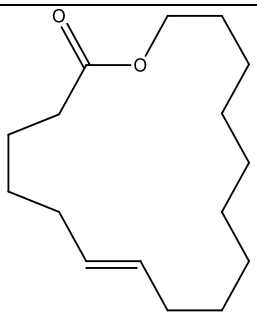
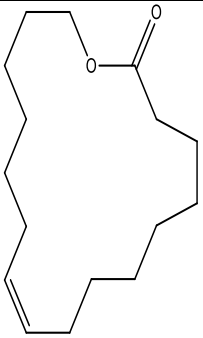
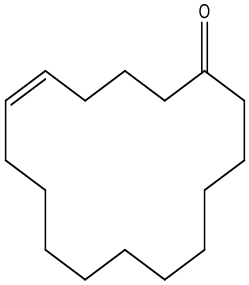
For the purposes of this screening assessment, the 11 substances discussed are divided into two subgroups and one individual substance: eight macrocyclic lactones and ketones (Table 2-1), two ionones (Table 2-2) and cyclohexanone (Table 2-3). The eight macrocyclic lactone and ketone substances are characterized by a macrocyclic ring with 15-17 bonds, which includes a ketone or ester group as part of the ring. The two ionone substances are characterized by a characterized by a six carbon ring including one double bond (cycloalkene) and possessing four alkyl branches with one containing 5 carbons including a ketone group. Cyclohexanone is a cyclic six-carbon ring with one ketone group.

Table 2-1. Substance identities for the macrocyclic lactones and ketones subgroup[a]

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
106-02-5	Oxacyclohexadecan-2-one (Exaltolide)	 $C_{15}H_{28}O_2$	240.39

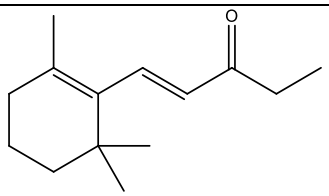
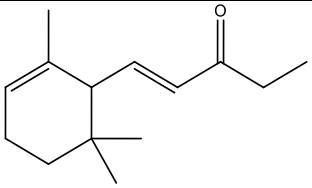
For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Hazardous Products Regulations, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for hazardous products intended for workplace use, handling and storage. Similarly, a conclusion based upon the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
109-29-5	Oxacycloheptadecan-2-one (Hexadecanolide)	 $C_{16}H_{30}O_2$	254.42
502-72-7	Cyclopentadecanone (Exaltone)	 $C_{15}H_{28}O$	224.39
541-91-3	Cyclopentadecanone, 3-methyl- (Muskone/Muscone)	 $C_{16}H_{30}O$	238.42
542-46-1	9-Cycloheptadecen-1-one, (Z)- (Civetone)	 $C_{17}H_{30}O$	250.43

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
7779-50-2	Oxacycloheptadec-7-en-2-one (Hexadecenlactone/ Ambrettolide)	 $C_{16}H_{28}O_2$	252.4
28645-51-4	Oxacycloheptadec-10-en-2-one (Isoambrettolide)	 $C_{16}H_{28}O_2$	252.4
37609-25-9	5-Cyclohexadecen-1-one (Musk amberol/Ambrettone)	 $C_{16}H_{28}O$	236.4

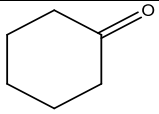
[a] Except for the DSL name, the majority of information is from McGinty et al. (2011a,b,c,d,e,f,g,h).

Table 2-2. Substance identities for the ionones subgroup

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
1335-94-0[a]	Irone (Irone)	 $C_{14}H_{22}O$	206.33
7779-30-8[b]	1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)- (1-Methyl-α-ionone)	 $C_{14}H_{22}O$	206.33

[a] Information from ChemIDplus (2016).
[b] Except where indicated, all information from Scognamiglio et al. (2013).

Table 2-3. Substance identity for the cyclohexanone subgroup

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
108-94-1[a]	Cyclohexanone (Cyclohexanone)	 $C_6H_{10}O$	98.14

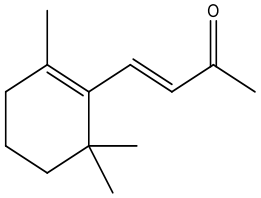
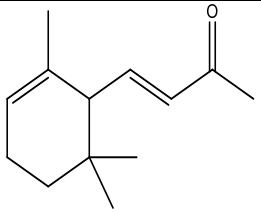
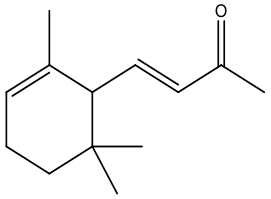
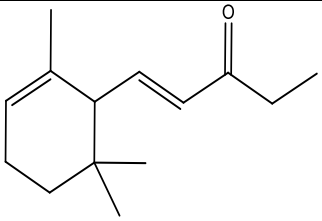
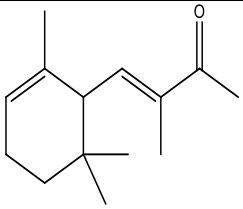
[a] all information from OECD (2002).

2.1 Selection of analogues

A read-across approach using data from analogues has been used to inform the human health assessment of the ionones subgroup. Analogues were selected that were structurally similar and/or functionally similar to substances within this group (similar physical-chemical properties, toxicokinetics) and that had relevant empirical data that could be used to read across to substances with limited empirical data.

Information on the identities and chemical structures of the analogues used to inform the ionone subgroup is presented in Table 2-4.

Table 2-4. Substance identity of analogues used in the human health assessment

CAS RN for analogue	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
14901-07-6	4-(2,6,6-trimethylcyclohex-1-en-1-yl)but-3-en-2-one (β-ionone)	 $C_{13}H_{20}O$	192.30
127-41-3	(E)-(1)-4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (α-ionone)	 $C_{13}H_{20}O$	192.3
8013-90-9	Ionone	 (60/40 mixture of α- and β-ionone) $C_{13}H_{20}O$	192.3
1335-46-2	(1E)-1-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-1-en-3-one (methyl-ionone)	 $C_{14}H_{22}O$	206.32
127-51-5	3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-(α-iso-methylionone)	 $C_{14}H_{22}O$	206.33

2.1.1 Justification of analogues

Two of the analogue substances (β-ionone, α-ionone) for the Ionones subgroup are isomers of each other (α-ionone and β-ionone) and the third (Ionone) is a 60/40 mixture of α-ionone and β-ionone. They have similar physical and chemical properties and are

used as fragrance ingredients (ECHA 2017d,e,f). Two additional analogues (methyl-ionone and α-iso-methylionone), were used for the Ionones subgroup on the basis of structural similarity (i.e. characterized by a six carbon ring including one double bond (cycloalkane) and possessing four alkyl branches with one containing 5 carbons including a ketone group), similar physical and chemical properties and uses (ECHA 2017g,h). Toxicological data for these analogues can be found in Appendix B.

3. Physical and chemical properties

A summary of the key physical and chemical properties of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group are presented in Tables 3-1, 3-2 and 3-3. When experimental information was limited or not available for a property, data from analogues were used for read-across and/or (Q)SAR models were used to generate predicted values for the substance. Properties for the analogue substances are presented in Table 3-4. Additional physical chemical properties are presented in ECCC (2016b).

Table 3-1. Key physical and chemical property values for substances in the macrocyclic lactones and ketones subgroup[a]

CAS RN	Common Name	Water solubility (mg/L)	Log K_{ow}	Vapour Pressure (Pa)
106-02-5	Exaltolide	37.51	6.15	0.0069
109-29-5	Hexadecanolide	18.54	6.65	0.0033
502-72-7	Exaltone	105.97	5.55	0.056
541-91-3	Muskone/Muscone	34.086	5.96	0.063
542-46-1	Civetone	22.063	6.31	0.045
7779-50-2	Hexadecenlactone/ Ambrettolide	15.74	5.37	0.0030
28645-51-4	Isoambrettolide	15.74	5.37	0.0030
37609-25-9	Musk amberol/ Ambrettone	44.61	5.82	0.032

Abbreviations: K_{ow}, octanol–water partition coefficient.
[a] Data are estimates based upon the US EPA's EPI Suite (c2000-2012)

Table 3-2. Key physical and chemical property values for substances in the ionones subgroup[a]

CAS RN	Common Name	Water solubility (mg/L)	Log K_{ow}	Vapour Pressure (Pa)
1335-94-0	Irone	4.23	4.78	0.87
7779-30-8	1-Methyl-α-ionone	4.23	4.78	0.087

Abbreviations: K_{ow}, octanol–water partition coefficient

[a] Data are estimates based upon the US EPA's EPI Suite (c2000-2012)

Table 3-3. Key physical and chemical property values for cyclohexanone

CAS RN	Common Name	Water solubility (mg/L)	Log K_{ow}	Vapour Pressure (Pa)
108-94-1	Cyclohexanone	24,000[a]	1.13[a]	670[b]

Abbreviations: K_{ow}, octanol–water partition coefficient.
[a] Data are estimates based upon the US EPA's EPI Suite (c2000-2012)
[b] OECD (2002)

Table 3-4. Key physical and chemical property values for the analogue substances

CAS RN	Common Name	Water solubility (mg/L)	Log K_{ow}	Vapour Pressure (Pa)
14901-07-6[a]	β-ionone	160	1.903	3.03
127-41-3[a]	α-ionone	400	3.85	3.61
8013-90-9[a]	Ionone	NA	NA	NA
1335-46-2[a]	methyl-ionone	>21-<44	>4.5-<5	0.4
127-51-5[a]	α-iso-methylionone	>21-<44	4.7	0.22

Abbreviations: NA, not available; K_{ow}, octanol–water partition coefficient.
[a]Data from ECHA (2017d,e,f, g, h).

4. Sources and uses

The Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone substances in this group are used primarily as fragrances or fragrance ingredients. Four of the substances, exaltolide, muskone/muscone, civetone and cyclohexanone are naturally occurring.

All of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group have been included in a survey issued pursuant to section 71 of CEPA (Canada 2012). Data compiled from the survey responses is summarized in Table 4-1.

Table 4-1. Summary of information on Canadian manufacturing and imports of Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group in 2011, submitted pursuant to a survey under section 71 of CEPA (Environment Canada 2013)[a]

Subgroup	Common name	Total manufacture[a] (kg)	Total imports[a] (kg)
Macrocyclic lactones and ketones	Exaltolide	0[b]	1,000 - 10,000
Macrocyclic lactones and ketones	Hexadecanolide	NR	NR
Macrocyclic lactones and ketones	Exaltone	NR	NR
Macrocyclic lactones and ketones	Muskone/Muscone	NR	NR
Macrocyclic lactones and ketones	Civetone	NR	NR
Macrocyclic lactones and ketones	Hexadecenlactone/ Ambrettolide	NR	NR
Macrocyclic lactones and ketones	Isoambrettolide	0[b]	100-1,000
Macrocyclic lactones and ketones	Musk amberol/Ambrettone	NR	NR
Ionones	Irone	NR	NR
Ionones	1-Methyl-α-ionone	151	180
Cyclohexanone	Cyclohexanone	950	166,809

Abbreviations: NR, not reported above the reporting threshold of 100 kg (Canada 2012).

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

[b]Value reported was 0 kg (Environment Canada 2013)

In the U.S., the Chemical Data Access Tool (CDAT) website reported the national production volume (2012 reporting year) for exaltolide and cyclohexanone was between 1 000 000 and 10 000 000 pounds (~450 000- 4 500 000 kg) and >2 billion pounds (>900 million kg), respectively (US EPA 2016). In Europe, exaltolide, isoambrettolide, and cyclohexanone are imported and/or manufactured at 1 to 10 100 to 1 000 and 1 000 000 to 10 000 000 tonnes per year, respectively (ECHA 2017a,b,c).

Tables 4-2 and 4-3 present a summary of the major uses of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group in Canada, according to information reported in response to a survey conducted under section 71 of CEPA (Environment Canada 2013). Additional Canadian uses are included in Tables 4-4, 4-5, and 4-6. On the basis of publically available product material safety data sheets (MSDSs), some substances in this group may also be found in vehicle air fresheners (MSDS 2015a; MSDS 2013b), automotive maintenance products (MSDS 2013a) and cement adhesives (MSDS 2014) in Canada.

Table 4-2. Summary of Canadian uses of substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group (on the basis of information obtained from section 71 survey conducted under CEPA)

Major uses[a]	Exaltolide	Hexadecanolide	Exaltone	Muskone/Muscone
Lubricants and greases	N	N	N	N
Cleaning and furnishing care	N	N	N	N
Laundry and dishwashing	N	N	N	N
Personal care	Y	Y	Y	Y
Air care	Y	N	N	N
Apparel and footwear	N	N	N	N
Pet care	N	N	N	N
Automotive care	N	N	N	N
Drugs	Y	N	N	N
Natural health	Y	N	N	N
Ink, toner and colourants	N	N	N	N
Paints and coatings	N	N	N	N
Building or construction materials	N	N	N	N
Adhesives and sealants	N	N	N	N
Automotive, aircraft and transportation	N	N	N	N
Chemical reagent	N	N	N	N
Electrical and Electronics	N	N	N	N

Abbreviations: Y, use was reported for this substance; N, use was not reported for this substance.
[a] Uses reported in response to the survey conducted under section 71 of CEPA (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

Table 4-3. Summary of Canadian uses of substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group (on the basis of information obtained from section 71 survey conducted under CEPA)

Major uses[a]	Isoambrettolide	Musk amberol/Ambrettone	1-Methyl-α-ionone	Cyclohexanone
Lubricants and greases	N	N	Y	Y
Cleaning and furnishing care	N	N	Y	N
Laundry and dishwashing	N	N	Y	N
Personal care	Y	Y	Y	N
Air care	N	N	Y	N
Apparel and footwear	N	N	Y	N
Pet care	N	N	Y	N
Automotive care	N	N	Y	N
Drugs	Y	N	N	N
Natural health	N	N	N	N
Ink, toner and colourants	N	N	N	Y
Paints and coatings	N	N	N	Y
Building or construction materials	N	N	N	Y
Adhesives and sealants	N	N	N	Y
Automotive, aircraft and transportation	N	N	N	Y
Chemical reagent	N	N	N	Y
Electrical and Electronics	N	N	N	Y

Abbreviations: Y, use was reported for this substance; N, use was not reported for this substance.
[a] Uses reported in response to the survey conducted under section 71 of CEPA (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

Table 4-4. Additional uses in Canada for each of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

Use	Exaltolide	Hexadecanolide	Exaltone	Muskone/Muscone
Internal Drug Product Database as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products in Canada[a]	Y	N	N	N
Natural Health Products Ingredients Database[b]	Y	N	N	Y

Use	Exaltolide	Hexadecanolide	Exaltone	Muskone/Muscone
Licensed Natural Health Products Database as medicinal or non-medicinal ingredients in natural health products in Canada[c]	Y	N	N	N
Notified to be present in cosmetics, based upon notifications submitted under the *Cosmetic Regulations* to Health Canada[d]	N	Y	Y	N
Formulant in pest control products registered in Canada[e]	Y	Y	Y	Y

Abbreviations: Y, use was reported for this substance; N, use was not reported for this substance.
[a] DPD [modified 2016]
[b] NHPID [modified 2018]
[c] LNHPD [modified 2018]
[d] personal communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau, Nov 2016; unreferenced
[e] Personal communication with the Pest Management Regulatory Agency of Health Canada, Nov 2016; unreferenced

Table 4-5. Additional uses in Canada for each of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

Use	Civetone	Hexadecenlactone/ Ambrettolide	Isoambrettolide	Musk amberol/Ambrettone
Natural Health Products Ingredients Database[a]	N	Y	N	N
Formulant in pest control products registered in Canada[b]	Y	Y	Y	Y

Abbreviations: Y, use was reported for this substance; N, use was not reported for this substance.
[a] NHPID [modified 2018]
[b] Personal communication with the Pest Management Regulatory Agency of Health Canada, Nov 2016; unreferenced

Table 4-6. Additional uses in Canada for each of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

Use	Irone	1-Methyl-α-ionone	Cyclohexanone
Food packaging materials[a]	N	N	Y
Natural Health Products Ingredients Database[b]	N	Y	Y
Notified to be present in cosmetics, based upon notifications submitted under the *Cosmetic Regulations* to Health Canada[c]	Y	Y	N
Formulant in pest control products registered in Canada[d]	N	Y	Y

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

[a] Personal communication from the Food Directorate of Health Canada to the Existing Substances Risk Assessment Bureau, Nov 2016; unreferenced

[b] NHPID [modified 2018]

[c] personal communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau, Nov 2016; unreferenced

[d] Personal communication with the Pest Management Regulatory Agency of Health Canada, Nov 2016; unreferenced

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone 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 on the basis of 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., median lethal dose [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, and 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 [Q]SAR Toolbox 2016), and in response to surveys under section 71 of CEPA, or they were generated using selected (quantitative) structure-activity relationship ([Q]SAR) 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 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 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 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 (Q)SAR 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 upon 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 substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group, and the hazard, exposure and risk classification results, are presented in ECCC (2016b).

The hazard and exposure classifications for the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group are summarized in Table 5-1.

Table 5-1. Ecological Risk Classification (ERC) results for the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Exaltolide	low	low	low
Hexadecanolide	low	low	low
Exaltone	low	low	low
Muskone/Muscone	low	low	low
Civetone	low	low	low
Hexadecenlactone/ Ambrettolide	low	low	low
Isoambrettolide	low	low	low
Musk amberol/ Ambrettone	low	low	low
Irone	moderate	low	low
1-Methyl-α-ionone	moderate	low	low
Cyclohexanone	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, exaltolide, hexadecanolide, exaltone, muskone/muscone, civetone, hexadecenlactone/ambrettolide, isoambrettolide, musk amberol/ambrettone and cyclohexanone were classified as having an overall low potential for ecological risk. It is therefore unlikely that these substances are resulting in concerns for the environment in Canada.

According to the information considered under ERC, 1-methyl-α-ionone and irone were classified as having low exposure potentials. 1-methyl-α-ionone and irone were classified as having moderate hazard potentials on the basis of reactive modes of action[5]. 1-methyl-α-ionone and irone were also profiled to have moderate potential to cause adverse effects in aquatic food webs given their bioaccumulation potential. Structural alerts from the OECD (Q)SAR toolbox (OECD QSAR Toolbox 2016) identified these substances as being potential protein binders. 1-methyl-α-ionone and irone were classified as having low potential for ecological risk owing to their low exposure potential. The potential effects and how they may manifest in the environment were not further investigated owing to the low exposure of these substances. On the basis of current use patterns, these substances are unlikely to be resulting in concerns for the environment in Canada.

[5] Reactive mode of actions are defined as effects, which typically occur at lower concentrations relative to narcosis, and are caused by specific interactions of a chemical at the molecular level (e.g., via receptor binding, enzyme inhibition).

6. Potential to cause harm to human health

6.1 Exposure assessment

6.1.1 Environmental media and food

Limited environmental monitoring data relevant to current exposures in Canada have been identified for substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group. Exaltolide has been reported in surface water in Portugal, but was not detected in tap water in the same study (Homem et al. 2016). It has also been reported in surface waters in Spain (Montes-Grajales et al. 2017).

Cyclohexanone is reported as being used in food packaging in Canada (Personal communication from the Food Directorate of Health Canada to the Existing Substances Risk Assessment Bureau, Nov 2016; unreferenced).

Some substances in this group are known to be used as food flavouring agents in the US, Europe, Australia and New Zealand; therefore it is possible that the substances are present as flavouring agents in foods sold in Canada (Personal communication from the Food Directorate of Health Canada to the Existing Substances Risk Assessment Bureau, Nov 2016; unreferenced). The JECFA evaluated numerous flavouring groups, which included 6 substances (exaltolide, cyclohexanone, muskone/muscone, civetone, hexadecenlactone/ambrettolide, isoambrettolide) in this group (JECFA 1998, 2000, 2003, 2006, 2011). The JECFA concluded there was “no safety concern at estimated levels of intake” for all 6 substances in this group, when used as a food flavouring agent.

Overall, due to their limited commercial quantities in Canada, limited potential exposure from foods sold in Canada, and the low-moderate volatility and water solubility of the substances, exposure from environmental media and food is considered to be minimal for the substances in this group.

6.1.2 Products available to consumers

Product scenarios that result in the highest levels of potential exposure for each substance by the inhalation, oral and dermal routes (when applicable) are presented in Table 6-1. Potential exposures were estimated using conservative assumptions and default values from sentinel exposure scenarios; see Appendix A for details. Additional potential use scenarios (natural health products, cleaning products, cement adhesives for polyvinyl chloride (PVC) pipe, vehicle air fresheners) were considered, but either resulted in lower exposures than those presented in Table 6-1 or were determined to be not relevant to the general population of Canada.

Dermal absorption data were not identified for any of the 8 macrocyclic lactones and ketones or the two ionones (irone and 1-methyl-α-ionone). Belsito et al. (2013) showed human skin dermal absorption rates of 11 and 15% for two polycyclic musk substances,

acetyl cedrene and 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) ethanone (OTNE). On the basis of the evidence for these two polycyclic substances, a maximum dermal absorption rate of 15% is considered appropriate for the macrocyclic lactones and ketones subgroup.

1-Methyl α-ionone, but not irone, were part of the “alkyl cyclic ketone” grouping[6] of 23 substances which included acetyl cedrene and OTNE (Belsito et al. 2013). Additionally, Lalko et al. (2007a) provided data for methyl-ionone, which is used as an analogue for the ionones subgroup. Pig skin membrane was exposed to 10% methyl-ionone in ethanol for 6 h and 10% was absorbed. The same protocol and concentration of methyl-ionone was used on intact skin of the naked rat and 22% and 48% was absorbed after 1 and 16 hours, respectively. Although the absorption rate was high in "naked" rat skin, pig skin is considered to be closer to human skin in composition and function; 10% absorption with methyl-ionone in pig skin may be analogous to 15% absorption with OTNE in human skin. On the basis of the combined evidence for 1-methyl-α-ionone and the analogue methyl-ionone, a maximum dermal absorption rate of 15% is considered appropriate for the ionones subgroup.

Dermal absorption of 0.1 to 2% was observed in humans exposed to pure cyclohexanone liquid (IARC 1999; JECFA 2003). Thus, the maximum dermal absorption rate was conservatively considered to be 2% for cyclohexanone.

Table 6-1. Summary of estimated potential exposures by adults[a]

Subgroup or substance	Product scenario	Route of expo-sure	Per event exposure (mg/kg bw)	Mean event concen-tration (mg/m^3)	Daily systemic exposure (mg/kg bw/ day)
Macrocyclic lactones and ketones [c] and ionones[d]	Body Lotion	Dermal	0.062 (external); 0.0093 (internal)[b]	N/A	0.068 (external); 0.01 (internal)
Macrocyclic lactones and ketones [c] and	Body Lotion	Inhalation	0.0035	0.045	[0.017 mg/m^3]

[6] Belsito et al. (2013) defined this grouping as substances being composed of an alkyl group, R1, and various substituted and bicyclic saturated or unsaturated cyclic hydrocarbons, and R2 group, in which one of the rings may include up to 12 carbons, and each substance included a ketone carbonyl group (C=O).

Subgroup or substance	Product scenario	Route of exposure	Per event exposure (mg/kg bw)	Mean event concentration (mg/m^3)	Daily systemic exposure (mg/kg bw/day)
Ionones[d]					
Macrocyclic lactones and ketones (exaltolide)	Lipstick	Oral	N/A	N/A	0.00056
Macrocyclic lactones and ketones (exaltolide)	Sunscreen (face)	Dermal	0.46 (external); 0.069 (internal)	N/A	0.033 (internal)
Macrocyclic lactones and ketones (exaltolide)	Eau de toilette	Dermal	0.14 (external); 0.021 (internal)	N/A	0.036 (internal)
Macrocyclic lactones and ketones (exaltolide)	Eau de toilette	Inhalation	0.000036	0.046	N/A
Ionones [d]	Body Fragrance Product	Dermal	0.0047 (external); 0.0007 (internal)	N/A	0.0012 (internal)
Ionones[d]	Body Fragrance Product	Inhalation	0.00039	0.49	N/A
Ionones (1-Methyl-α-ionone)	Hair dye (permanent)	Dermal	0.42 (external); 0.063 (internal)	N/A	0.00062 (internal)
Ionones (1-Methyl-α-ionone)	Hair dye (permanent)	Inhalation	0.062	6.5	N/A
Cyclohexanone	Wall paint (brush and	Dermal	0.051 (external);	N/A	N/A

Subgroup or substance	Product scenario	Route of exposure	Per event exposure (mg/kg bw)	Mean event concentration (mg/m^3)	Daily systemic exposure (mg/kg bw/day)
	roller, waterborne)		0.001 (Internal)		
Cyclohexanone	Wall paint (brush and roller, waterborne)	Inhalation	0.11	6.72	N/A

Abbreviations: N/A, not applicable.
[a]Direct exposures from use of products by adults were evaluated. For the survey, these sentinel products were notified to be not used by children (Environment Canada 2013).
[b]Estimates of external exposure are estimates of dermal deposition. Estimates of systemic exposure are estimates of systemic exposure based upon the dermal absorption values for each substance.
[c] Exaltolide; Hexadecanolide; Exaltone; Muskone/Muscone; Civetone; Hexadecenlactone/Ambrettolide; Isoambrettolide; Musk amberol/Ambrettone
[d] Irone; 1-Methyl-α-ionone

6.2 Health effects assessment

Summaries of critical effects data for each subgroup are presented in the sections below.

6.2.1 Macrocyclic lactones and ketones subgroup

Repeat dose oral studies were identified for only one of the 8 substances. The short no observed adverse effect level (NOAEL) for muskone/muscone is considered to be 1000 mg/kg bw/day, on the basis of no adverse effect in rats orally dosed up to 1000 mg/kg bw/day by gavage for four weeks (McGinty et al. 2011d). Several repeat dose oral studies investigated the beneficial effects of muscone/muskone when administered after an intervention in experimental animals, such as modeling of diabetes or injury to organs or to the spine. In all cases, the studies were short term and used doses less than 100 mg/kg bw/day (Liang et al. 2010; Meng et al. 2014; Wang et al. 2014; Jiang et al. 2016; Kailiang et al. 2016).

No repeat dose dermal studies were identified for any of the 8 substances in this subgroup. Repeat dose inhalation studies were identified for only one of the 8 substances. For exaltone, an inhalation Lowest Observed Effect Level (LOEL) of 1.6×10^{-3} $\mu g/m^3$ based upon degeneration of mitral cells in the olfactory bulb of rats exposed to exaltone by inhalation for 4 to 7 weeks (Pinching and Doving 1974). There was insufficient information to determine if this effect was adverse.

Reproductive/developmental toxicity studies were not identified for any of the 8 substances. However, in vitro studies were negative for androgen receptor activities in

modified Chinese hamster ovary cells when tested with exaltolide (Araki et al. 2005). Although increased proliferation of MCF-7 cells was observed when tested with muskone/muscone, this proliferation occurred at the very high dose of 2384 mg/L (Bitsch et al. 2002).

In vitro mutagenicity studies in bacterial cells, available for six of the eight substances were all negative. DNA damage in E. coli, tested with exaltolide, hexadecanolide, and musk amberol/ambrettone, and chromosome aberration in human lymphocytes, tested with hexadecanolide and exaltone, were also negative (McGinty et al. 2011a,b,c,h). For exaltolide, in vivo micronuclei studies in mice were negative (two studies identified; McGinty et al. 2011a,i). Although no long-term studies were identified for any of the macrocyclic lactones and ketones, in vitro studies for carcinostatic activity were conducted with exaltone, muskone/muscone and civetone; one of the three substances (civetone) exhibited the highest anti-invasive activity and the highest carcinostatic activity (tested in culture with movement through a porous synthetic membrane) when compared to other macrocyclic ketones tested (CAS RNs 502-72-7, 541-91-3 and 3100-36-5). The authors stated that these studies demonstrated anticancer potential (Asada et al. 2011). Available in vitro and in vivo genotoxicity data indicates that macrocyclic lactones and ketones are not genotoxic and in vitro assays investigating markers of carcinogenicity for three of the 8 substances were negative.

All substances were tested for skin sensitization in both humans and guinea pigs. Most substances were negative for sensitization when tested at concentrations ranging from 0.05 to 10%, and some tested at higher concentrations (25-75%) were also negative in guinea pigs or humans (McGinty et al. 2011a,b,c,d,e,f,g,h,i). Five substances, hexadecanolide, exaltone, hexadecenlactone/ambrettolide, isoambrettolide and musk amberol/ambrettone, were tested in large numbers of fragrance-sensitive or contact-dermatitis patients at concentrations ranging from 0.2 to 10% in petrolatum and again, negative or low incidences (0.6 to 3.4%) of positive sensitization were observed in these studies (McGinty et al. 2011b,c,f,g,h).

6.2.2 Ionones subgroup

No skin sensitization was observed in humans challenged with 10% irone (Greif 1967; Anonymous 1975). Skin sensitization studies were conducted with all four analogues in both experimental animals and humans. No sensitization was observed in rabbits or guinea pigs at concentrations tested up to 100%, depending on the substance, and negative sensitization was observed in humans tested with challenge concentrations ranging from 1 to 10%, depending on the substance (Lalko et al. 2007a,b,c,d).

In vitro mutagenicity assays in S. typhimurium with and without metabolic activation were negative with 1-methyl-alpha ionone (US NTP [date unknown]; EFSA 2015).

As there are limited studies for irone and 1-methyl-α-ionone, the four analogues provided additional data on repeated dose oral and dermal studies, as well as limited

toxicokinetic data based upon oral dosing in experimental animals. For α-iso-methylionone, a 2-week oral gavage study in rats resulted in increased salivation and pale kidneys at a dose of 1000 mg/kg bw/day, the only dose tested (Politano et al. 2012). For both α- and β-ionone, 13-week oral studies conducted in rats resulted in the determination of the same NOAEL (10 mg/kg bw/day) based upon almost identical effects observed at the same lowest observed adverse effect level (LOAEL) (100 mg/kg bw/day), such as decreased body-weight gain, food consumption and serum glucose concentrations (additional effects for β-ionone included increased water intakes and mild functional kidney changes) (JECFA 1984; Lalko et al. 2007b,c). A 17-week oral feeding study in rats conducted with the ionone mixture did not show adverse effects and the NOAEL was considered to be the highest dose tested of 500 mg/kg bw/day (Lalko et al. 2007d). In a 13-week dermal study in rats conducted with α-iso-methylionone, the NOAEL for systemic toxicity was 50 mg/kg bw/day based upon increased relative kidney weights in both sexes and a significant increase in albuminuria in urine of males at 170 mg/kg bw/day. At 50 mg/kg bw/day and above, there was dose-dependent increase in severity of erythema and eschar formation at the application site. Due to the effects on the skin, Lapczynski et al. (2007) stated that an NOAEL for local effects could not be established.

Pregnant rats were gavaged with 0, 3, 10 or 30 mg/kg bw/day α-iso-methylionone in corn oil on gestation days (GDs) 7 to 17 and sacrificed on GD 21. No effects were observed based upon clinical signs and gross pathology, maternal and fetal weights, and uterine, litter and developmental parameters (Lapczynski et al. 2007; Politano et al. 2007). For another analogue, two developmental toxicity studies were conducted in which β-ionone was administered once during pregnancy. Pregnant hamsters were gavaged with 0, 48, 240 or 480 mg/kg bw β-ionone in Tween 20:acetone (95:5) on GD 8 and sacrificed on GD 14. No effects were observed based upon clinical signs, maternal weight, or on developmental parameters. In the other study, pregnant rats were gavaged with 250, 500, 750 or 1000 mg/kg bw β-ionone in corn oil on GD 11 and sacrificed on GD 21. The NOAEL for developmental toxicity was 750 mg/kg bw. Effects observed in rats dosed with 1000 mg/kg bw were increased number of resorptions/implantation, resorptions/implantation/litter and decreased uterus weight and decreased number of live fetuses/implantations/litter (Gomes-Carneiro et al. 2003; Lalko et al. 2007c). Eight week oral studies in rats were also conducted with the ionone mixture but were insufficient to determine critical effect levels due to the limited protocols for these studies (dosing every second day and limited endpoint evaluation, such as liver homogenates and/or specific parameters in blood cells and adrenal glands) (Lalko et al. 2007d). Similarly, an inhalation study with one and 5-week exposure periods was conducted in rats with β-ionone, but was insufficient to determine a critical effect level (only one dose tested) (Lalko et al. 2007b).

Table 6-3. Critical effects data for the ionones

Exposure Route	Duration	Species	Critical effect level	Critical health effect endpoint
Oral (feeding)	13 weeks (α-ionone)	Rat	NOAEL = 10 mg/kg bw/day	Slightly decreased body weight gain and food consumption in both sexes and decreased serum glucose concentration in females at 100 mg/kg bw/day.
Oral (feeding)	13 weeks (β-ionone)	Rat	NOAEL = 10 mg/kg bw/day	Decreased body weight gain, food consumption and serum glucose concentrations, increased water intakes and mild renal functional changes at 100 mg/kg bw/day.
Oral (feeding)	17 weeks (Ionone)	Rat	NOAEL = 500 mg/kg bw/day	No effects (Highest dose).
Dermal	13 weeks (α-iso-methyl-ionone)	Rat	NOAEL = 50 mg/kg bw/day	Increased relative kidney weights in both sexes and a significant increase in albuminuria in urine of males at 170 mg/kg bw/day.

Abbreviations: NOAEL, no observed adverse effect level.

6.2.3 Cyclohexanone

Cyclohexanone has been reviewed internationally by the OECD (2002), EFSA (2016), JECFA (2003) and IARC (1999). There is also a US IRIS review (US EPA 1987). The majority of information presented here is based upon the OECD (2002) review which was sponsored by Canada, along with any updated information provided in the other international reviews. A summary of critical effects and levels for this substance is presented here.

Several repeat dose studies via the oral route have been conducted in rats and mice for periods ranging from 25 days to 25 weeks. These studies resulted in the determination of NOAELs of 720 mg/kg bw/day in rats and 1600 mg/kg bw/day in mice (on the basis of decreased body-weight gain at 910 and 2600 mg/kg bw/day, respectively). Dermal studies of 5 days in rabbits and 3 to 8 weeks in guinea pigs resulted in the determination of a NOAEL of 242 mg/kg bw/day in guinea pigs (highest dose tested). Inhalation studies of 10 weeks in rabbits and 6 months in rats resulted in the determination of a No observed adverse effect concentration (NOAEC) of 762 mg/m^3 in rabbits (on the basis of eye irritation at 1236 mg/m^3) (Treon et al. 1943; OECD 2002).

Two inhalation reproductive studies conducted in rats, resulted in the determination of a reproductive and developmental toxicity NOAEC of 2000 mg/m^3 (on the basis of

decreased male fertility in the F1 generation and decreased pup survival and body weights at 5600 mg/m^3) as reported by OECD (2002). Two inhalation developmental toxicity studies were conducted in rats; in one, there was a maternal NOAEC of 400 mg/m^3 (on the basis of grey mottling of lungs at 1000 mg/m^3 which was considered to be adverse) and a developmental NOAEC of 2000 mg/m^3 (highest dose tested). In the other inhalation developmental toxicity study, the maternal and developmental NOAEC were both determined to be 2609 mg/m^3 based upon decreased body-weight gain in dams and decreased body weights and increased incidence of skeletal variations in fetuses at 5620 mg/m^3 (OECD 2002). An oral developmental toxicity study conducted in mice resulted in a maternal NOAEL of 1100 mg/kg bw/day (on the basis of decreased body-weight gain, clinical signs of toxicity and increased mortality at 2200 mg/kg bw/day) and a developmental LOAEL of 1100 mg/kg bw/day (on the basis of decreased pup weights) (OECD 2002; JECFA 2003).

The overall in vitro and in vivo genotoxicity of cyclohexanone is considered to be negative. Several in vitro genotoxicity studies were conducted in bacterial and mammalian cells, including human lymphocytes and fibroblasts. Available in vivo studies included two chromosome aberration assays in rats, a dominant lethal assay in mice, a sex-linked recessive lethal assay in Drosophila melanogaster, and a study of phenocopies of tumour mutations in D. melanogaster (OECD 2002; JECFA 2003: Piesova et al. 2003; EFSA 2016).

Two-year oral carcinogenicity studies were conducted in both rats and mice via addition of cyclohexanone to drinking water. Although neoplasms in different organs were observed in both species, lack of a dose response in both studies prompted the authors to conclude that the evidence for carcinogenicity was weak (OECD 2002; JECFA 2003). IARC (1999) reviewed the same carcinogenicity studies and concluded that cyclohexanone is not classifiable as to its carcinogenicity in humans (Groups 3).

No skin sensitization was observed in experimental animals challenged with 100% cyclohexanone (OECD 2002).

Critical effect levels are shown in the table below.

Table 6-4. Critical effects data for cyclohexanone

Exposure Route	Duration	Species	Critical effect level	Critical health effect endpoint
Dermal	3-8 weeks	Guinea pig	NOAEL = 242 mg/kg bw/day	No effects (highest dose tested)
Inhalation	Gestation days 5-20 (16 days; 7 h/day)	Rat	Maternal NOAEC = 400 mg/m^3; Developmental NOAEC = 2000 mg/m^3.	Maternal: Grey mottling of lungs; Developmental: No effect at highest dose tested.

Oral	Gestation days 8-12 (5 days)	Mouse	Maternal NOAEL = 1100 mg/kg bw/day; Developmental LOAEL = 1100 mg/kg bw/day	Maternal: Decreased body-weight gain, clinical signs of toxicity and increased mortality; Developmental: Decreased pup weights.

Abbreviations: LOAEL, lowest observed adverse effect level; NOAEC, no observed adverse effect concentration; NOAEL, no observed adverse effect level.

6.3 Characterization of risk to human health

As noted in section 6.1, environmental media and food are not expected to be significant sources of exposure for the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group. Exposure is expected to occur mainly from use of cosmetics for the macrocyclic lactones and ketones, and ionones subgroups and from use of do-it-yourself products for the cyclohexanone subgroup.

6.3.1 Macrocyclic lactones and ketones subgroup

Table 6-5 provides all relevant exposure and hazard values for the macrocyclic lactones and ketones subgroup, as well as resultant margins of exposure, for determination of risk.

Table 6-5. Relevant exposure and hazard values for macrocyclic lactones and ketones, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure	Critical effect level[a]	Critical health effect endpoint	Margin of exposure (MOE)
Daily dermal exposure to body lotion	0.01 mg/kg bw/day (internal)	Oral NOAEL = 1000 mg/kg bw/day in 4 wk rat study	No effects (highest dose)	100,000
Daily inhalation exposure to body lotion	0.017 mg/m^3	Oral NOAEL = 1000 mg/kg bw/day in 4 wk rat study (equivalent to 3226 mg/m^3)[b]	No effects (highest dose)	189,800

Exposure scenario	Systemic exposure	Critical effect level[a]	Critical health effect endpoint	Margin of exposure (MOE)
Daily dermal exposure to sunscreen	0.033 mg/kg bw/day (internal)	Oral NOAEL = 1000 mg/kg bw/day in 4 wk rat study	No effects (highest dose)	30,300
Per event dermal exposure to eau de toilette	0.021 mg/kg bw (internal)	Oral NOAEL = 1000 mg/kg bw/day in 4 wk rat study	No effects (highest dose)	47,600
Per event inhalation exposure to eau de toilette	0.046 mg/m^3	Oral NOAEL = 1000 mg/kg bw/day in 4 wk rat study (equivalent to 3226 mg/m^3)[b]	No effects (highest dose)	70,100

Abbreviations: NOAEL, no observed adverse effect level.
[a] Based upon muscone/muskone (CAS RN 541-91-3).
[b] As per Health Canada (1994).

The substances in the macrocyclic lactones and ketones subgroup were identified as being used in body lotion, sunscreen, lipstick, and eau de toilette, in Canada. On the basis of the conservative parameters used in modelling exposure to products, the calculated margins are considered adequate to address uncertainties in the health effects and exposure databases for the macrocyclic lactones and ketones subgroup.

Although no adequate dermal studies were identified for this subgroup, the human skin sensitization studies conducted with all 8 substances in the subgroup showed no sensitization in the majority of tests (concentrations tested ranged from 0.5 to 30%, depending on the substance). A quantitative estimate of human sensitization was available for exaltolide, showing that 10% exaltolide (0.4 mg/kg bw) was not irritating in humans. The maximum concentration identified was 2.6% exaltolide in facial sunscreen, which was used in the derivation of the exposure estimate for sunscreen as shown in the table above.

6.3.2 Uncertainties in evaluation of risk to human health for the macrocyclic lactones and ketones subgroup

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

Table 6-6. Sources of uncertainty in the risk characterization of macrocyclic lactones and ketones

Key source of uncertainty	Impact
Exposure	

Key source of uncertainty	Impact
Lack of Canadian occurrence data for all substances in environmental media and products available to consumers.	+
Route-to-route extrapolation of oral dose toxicity studies for dermal and inhalation exposures	+
Hazard	
Limited health effects database (lack of toxicokinetic studies, repeated dose and reproductive/developmental toxicity studies by the dermal and inhalation routes; lack of chronic experimental animal studies by inhalation, dermal and oral routes of exposure).	+/-

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

6.3.3 Ionones subgroup

Table 6-7 provides all relevant exposure and hazard values for the ionones subgroup, as well as resultant margins of exposure, for determination of risk. Critical effect levels determined for this subgroup are all on the basis of health effects data for four analogue substances (α-ionone, α-iso-methylionone, β-ionone, and Ionone).

Table 6-7. Relevant exposure and hazard values for ionones, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure	Critical effect level	Critical health effect endpoint	Margin of exposure (MOE)
Daily dermal exposure to body lotion	0.068 mg/kg bw/day (external)	Dermal NOAEL = 50 mg/kg bw/day in 13-wk rat dermal study (α-iso-methylionone)	Increased relative kidney weights in both sexes and a significant increase in albuminuria in urine of males at 170 mg/kg bw/day.	735

Exposure scenario	Systemic exposure	Critical effect level	Critical health effect endpoint	Margin of exposure (MOE)
Daily inhalation exposure to body lotion	0.017 mg/m^3	Oral NOAEL = 10 mg/kg bw/day in 13-wk rat feeding study (equivalent to 32.3 mg/m^3)[a] (β-ionone)	Decreased bw-gain, food consumption and serum glucose concentrations, increased water intakes and mild renal functional changes at 100 mg/kg bw/day	1900
Daily inhalation exposure to body lotion	0.017 mg/m^3	Oral NOAEL = 10 mg/kg bw/day in 13-wk rat feeding study (equivalent to 32.3 mg/m^3)[a] (α-ionone)	Slightly decreased bw-gain and food consumption in both sexes and decreased serum glucose concentration in females at 100 mg/kg bw/day	1900

Abbreviations: NOAEL, no observed adverse effect level.
[a]As per Health Canada (1994).

Irone and 1-methyl- α-ionone were identified as being used in body lotion and body fragrance, and 1-methyl- α-ionone was identified as being used in hair dye in Canada. As shown in the table above, MOEs based upon the use scenario with the highest exposure estimates (body lotion) and NOAELs of 10 mg/kg bw/day for the two selected oral critical studies and a NOAEL of 50 mg/kg bw/day for the selected dermal critical study ranged from 735 to 1900. Another critical study using CAS RN 8013-90-9 (ionone mixture) resulted in an oral NOAEL of 500 mg/kg bw/day on the basis of 17 weeks exposure in rats (see table 6-3). Utilization of this study would have resulted in a much higher MOE based upon daily exposure to body lotion. On the basis of the conservative parameters used in modelling exposure to products, the calculated MOEs are considered adequate to address uncertainties in the health effects and exposure databases for the ionones subgroup.

6.3.4 Uncertainties in evaluation of risk to human health for the ionones subgroup

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

Table 6-8. Sources of uncertainty in the risk characterization of ionones

Key source of uncertainty	Impact
Exposure	
Lack of Canadian occurrence data for all substances in environmental media and products available to consumers.	+
Route-to-route extrapolation of oral dose toxicity studies for dermal and inhalation exposures	+
Hazard	
There is a lack of toxicokinetic studies, repeated dose (including chronic) and reproductive/developmental toxicity studies by inhalation, dermal and oral routes of exposure.	+/-

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

6.3.5 Cyclohexanone

Table 6-9 provides all relevant exposure and hazard values for cyclohexanone, as well as resultant margins of exposure for determination of risk. Critical effect levels determined for this substance are on the basis of health effects data for cyclohexanone.

Table 6-9. Relevant exposure and hazard values for cyclohexanone, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure	Critical effect level	Critical health effect endpoint	Margin of exposure (MOE)
Per event dermal exposure to waterborne wall paint (brush and roller)	0.051 mg/kg bw (external)	NOAEL = 242 mg/kg bw/day in 3 to 8 wk guinea pig study	No effects (highest dose)	4750
Per event dermal exposure to waterborne wall paint (brush and roller)	0.001 mg/kg bw (internal)	Oral Developmental LOAEL = 1100 mg/kg bw/day in mouse dams exposed during GD 8-12 (5 days)	Decreased pup weight	1,100,000
Per event inhalation exposure to waterborne wall paint (brush and roller)	6.72 mg/m^3	Inhalation maternal NOAEC = 400 mg/m^3 in rat dams exposed during GD 5-20 (16 days)	Maternal: Grey mottling of lungs at 1000 mg/m^3	60[a] - 300

Exposure scenario	Systemic exposure	Critical effect level	Critical health effect endpoint	Margin of exposure (MOE)
		Developmental NOAEC = 2000 mg/m^3.	No develop-mental effects: Highest dose	

Abbreviations: NOAEC, no observed adverse effect concentration; NOAEL, no observed adverse effect level.
[a] This MOE was considered adequate in consideration of the uncertainties which included the relevance of the potential effect to the exposure scenario, as well as the relative significance of the effect (lung effects not observed in rats in other inhalation developmental and reproductive toxicity studies).

Cyclohexanone was identified as being used in wall paint in Canada. On the basis of the conservative parameters used in modelling exposure to products, the calculated margins of 4 750 to 1 100 000 for dermal exposure and the range of 60 to 300 for inhalation exposure are considered adequate to address uncertainties in the health effects and exposure databases. The majority of international reviews focused on hazard and did not conduct exposure assessments for cyclohexanone, other than an assessment of its use as a flavouring substance conducted by JECFA (2003) and EFSA (2016). Note that this current document conducts an exposure and risk characterization of cyclohexanone use in products available to consumers by the dermal and inhalation routes of exposure.

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from the substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group. It is concluded that the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group 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 the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group 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 the eleven substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group do not meet any of the criteria set out in section 64 of CEPA.

References

Anonymous. 1975. Fragrance raw materials monographs - Methyl ionone. Food and Cosmetics Toxicology 13:863.

Araki N., Ohno K, Nakai M, Takeyoshi M, Lida M. 2005. Screening for androgen receptor activities in 253 industrial chemicals by in vitro reporter gene assays using AR-EcoScreen™ cells. Toxicology in Vitro 19:831–842.

Asada R, Kageyama K, Tanaka H, Saitoh Y, Miwa N. 2011. Antitumor and anti-invasive effects of diverse musk-fragrant macrocyclic ketones and their enhancement by hyperthermia. Molecular Medicine Reports 5:148-152.

Belsito D, Bickers D, Bruze M, Calow P, Dagli ML, Fryer AD, Greim H, Miyachi Y, Saurat JH, Sipes IG. 2013. A toxicological and dermatological assessment of alkeyl cyclic ketones when used as fragrance ingredients. Food Chem Toxicol 62:S1-S44.

Bitsch N, Dudas C, Korner W, Failing K, Biselli S, Rimkus G, Brunn H. 2002. Estrogenic activity of musk fragrances detected by the E-screen assay using human MCF-7 cells. Arch Environ Contam Toxicol 43:257-264.

Canada. 1999. Canadian Environmental Protection Act, 1999. S.C. 1999, c.33. Canada Gazette Part III, vol. 22, no. 3..

Canada, Dept. of the Environment. 2012. Canadian Environmental Protection Act, 1999: Notice with respect to certain substances on the Domestic Substances List. Canada Gazette, Part I, vol. 146, no. 48, Supplement..

ChemIDplus [database]. 2016. Bethesda (MD): US National Library of Medicine. [updated NS; accessed 2018 Aug. 9]..

[ConsExpo Web] Consumer Exposure Web Model. 2016. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]..

[DPD] Drug Product Database [database]. [modified 2016 Jul 17]. Ottawa (ON): Health Canada. [accessed 2018 August 9]..

[ECCC] Environment and Climate Change Canada. 2016a. Science Approach Document: Ecological Risk Classification of Organic Substances. Gatineau (QC): ECCC.

[ECCC] Environment and Climate Change Canada. 2016b. Data used to create substance-specific hazard and exposure profiles and assign risk classifications in the Ecological Risk Classification of organic substances. Gatineau (QC). Available from: eccc.substances.eccc@canada.ca

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2017 Mar 12]. Categorization. Ottawa (ON): Government of Canada. [accessed 2018 Aug 9]..

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2018. Substances Identified as Being of Low Concern Using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances. [accessed November 2018]

[ECHA] European Chemicals Agency. 2017a. Pentadecan-15-olide (CAS RN 106-02-5). [accessed 2018 Aug 9].

[ECHA] European Chemicals Agency. 2017b. Oxacycloheptadec-10-en-2-one (CAS RN 28645-51-4). [accessed 2018 Aug 9].

[ECHA] European Chemicals Agency. 2017c. Cyclohexanone (CAS RN 108-94-1). [accessed 2018 Aug 9].

[ECHA] European Chemicals Agency. 2017d. Beta-ionone (CAS RN 14901-07-6). [accessed 2018 Aug 9]

[ECHA] European Chemicals Agency. 2017e. Alpha-ionone (CAS RN 127-41-3). [accessed 2018 Aug 9]

[ECHA] European Chemicals Agency. 2017f. Ionone (CAS RN 8013-90-9). [accessed 2018 Aug 9]

[ECHA] European Chemicals Agency. 2017g. Methyl-ionone (CAS RN 1335-46-2). [accessed 2018 Aug 9]

[ECHA] European Chemicals Agency. 2017h. 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (CAS RN 127-51-5). [accessed 2017 Aug 1]

[EFSA] European Food Safety Authority. 2015. Scientific opinion on flavouring group evaluation 210 revision 2 (FGE.210Rev2): Consideration of genotoxic potential for α,β-unsaturated alicyclic ketones and precursors from chemical subgroup 2.4 of FGE.19. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). EFSA Journal 13(7):4172-4204.

[EFSA] European Food Safety Authority. 2016. Scientific opinion on Flavouring Group Evaluation 51, Revision 2 (FGE.51Rev2): Consideration of alicyclic ketones and secondary alcohols and related esters evaluated by JECFA (59th meeting) structurally related to alicyclic ketones secondary alcohols and related esters in FGE.09Rev6 (2015) EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). EFSA Journal 14(1):4338-4394.

Environment Canada. 2013. DSL Inventory Update data collected under the Canadian Environmental Protection Act, 1999, section 71: Notice with respect to certain substances on the Domestic Substances List. Data prepared by: Environment Canada, Health Canada; Existing Substances Program.

[EPI Suite] Estimation Program Interface Suite for Microsoft Windows [estimation model]. c2000-2012. Ver. 4.11. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation.

Gomes-Carneiro MR, De-Oliveira, ACAX, De-Carvalho RR, Araujo IB, Souza CAM, Kuriyama SN, Paumgartten FJR. 2003. Inhibition of cyclophosphamide-induced teratogenesis by β-ionone. Toxicology Letters 138:205–213.

Greif N 1967. Cutaneous safety of fragrance material as measured by the maximization test. Am. Perfumer and Cosmetics 82:54-57.

Health Canada. 1994. Human health risk assessment for priority substances. Ottawa (ON): Minister of Supply and Services Canada. Cat. No.: En40-215/41E.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Government of Canada.

Health Canada. [modified 2015 Dec 14]. Cosmetic ingredient hotlist: list of ingredients that are prohibited for use in cosmetic products. Ottawa (ON): Health Canada, Consumer Product Safety Directorate. [accessed 2018 Aug 9]. .

Health Canada. 2016. Science Approach Document: Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances. September 2016. 54 pp.

Homem V, Alves A, Alves A, Santo L. 2016. Ultrasound-assisted dispersive liquid–liquid microextraction for the determination of synthetic musk fragrances in aqueous matrices by gas chromatography–mass spectrometry. Talanta 148:84-93.

[IARC] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 1999. Cyclohexanone. IARC Monogr Eval Carcinog Risks Hum. 71:1359-1364.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 1984. Ionone (alpha- and β-ionone). Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 19. World Health Organization, Geneva.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 1998. Aliphatic lactones. Safety evaluation of certain food additives and contaminants. WHO Food Additive Series 40. Prepared by the 49th meeting of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2000. Safety evaluation of certain food additives and contaminants: aliphatic primary alcohols, aldehydes, carboxylic acids, acetals, and esters containing additional oxygenated functional groups. WHO Food Additive Series 44. World Health Organization, Geneva. Prepared by the 53rd meeting of the Joint FAO/WHO Expert Committee on Food Additives. On the cover: First draft prepared by PJ Abbott (Australia New Zealand Food Authority, Canberra, Australia).

[JECFA] Joint FAO/WHO Expert Committee on Food Additives, 2003. Safety evaluation of certain food additives: alicyclic ketones, secondary alcohols and related esters. WHO Food Additives Series: 50. World Health Organization, Geneva. Prepared by the fifty-ninth meeting of the JECFA. On the cover: First prepared by I.G. Sipes (University of Arizona, Tucson, Arizona, USA) and A.G. Renwick (University of Southampton, Southampton, England).

[JECFA] Joint FAO/WHO Expert Committee on Food Additives, 2006. Safety evaluation of certain food additives. WHO Food Additives Series: 54. World Health Organization, Geneva. Prepared by the sixty-third meeting of the JECFA.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2011. Evaluation of certain food additives and contaminants. WHO Technical Report Series 960. Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva.

Jiang T, Huang L, Zhou S, Cui J, YE Q. 2016. Brain protection of muscone in rats with brain injury. Zhongguo Zhong Xi Yi Jie He Za Zhi [Chinese Journal of Integrated Traditional and Western Medicine] 36(6):724-728. [In Chinese with English abstract].

Kailiang Z, Yihui Z, Dingsheng L, Xianyao T. 2016. Effects of muscone on random skin flap survival in rats. J Reconstr Microsurg. 32(3):200-207.

Lalko J, Lapczynski A, McGinty D, Bhatia S, Letizia CS, Api AM. 2007a. Fragrance material review on methyl ionone (mixture of isomers). Food Chem Tox. 45:S300-S307.

Lalko J, Lapczynski A, Politano VT, McGinty D, Bhatia S, Letizia CS, Api AM. 2007b. Fragrance material review on α-ionone. Food Chem Tox. 45:S235-S240.

Lalko J, Lapczynski A, McGinty D, Bhatia S, Letizia CS, Api AM. 2007c. Fragrance material review on β-ionone. Food Chem Tox. 45:S241-S247.

Lalko J, Lapczynski A, McGinty D, Bhatia S, Letizia CS, Api AM. 2007d. Fragrance material review on ionone. Food Chem Tox. 45:S251-S257.

Lapczynski A, Lalko J, Politano VT, McGinty D, Bhatia S, Letizia CS, Api AM. 2007. Fragrance material review on alpha-iso-ionone. Food Chem Tox. 45:S281-S288.

Liang QQ, Zhang M, Zhou Q, Shi Q, Wang YJ. 2010. Muscone protects vertebral end-plate degeneration by antiinflammatory property. Clin Orthop Relat Res. 46)8:1600–1610.

[LNHPD] Licensed Natural Health Products Database [database]. [modified 2018 Feb 06]. Ottawa (ON): Health Canada. [accessed 2018 Aug 9]..

Loretz LG, Api AM, Barraj LM, Burdick J, Dressler WE, Gettings SD, Han Hsu H, Pan YHL, Re TA, Renskers KJ, Rothenstein A, Scrafford CG, Sewall C. 2005. Exposure data for cosmetic products: lipstick, body lotion, and face cream. Food Chem Toxicol 43: 279-291.

McGinty G, Letizia CS, Api AM. 2011a. Fragrance material review on omega-pentadecalactone. Food Chem Toxicol 49:S193-S201.

McGinty D, Letizia CS, Api AM. 2011b. Fragrance material review on hexadecanolide. Fd Chem Toxicol 49:S183-188.

McGinty D, Letizia CA, Api AM. 2011c. Fragrance material review on cyclopentadecanone. Food and Chemical Toxicology 49:S142–S148.

McGinty D, Letizia CS, Api AM. 2011d. Fragrance material review on 3-methyl-1-cyclopentadecanone. Food and Chemical Toxicology 49:S120–S125.

McGinty D, Letizia CS, Api AM. 2011e. Fragrance material review on cycloheptadeca-9-en-1-one. Food and Chemical Toxicology 49:S93–S97.

McGinty D, Letizia CS, Api AM. 2011f. Fragrance material review on omega-6-hexadecenlactone. Food and Chemical Toxicology 49:S207–S211.

McGinty D, Letizia CS, Api AM. 2011g. Fragrance material review on oxacycloheptadec-10-ene-2-one. Food and Chemical Toxicology 49:S189-S192.

McGinty D, Letizia CS, Api AM. 2011h. Fragrance material review on 5-cyclohexadecen-1-one. Food and Chemical Toxicology 49:S98–S103.

Meng Y, Xiao Q, Bai J, Xiao X, Zhang S, Zhu X, Cheng G, Yin D. 2014. Resolution and chiral recognition of muscone as well as actions on neural system. Journal of Asian Natural Products Research 16(12):1166-1170.

Montes-Grajales D, Fennix-Agudelo M, and Miranda-Castro W. 2017. Occurrence of personal care products as emerging chemicals of concern in water resources: A review. Science of the Total Environment. 595: 601-614.

[MSDS] Material Safety Data Sheet. 2013a. Wynn's signature series engine tune up. Mississauga, ON, Canada: Wynn's Canada Ltd. 20 Jan. 2015. [accessed 2016 Jul 19]. [restricted access].

[MSDS] Material Safety Data Sheet. 2013b. Glade membrane. Compton, CA: Auto Expressions, LLC. 30 July 2013. [accessed 2016 Jul 19]. [restricted access].

[MSDS] Material Safety Data Sheet. 2014. IPEX SYS 636 GRY Low VOC Cement for PVC Plastic Pipe. Gardena, CA: IPS Corporation. Nov 2014. [accessed 2016 Jul 19]. [restricted access].

[MSDS] Material Safety Data Sheet. 2015a. Armor All Air Fresheners Pure Linen Scented Oil Vent Clip. Danbury, CT: The Armor All/STP Products Company. 07 Jan 2015. [accessed 2016 Jul 19]. [restricted access].

[MSDS] Material Safety Data Sheet. 2015b. Covergirl Lip Perfection lipstick, BlastFlipstick, Colorlicious lipstick. Cincinnati, OH: The Procter & Gamble Company. 25 Feb 2015. [accessed 2016 Jul 19]. [restricted access].

[MSDS] Material Safety Data Sheet. 2015c. Red Door EDT Spray Naturel. Stamford, USA: Elizabeth Arden Inc. 20 Jan. 2015. [accessed 2016 Jul 19]. [restricted access].

[NCI] National Chemical Inventories [database on a CD-ROM]. 2014. Columbus (OH): American Chemical Society, Chemical Abstracts Service. [cited 2014]. https://www.cas.org/products/nciglobal

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2018 Nov 09]. Ottawa (ON): Health Canada. [accessed 2018 Aug 9].

[OECD] Organisation for Economic Cooperation and Development. 2002. Cyclohexanone; CAS No. 108-94-1. OECD SIDS (Screening Information Data Set) Initial Assessment Report. Assessed at SIDS Initial Assessment Meeting 2 in 1994 and sponsored by Canada. 165 pp.

OECD QSAR Toolbox. [read across tool]. 2016. Paris (FR): Organisation for Economic Co-operation and Development, Laboratory of Mathematical Chemistry.

Piesova ES, Dianovsky L, Holeckova B. 2003. The induction of micronuclei into bovine lymphocyte cultures exposed to cyclohexanone. Folia Veterinaria 47(3):161-163.

Pinching AJ, Doving KB. 1974. Selective degeneration in the rat olfactory bulb following exposure to different odours. Brain Research 82:195-204.

Politano VT, Lewis EM, Hoberman AM, Christian MS, Diener RM, Api AM. 2007. Evaluation of the developmental toxicity of alpha-iso-methylionone in rats. Int J Toxicol. 26:271-276.

Politano VT, Lapczynski AA, Ritacco G, Api AM. 2012. Ninety-day toxicity study of alpha-iso-methylionone in rats. Int J Toxicol. 31(6):595-601.

SCCS [Scientific Committee on Consumer Safety]. 2012. The SCCS's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 8th Revision.

Scognamiglio J, Letizia CS. Api AM. 2013. Fragrance material review on 1-(2,6,6-trimethyl-2-cyclohexen-1-yl) pent-1-en-3-one. Food and Chemical Toxicology 62: S115-S119.

Statistics Canada. 2012. Canadian Health Measure Survey. (CHMS). Cycle 2. 2009-2011. Available at.

Treon JF, Crutchfield WE Jr, Kitzmiller KV. 1943. The physiological response of animals to cyclohexane, methylcyclohexane, and certain derivatives of these compounds: II. Inhalation. J Ind Hyg Tox. 25(8): 323-347.

[US EPA] United States Environmental Protection Agency. 1987 (updated 2002). Integrated Risk Information System (IRIS) chemical assessment summary: Cyclohexanone; CASRN 108-94-1. Last revised 1987, Screening-level literature review findings message added 2002.

[US EPA] United States Environmental Protection Agency. 2014. E-FAST-Exposure and Fate Assessment Screening Tool Version 2014. [Updated 2016 Sept 8] Accessed 2018 Aug 9.

[US EPA] United States Environmental Protection Agency. 2016. Chemical Data Access Tool (CDAT) [database on the Internet]. Updated 2016 Apr 4. [cited 2017 Jan. 25].

[US NTP] United States National Toxicology Program. [Date unknown]. 1(2,6,6-Trimethyl-2-cyclohexene-1-yl) 1penten-3-one M910033.

Wang X, Meng H, Chen P, Yang N, Lu X, Wang Z, Gao W, Zhou N, Zhang M, Xu Z et al. 2014. Beneficial effects of muscone on cardiac remodeling in a mouse model of myocardial infarction. International Journal of Molecular Medicine 34:103-111.

Wild D, King MT, Gocke E, Eckhard K, 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, BASC and micronucleus tests. Food and Chemical Toxicology 21(6):707-719.

Appendix A: Estimated potential exposures to substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group

Sentinel exposure scenarios were used to estimate the potential exposure to substances in the Macrocyclic Lactones and Ketones, Ionones and Cyclohexanone Group; scenario assumptions are summarized in Table A-1. For the substances surveyed, these sentinel products were notified to be not used by children (Environment Canada 2013). Exposures were estimated based upon the assumed weight (70.9 kg) of an adult (Health Canada 1998), inhalation rate of an adult (16.2 m^3/day) and use behaviours of an adult. Exposures were estimated using ConsExpo Web version (ConsExpo Web 2016) with inhalation exposure for wall paint being estimated using the US EPAs EFAST Consumer Exposure Module (US EPA 2014) model. Default parameters from ConsExpo Web version were used unless otherwise specified. For estimated potential exposures via the dermal route, dermal absorption was assumed to be 15% for the macrocyclic lactones and ketones and ionones and 2% for cyclohexanone. An overall retention factor of 1 was used unless otherwise specified.

Table A-1. Sentinel exposure scenario assumptions.

Scenario	Substances (common name)	Assumptions
Body lotion	Exaltolide; Hexadecanolide; Exaltone; Muskone/Muscone; Civetone; Hexadecenlactone/Ambrettolide; Isoambrettolide; Musk amberol/Ambrettone	Concentration of each substance: 0.1% (expert judgment) Frequency: 1.1 times per day (Loretz et al. 2005) Dermal: Direct product contact, instant application Product amount: 4.4 g (Loretz et al. 2005) Surface Area: 16,925 cm^2 (Health Canada 1998) Inhalation: Exposure to vapour, constant rate Exposure duration: 8 hours (expert judgement) Product amount: 4.4 g (Loretz et al. 2005) Room volume: 20 m3 (ConsExpo Web 2016) Ventilation rate: 0.6/hour (ConsExpo Web 2016) Adult inhalation rate: 16.2 m^3/day (Health Canada 1998)
Lipstick	Exaltolide	Oral: Concentration: 0.1% (MSDS 2015b) Frequency: 4 times per day (ConsExpo Web 2016) Direct product contact, direct oral intake Amount ingested: 0.01 g (ConsExpo Web 2016)
Sunscreen (face)	Exaltolide	Dermal: Concentration: 2.56% (Personal communication from the Natural and Non-prescription Health

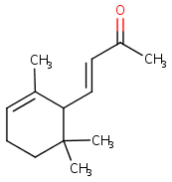
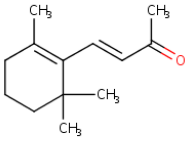
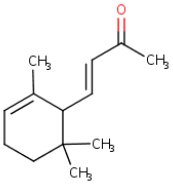
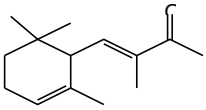
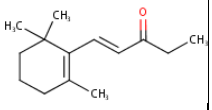
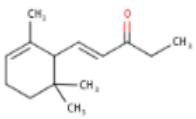
		Products Directorate of Health Canada to the Existing Substances Risk Assessment Bureau, Nov 2016; unreferenced) Frequency: 177 times per year (expert judgement) Direct product contact, instant application Surface area: 637 cm^2 (Health Canada 1998) Product amount: 1.27 g (expert judgement)
Eau de toilette	Exaltolide	Concentration: 3% (MSDS 2015c) Frequency: 1.7 time per day (Loretz et al. 2005) Inhalation: Exposure to spray, spraying Adult inhalation rate: 16.2 m^3/day (Health Canada 1998) Dermal: Direct product contact, instant application Surface area: 100 cm^2 (ConsExpo Web 2016) Product amount: 0.33 g (Loretz et al. 2005)
Body Fragrance Product	Irone; 1-Methyl-α-ionone	Concentration: 0.1% (expert judgment) Frequency: 1.7 time per day (Loretz et al. 2005) Inhalation: Exposure to spray, spraying, spraying towards person Adult inhalation rate: 16.2 m^3/day (Health Canada 1998) Inhalation cut off diameter: 49 µm Dermal: Direct product contact, instant application Surface area: 100 cm^2 (ConsExpo Web 2016) Product amount: 0.33 g (Loretz et al. 2005)
Hair dye (permanent)	1-Methyl-α-ionone	Concentration: 0.1-0.3% (personal communication from Consumer Product Safety Directorate to Existing Substances Risk Assessment Bureau, Nov 2016) Frequency: 3.57 times per year (Statistics Canada 2012) Inhalation: Exposure to vapour, instantaneous release Exposure duration: 60 min (expert judgement) Product amount : 100g (ConsExpo Web 2016) Room volume: 20 m^3 (ConsExpo Web 2016) Ventilation rate: 2/hour (ConsExpo Web 2016) Adult inhalation rate: 16.2 m^3/day (Health Canada 1998) Dermal: Direct product contact, instant application

		Product amount: 100 g (ConsExpo Web 2016) Retention factor: 0.1% (SCCS 2012)
Wall paint (brush and roller, waterborne)	Cyclohexanone	Maximum concentration of additives in waterborne paint: 2% (ConsExpo Web 2016) Frequency: 2 times per year (ConsExpo Web 2016) Dermal: Direct product contact, constant rate Exposed area: 2190 cm^2 (ConsExpo Web 2016) Contact rate: 30 mg/min (ConsExpo Web 2016) Release duration: 120 min (ConsExpo Web 2016) Inhalation (US EPA 2014): Exposure duration: 132 min (ConsExpo Web 2016) Room volume : 36 m^3 (US EPA 2014) Whole House Volume : 523 m^3 (US EPA 2014) Product amount: 3,750 g (ConsExpo Web 2016) Ventilation rate: 0.6/hour (ConsExpo Web 2016) Adult inhalation rate: 16.2 m^3/day (Health Canada 1998)

Appendix B: Read across within the ionones subgroup

Physical Chemical data for target substances and analogues can be found in section 3.0.

Table B-1. Ionones subgroup

Chemical name	α-ionone	β-ionone	Ionone (mixture of α- and β-ionone)	α-iso-methyl-ionone[b]	Ionones (Irone and (1-methyl-α-ionone)
Role	Analogue	Analogue	Analogue	Analogue[b]	Target group
CAS#	127-41-3	14901-07-6	8013-90-9	127-51-5[b]	2 CAS RNs (1335-94-0; 7779-30-8)
Chemical structure					
Chemical structure					
Toxicolo-gical data					
Toxico-kinetics & metabolism	Major urinary metabolite identified: 5-oxo-cis-tetrahydro-ionone in rabbits fed pure α-ionone (Lalko et al. 2007b).[a]	Urinary metabolites: β -ionone, derivatives of β-ionone and β-ionol and glucuronides of these derivatives in dogs and rabbits (Lalko et al. 2007c).	ND	ND	ND
Repeat dose toxicity (Oral)	NOAEL = 10 mg/kg bw/day (13-wk rat feeding	NOAEL = 10 mg/kg bw/day (13-wk rat feeding	NOAEL = 500 mg/kg bw/day (highest	LOAEL = 1000 mg/kg bw per day (only dose;	ND

Chemical name	α-ionone	β-ionone	Ionone (mixture of α- and β-ionone)	α-iso-methyl-ionone[b]	Ionones (Irone and (1-methyl-α-ionone)
Role	Analogue	Analogue	Analogue	Analogue[b]	Target group
CAS#	127-41-3	14901-07-6	8013-90-9	127-51-5[b]	2 CAS RNs (1335-94-0; 7779-30-8)
	study; slightly decreased bw-gain and food consumption in both sexes at 100 mg/kg bw/day).	study; decreased bw-gain and food consumption in both sexes at 100 mg/kg bw/day).	dose; 17-wk feeding study).	14-day rat gavage study; increased salivation and pale kidneys).	
Repeat dose toxicity (Dermal)	ND	ND	ND	NOAEL = 50 mg/kg bw/day (13-wk rat dermal study; increased relative kidney weights in both sexes at 170 mg/kg bw/day).	ND
Repeat dose toxicity (Dermal)	ND	LOEL = 1.6 x 10^{-9} M in (1 and 5 wk rat study; mitral cells degeneration in olfactory bulb) (Lalko et al. 2007c).	ND	ND	ND

Chemical name	α-ionone	β-ionone	Ionone (mixture of α- and β-ionone)	α-iso-methyl-ionone[b]	Ionones (Irone and (1-methyl-α-ionone)
Role	Analogue	Analogue	Analogue	Analogue[b]	Target group
CAS#	127-41-3	14901-07-6	8013-90-9	127-51-5[b]	2 CAS RNs (1335-94-0; 7779-30-8)
Reproductive and/or develop-mental toxicity (oral)	ND	Developmental NOAEL = 750 mg/kg bw/day in rats exposed GD 11 (1 day); Increased number of resorptions/ implantation and resorptions/ implantation/ litter at 1000 mg/kg bw/day.	No toxicity in non-standard oral rat reproductive toxicity study up to F2 generation (8-10 mg/kg bw/day F0; 15 mg/kg bw/day F1).	Developmental NOAEL = 30 mg/kg bw/day in rats exposed during GD 7-17 (11 days). Highest dose.	ND
Genetic toxicity	In vitro genotoxicity equivocal (positive chromosome aberration; negative mutagenicity). In vivo mouse micronucleus test negative (Lalko et al. 2007b).	In vitro mutagenicity negative (Lalko et al. 2007c).	In vitro genotoxicity equivocal (positive DNA damage and repair; negative mutagenicity) (Lalko et al. 2007d).	In vitro mutagenicity negative (Lapczynksi et al. 2007).	One/2 substances (1-methyl-α-ionone) tested. In vitro mutagenicity negative (Wild et al. 1983 cited in EFSA 2015).[c]

Abbreviation: LOEL, Lowest Observed Effect Level; LOAEL, lowest observed adverse effect level; ND, No data; NOAEL, no observed adverse effect level.

a. A reference or references are cited if the information was not previously mentioned in the text of the report.

b. Another analogue, CAS RN 1335-46-0, methyl-ionone, is a structural isomer of both substances in the Ionones subgroup, has the same molecular weight as both substances as well as α-iso-methyl-ionone, and has log Kow and vapour pressure values within the same range as both substances as well as α-iso-methyl-ionone, but very limited toxicological data. However, dermal absorption data were available for this substance, as shown in the section, "Exposure assessment ":

c. EFSA (2015) cites the results of genotoxicity studies using methyl-α-ionone and assigns it as CAS RN 7779-30-8. A check of the original article (Wild et al. 1983) cited in EFSA (2015) shows that they are identified by their FEMA (Flavor and Extract Manufacturers' Association) and CE (Council of Europe) numbers only. It is not clear whether the

data cited in EFSA (2015) applies to CAS RN 7779-30-8 or CAS RN 127-42-4, as both substances are listed under FEMA number 2711, whereas the CE number 143 applies to CAS RN 7779-30-8 only. However, ChemIDplus associates methyl-α-ionone with CAS RNs 127-42-4, 79-69-6 and 93302-56-8.