

Draft Screening Assessment
Fatty Acids and Derivatives Group

Environment and Climate Change Canada
Health Canada

August 2018

Synopsis

Pursuant to section 68 or 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 10 of 16 substances referred to collectively under the Chemicals Management Plan as the Fatty Acids and Derivatives Group. These 10 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other considerations. Four of the 16 substances were subsequently determined to be of low concern through other approaches, and proposed decisions for these substances are provided in separate reports.^{1,2} Additionally, two substances were placed into another substance group, to which they are more appropriately suited, on the basis of chemical structure and uses.³ Accordingly, this screening assessment addresses the 10 substances listed in the table below. The 10 substances addressed in this draft screening assessment report will hereinafter be referred to as the Fatty Acids and Derivatives Group.

Substances in the Fatty Acids and Derivatives Group

CAS RN ^a	<i>Domestic Substances List</i> name	Common name
112-38-9	10-Undecenoic acid	Undecylenic acid
463-40-1	9,12,15-Octadecatrienoic acid, (Z,Z,Z)	α -Linolenic acid (ALA)
8001-20-5 ^{b,c}	Tung Oil	Tung Oil
8002-65-1 ^b	Fats and Glyceridic oils, margosa	Fats and glyceridic oils, margosa
61788-89-4 ^b	Fatty acids, C18-unsaturated, dimers	Dimer acid
61790-12-3 ^b	Fatty acids, tall-oil	Tall oil fatty acid (tall oil acid)
61790-44-1 ^b	Fatty acids, tall-oil, potassium salts	Potassium tallate
68937-90-6 ^{b,c}	Fatty acids, C18-unsaturated, trimers	Trimer acid
90028-66-3 ^{b,d}	Evening primrose, <i>Oenothera biennis</i> , ext.	Evening primrose oil
92044-87-6 ^{b,d}	Fatty acids, coco, 2-ethylhexyl esters	Ethylhexyl cocoate

¹ Proposed conclusions for the substance bearing CAS RN 68139-89-9 are provided in the “Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances” draft screening assessment.

² Proposed conclusions for the substances bearing CAS RNs 53980-88-4, 68647-55-2, and Confidential Domestic Substances List (CDSL) # 11556-0 are provided in the “Rapid Screening of Substances with Limited General Population Exposure” draft screening assessment.

³ Proposed conclusions for the substances bearing CAS RNs 68476-03-9 and 73138-45-1 are provided in the “Assessment of seven hydrocarbon-based substances”.

^a 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.

^b The substance bearing this CAS RN is a UVCB (unknown or variable composition, complex reaction products, or biological materials).

^c The substance bearing this CAS RN was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other human health concerns.

^c The substance bearing this CAS RN was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other ecological considerations.

Four of the 10 fatty acids and derivatives were reported, pursuant to a survey under section 71 of CEPA, to have been manufactured in Canada in 2011 at quantities of 1 430 kg for tall oil acid, 10 000 to 100 000 kg for potassium tallate, and 100 to 1 000 kg each for dimer and trimer acids. Seven of the ten substances were reported to have been imported into Canada the same year at quantities of 1 000 to 10 000 kg for ALA, 120 412 kg for tung oil, 6 317 473 kg for tall oil acid, 47 992 kg for potassium tallate, 293 472 kg for dimer acid, 1 088 638 kg for trimer acid and 6 470 kg for ethylhexyl cocoate. The remaining three substances, undecylenic acid, fats and glyceridic oils, margosa, and evening primrose oil were not reported to be manufactured or imported into Canada in 2011 above the reporting threshold of 100 kg.

Undecylenic acid and ALA are naturally occurring compounds, and the remaining substances in this group are derived from natural sources such as plants. The substances in the Fatty Acids and Derivatives Group have a number of reported uses, including lubricants and greases, adhesives and sealants, paints and coatings, fuels and related products, and food packaging. Some of these products are available to consumers. Several of the substances included in the Fatty Acids and Derivatives Group are used in cosmetics, as well as in natural and non-prescription health products.

The ecological risks of the substances in the Fatty Acids and Derivatives 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, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are established principally on the basis of mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. The ERC identified the substances in this assessment as having low-to-moderate potential to cause ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from the 10 substances in the Fatty Acids and Derivatives Group. It is proposed to conclude that undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid, and ethylhexyl cocoate 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.

ALA was assessed together with a group of aliphatic acids by the Organisation for Economic Co-operation and Development in 2014. ALA and the major components of fats and glyceridic oils, margosa, tall oil, evening primrose oil, dimer/trimer acid and the free fatty acids of ethylhexyl cocoate were not identified by OECD as possessing properties indicating a hazard for human health for systemic health effects, as supported by the toxicity information of tung oil.

The European Food Safety Authority concluded in 2010 that laboratory studies on the conjugated form of a major component of tung oil did not indicate a risk for genotoxicity, reproductive toxicity or carcinogenicity.

In a Multi-Chemical Tiered I Human Health Risk Assessments carried out by the Australian Government Department of Health in 2017, dimer acid was considered as not to pose unreasonable risk to human health.

On the basis of information from the above-noted international assessments, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer and trimer acids were not identified as having systemic health effects of concern and risk to human health is considered to be low.

General population exposure to undecylenic acid can occur from its use as a flavouring agent in certain foods, from cosmetics, as well as from natural health products. Exposure to ethylhexyl cocoate can occur from its use in cosmetics. The available health effects information on undecylenic acid and its sodium salt, as well as ethylhexyl cocoate and its hydrolyzed products, indicates effects on the body/organs weights and effects on the clinical chemistry parameters. The margins of exposure between estimated levels of exposure for both these substances and the critical effect levels in laboratory studies are considered adequate to address uncertainties in the health effects and exposure databases.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid, and ethylhexyl cocoate do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid, and ethylhexyl cocoate do not meet any of the criteria set out in section 64 of CEPA.

Table of Contents

Synopsis	i
1. Introduction	1
2. Identity of substances	3
2.1 Selection of analogues	5
3. Physical and chemical properties	5
4. Sources and uses	6
5. Potential to cause ecological harm	11
5.1 Characterization of ecological risk	11
6. Potential to cause harm to human health	14
6.1 Overview and approach.....	14
6.2 General information on fatty acids and derivatives	15
6.3 ALA, tung oil, fats and glyceridic oils, margosa, evening primrose oil, tall oil acid, potassium tallate, dimer and trimer acids	15
6.4 Undecylenic acid and ethylhexyl cocoate	22
7. Conclusion	32
References	34
Appendices	42
Appendix A. Substance identity information.....	42
Appendix B. Parameters used to estimate exposures.	43

List of Tables

Table 1-1. Substances in the Fatty acids and Derivatives Group that were addressed under other approaches	1
Table 2-1. Substance identities	4
Table 3-1. Experimental physical and chemical property values (at standard temperature) for the fatty acids and derivatives.....	6
Table 4-1. Summary of information on Canadian manufacturing and imports of Fatty Acids and Derivatives Group submitted pursuant to a section 71 survey of CEPA.....	8
Table 4-2. Summary of the major uses of the fatty acids and derivatives in Canada (based on consumer and commercial DSL codes reported by the user, pursuant to a section 71 survey of CEPA	9
Table 4-3. Additional uses in Canada for each of the substances in the Fatty Acids and Derivatives Group.....	10
Table 5-1. Ecological risk classification results for the 10 substances in the Fatty Acids and Derivatives Group.....	12
Table 6-1. Eestimated exposures to undecylenic acid from the use of cosmetics.....	23
Table 6-2. Relevant exposure and hazard values for undecylenic acid, as well as margins of exposure, for determination of risk.....	25
Table 6-3. Sources of uncertainty in the risk characterization for undecylenic acid.	27
Table 6-4. Estimated exposures to ethylhexyl cocoate from the use of cosmetics.....	27

Table 6-5. Relevant exposure and hazard values for ethylhexyl cocoate, as well as margins of exposure, for determination of risk.....	31
Table 6-6. Determination of risk using relevant dermal exposures and 12-day dermal study for 2-EH.....	31
Table 6-7. Sources of uncertainty in the risk characterization for ethylhexyl cocoate. ..	32

1. Introduction

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 10 of 16 substances, referred to collectively under the Chemicals Management Plan as the Fatty Acids and Derivatives Group, to determine whether they present or may present a risk to the environment or to human health. These 10 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other considerations (ECCC, HC [modified 2007]).

Four other substances (listed in Table 1-1 below) were considered in the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016) and either in the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Document (Health Canada 2016) or via the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2017a). The four substances were identified as being of low concern to both human health and the environment and are therefore not further addressed in this report. Proposed conclusions for one substance is provided in the Substances Identified as Being of Low Concern based on the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Draft Screening Assessment (ECCC, HC 2017b), while proposed conclusions for the other three substances are provided in the Rapid Screening of Substances with Limited General Population Exposure Draft Screening Assessment (ECCC, HC 2017a).

Table 1-1. Substances in the Fatty Acids and Derivatives Group that were addressed under other approaches

CAS RN ⁴	<i>Domestic Substances List</i> (DSL) name	Approach under which the substance was addressed	References
68139-89-9	Fatty acids, tall-oil, maleated	ERC/TTC	ECCC, HC 2017b
53980-88-4	2-Cyclohexene-1-octanoic acid, 5(or 6)-carboxy-4-hexyl-	ERC/Rapid Screening	ECCC, HC 2017a
68647-55-2	Fatty acids, tall-oil,	ERC/Rapid Screening	ECCC, HC 2017a

⁴ 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.

	esters with triethanolamine		
CDSL #11556-0	Fatty acids, reaction products with maleic anhydride	ERC/Rapid Screening	ECCC, HC 2017a

Additionally, two substances were placed into another substance groups, to which they are more appropriately suited, on the basis of similar structural features and/or functionalities of toxicological significance⁵.

The 10 substances addressed in this draft screening assessment report will hereinafter be referred to as the Fatty Acids and Derivatives Group. The ecological risk of the substances in the Fatty Acids and Derivatives Group were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food-web derived internal toxicity thresholds, bioavailability, and chemical and biological activity, and it considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of factors including potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

ALA and the major components of fats and glyceridic oils, margosa, tall oil, evening primrose oil, dimer/trimer acid and the free fatty acid of ethylhexyl cocoate were reviewed by the Organisation for Economic Co-operation and Development (OECD) Cooperative Chemicals Assessment Programme, and an OECD Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) is available. The OECD assessment undergoes rigorous review (including peer-review) and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in this process, and consider these assessments to be reliable. In addition, fats and glyceridic oils, margosa (CAS RN 8002-65-1, known as cold pressed neem oil) was reviewed by the United States Environmental Protection Agency (US EPA) for biopesticides registration, the conjugated form of a major component of tung oil was reviewed by the European Food Safety Authority (EFSA), and dimer acid was reviewed in a Multi-Chemical Tiered I Human Health Risk Assessment by the Australian Government Department of Health (AGDH). The OECD SIAR, US EPA, EFSA and AGDH reviews will be used to inform the health effects characterization in this screening assessment.

⁵ Conclusions for two substances (CAS RNs 68476-03-9 and 73138-45-1) will be provided in the upcoming “Draft Screening Assessments, seven hydrocarbon-based substances Group” assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to June 2017. Empirical data from key studies as well as some results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological portion of this assessment is based on the ERC document which was subject to an external peer-review and a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution⁶. This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

2. Identity of substances

The CAS RN, Domestic Substances List (DSL) names and common names and/or acronyms for the individual substances in the fatty acids and derivatives are presented in Table 2-1. Information on the identity of the components in the UVCB (Unknown or Variable Composition, Complex Reaction Products or Biological Materials) substances is presented in Appendix A. A list of additional chemical names (e.g., trade names) is available from the National Chemical Inventories (NCI 2015).

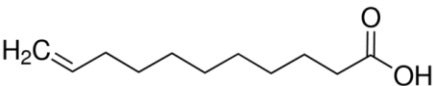
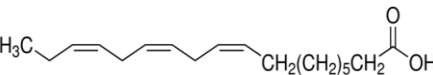
Fatty acids are organic compounds that contain at least one terminal carboxylic group and whose derivatives contain at least one ester linkage. The substances in this screening assessment consist of discrete or single component fatty acids (undecylenic acid, α -Linolenic acid), complex substances that include a mixture of multi-component

⁶A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

substances of saturated, unsaturated and undefined fatty acids (tung oil, fats and glyceridic oils, margosa, tall oil fatty acid, evening primrose oil, trimer acid and dimer acid), and direct reaction products of fatty acids including a potassium salt (potassium tallate) and a fatty acid ester (ethylhexyl cocoate). The degree of saturation and the carbon chain length distribution of the major components of this group of substances are presented in Appendix A.

Fats and glyceridic oils, margosa, CAS RN 8002-65-1, also referred to as clarified hydrophobic extract of neem oil is derived from the seeds of the neem tree (*Azadirachta indica*) and is a mixture of simple and complex terpenoids, steroids, fatty acids and essential oils (US EPA 2012). CAS RN 8002-65-1 refers to the fats and glyceridic oils, margosa that has been treated with alcohol to remove virtually all of the azadirachtin (CAS RN 11141-17-6) which is used in various applications but is not further assessed in this report. According to US EPA (2012), CAS RN 8002-65-1 contains between 0.05 to 0.3% of azadirachtin.

Table 2-1. Substance identities

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
112-38-9	10-Undecenoic acid (Undecylenic acid)	 $C_{11}H_{20}O_2$	184.28
463-40-1 (ALA)	9,12,15- Octadecatrienoic acid, (Z,Z,Z) (α -Linolenic acid)	 $C_{18}H_{30}O_2$	278.43
8001-20-5	Tung oil	UVCB	Unspecified
8002-65-1	Fats and glyceridic oils, margosa	UVCB	Unspecified
61790-12-3 (Tall oil acid)	Fatty acids, tall-oil (tall-oil fatty acid)	UVCB	Unspecified
61790-44-1	Fatty acids, tall-oil, potassium salts (Potassium tallate)	UVCB	Unspecified
90028-66-3 (Evening primrose oil)	Evening primrose, <i>Oenothera biennis</i> , ext. (Evening primrose oil)	UVCB	Unspecified

CAS RN (abbreviation)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
68937-90-6 (Trimer acid)	Fatty acids, C18-unsaturated, trimers (Trimer acid)	UVCB	801.03
61788-89-4 (Dimer acid)	Fatty acids, C18-unsaturated, dimers (Dimer acid)	UVCB	564.92
92044-87-6	Fatty acids, coco, 2-ethylhexyl esters (Ethylhexyl cocoate)	UVCB	Unspecified

UVCB (unknown or variable composition, complex reaction products, or biological materials).

2.1 Selection of analogues

A read-across approach using data from analogues or components of the target substances, where appropriate, has been used to inform the ecological and human health assessments. Analogues were selected that were structurally similar and/or functionally similar to substances within this group (e.g., in terms of physical-chemical properties, toxicokinetics) and that had relevant empirical data that could be used to read-across to substances without empirical ecological or health effects data. Details of the read-across data chosen to inform the ecological and human health assessments of the Fatty Acids and Derivatives Group are further discussed in the relevant sections of this report.

3. Physical and chemical properties

A summary of physical and chemical properties of the substances in the Fatty Acids and Derivatives Group are presented in Table 3-1. When experimental information was limited or not available for a property, (Q)SAR models were used to generate predicted values for the substance. Additional physical and chemical properties are reported in ECCC 2016b.

Physical and chemical property data were not available for all of the substances because many are UVCBs. Generally, the fatty acids have low water solubility and vapour pressures and moderate to high octanol-water partition coefficients ($\log K_{ow}$) and organic carbon-water partition coefficients ($\log K_{oc}$), suggesting that they are more likely to be found in soil and sediments. Given that potassium tallate (CAS RN 61790-44-1) is a fatty acid salt, its water solubility is expected to be greater (HERA 2002). According to OECD (2014), two clear trends are evident with increasing alkyl chain length: (1) increasing melting point, boiling point, and partition coefficient, and (2) decreasing water solubility and vapour pressure. Furthermore, within a given carbon chain length, melting

point increases with increasing saturation and decreases with increasing unsaturation (OECD 2014).

Fatty acid components of this group of substances are mainly linear fatty acids with a carbon chain length of C16 or C18, with some exceptions, such as undecylenic acid (CAS RN 112-38-9), a single component C11 fatty acid, and ethylhexyl cocoate (CAS RN 92044-87-61), a C12 and C14 predominant fatty acid and the dimerized or trimerized C18 of fatty acids (CAS RN 61788-89-45 and 68937-90-6 C18-unsaturated, dimers/trimers). While the chain length and number, location and isomer form of double bond(s) in carbon chains may alter their physical/chemical properties, the overall physical and chemical properties are expected to be similar among the complex substances, as they form a mixture of aforementioned single carbon chain fatty acids.

Table 3-1. Experimental physical and chemical property values (at standard temperature) for the fatty acids and derivatives

Property	Undecylenic acid ^a	ALA ^b	Fats and glyceridic oils, margosa ^c	Dimer acid ^d	Trimer acid ^e
Physical state	solid	liquid	liquid	liquid	liquid
Vapour pressure (Pa)	0.0192	7.2E-5	3.33E-5	< 0 (estimated)	< 0 (estimated)
Henry's law constant (Pa·m ³ /mol)	0.53 (estimated)	3.52 (estimated)	NA	NA	NA
Water solubility (mg/L)	38.46 at pH 4.27	0.124 (estimated)	52.3	> 0 - < 0.12	> 0 - < 0.37
log K _{ow} (dimensionless)	4.0	6.46	6.26	1 – 2.5 (pH 2)	2.2 – 8.9 (pH 2)
log K _{oc} (dimensionless)	2.84	4.068 (estimated)	NA	6.34 (estimated)	6.73 (estimated)

Abbreviations: NA, not available; K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient

^a ECHA (c2007-2017a), ChemIDPlus (1993-)

^b ChemIDPlus (1993-), EPISuite

^c US EPA (2012)

^d ECHA (c2007-2017b), ECCC

^e ECHA (c2007-2017c), ECCC

4. Sources and uses

Two of the fatty acids in this group occur naturally in the environment. Undecylenic acid is a natural component of human sweat (Alternative Medicine Review 2002) and occurs naturally in *Rohdororula glutinis* var. *lusitanica*, in the essential oils of *Juniperus chinensis*, and *Thujopsis dolabrata* and in skim milk powder (Burdock 2010). ALA is considered a dietary essential fatty acid and is found in certain vegetable oils (e.g. canola, soy), nuts (e.g., walnuts) and seeds (e.g., flaxseeds, chia) (IOM 2005; Dietitians

of Canada 2017). The remaining 8 substances are derived from natural sources (from plant and animal fats and oils) with the source often clearly indicated by their name. Tung oil is derived from the seeds of the tung tree or China wood oil tree (*Vernicia fordii* and *Vernicia montana*) (Shockey et al. 2016); fats and glyceridic oils, margosa, is derived from the seeds of the neem tree (*Azadirachta indica*) (US EPA 2012); and evening primrose oil is derived from the evening primrose plant (*Oenothera biennis*) (NTP 2009). Ethylhexyl cocoate is derived from coconut oil. Tall oil acid and potassium tallate are derived from tall oil, a by-product of the pulp from resinous woods (Robinson et al. 2009). Dimer and trimer acids are derived from C-18 unsaturated fatty acids, such as oleic acid and linoleic acid from natural oils (Riteks 2008).

All of the substances in the Fatty Acids and Derivatives Group have been included in surveys issued pursuant to section 71 of CEPA (Canada 2012). Table 4-1 presents a summary of the reported total manufacture and total import quantities for the fatty acids and derivatives.

Table 4-1. Summary of information on Canadian manufacturing and imports of Fatty Acids and Derivatives Group submitted pursuant to a section 71 survey of CEPA^a

Common name	Total manufacture (kg)	Total imports (kg)	Reporting year	Survey reference
Undecylenic acid	NR	NR	2011	Environment Canada 2013
ALA	NR	1 000 – 10 000	2011	Environment Canada 2013
Tung oil	NR	120 412	2011	Environment Canada 2013
Fats and glyceridic oils, margosa	NR	7	2011	Environment Canada 2013
Tall oil acid	1430	6 317 473	2011	Environment Canada 2013
Potassium tallate	10 000 – 100 000	47 992	2011	Environment Canada 2013
evening primrose oil	NR	NR	2011	Environment Canada 2013
Trimer acid	100 – 1 000	293 472	2011	Environment Canada 2013
Dimer acid	100 – 1 000	1 088 638	2011	Environment Canada 2013
Ethylhexyl cocoate	NR	6 470	2011	Environment Canada 2013

Abbreviations: NR, not reported

^a Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (Environment Canada 2012). See survey for specific inclusions and exclusions (schedules 2 and 3).

Table 4-2 presents a summary of the major uses of the fatty acids and derivatives according to information reported pursuant to a section 71 survey(s) of CEPA (Environment Canada 2013). Undecylenic acid and evening primrose oil did not have any reported uses above the reporting threshold of 100 kg. The major use of fats and glyceridic oils, margosa, was in personal care products. Table 4-3 summarizes additional Canadian uses except for trimer acid which was not identified in products used in any of these applications.

Table 4-2. Summary of the major uses of the fatty acids and derivatives in Canada (based on consumer and commercial DSL codes reported by the user, pursuant to a section 71 survey of CEPA)

Major uses	ALA	Tung oil	Tall oil acid	Potassium tallate	Trimer acid	Dimer acid	Ethylhexyl cocoate
Lubricants and greases	Y	Y	Y	Y	Y	Y	N
Adhesives and sealants	Y	N	Y	N	Y	Y	N
Paper products	N	N	Y	Y	N	Y	N
Food packaging	N	N	Y	Y	N	Y	N
Fuels and related products	Y	N	N	N	Y	Y	N
Paints and coatings	Y	Y	Y	N	Y	Y	N
Personal care	N	N	Y	N	Y	Y	Y
Building and construction materials	N	N	Y	N	N	Y	N
Oil and natural gas extraction	N	N	Y	N	Y	Y	N
Cleaning and furnishing care	N	N	Y	N	N	N	N
Automotive care	N	N	Y	N	N	N	N
Water treatment	N	N	Y	N	N	Y	N
Metal materials	N	N	Y	N	Y	Y	N
Floor coverings	N	N	N	N	Y	N	N
Other	Y	Y	Y	Y	Y	Y	Y

Abbreviations: Y, yes; N, no

^a Uses reported in response to the surveys conducted under section 71 of CEPA (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

Table 4-3. Additional uses in Canada for each of the substances in the Fatty Acids and Derivatives Group

Use	UA	ALA	Tung oil	Fats and glyceridic oils, margosa	Tall oil acid	PT	Evening primrose oil	Dimer acid	EhC
Food additive ^a	N	N	N	N	N	N	N	Y	N
Food packaging materials ^a	N	Y	Y	N	Y	Y	N	N	N
Incidental additive ^a	N	N	N	N	N	Y	N	Y	N
Internal Drug Product Database as medicinal or non-medicinal ingredients in final Pharmaceutical, Disinfectant or Veterinary drug products in Canada ^b	Y	Y	N	N	N	N	Y	N	N
Natural Health Products Ingredients Database ^c	Y	Y	N	Y	Y	N	Y	N	Y
Licensed Natural Health Products Database as medicinal or non-medicinal ingredients in natural health products in Canada ^d	Y	Y	N	Y	N	N	Y	N	N
List of Prohibited and Restricted Cosmetic Ingredients ^e	N	N	N	N	N	N	N	N	N
Notified to be present in cosmetics, based on notifications submitted under the <i>Cosmetic Regulations</i> to Health Canada ^f	Y	Y	N	Y	Y	N	Y	N	Y
Formulant in pest control products registered in Canada ^g	Y	Y	N ^h	N	Y	N ^h	N	Y	N

Abbreviations: UA, undecylenic acid; PT, potassium tallate; EhC, ethylhexyl cocoate; Y, yes; N, no

^a Personal communication, e-mail from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated May 25, 2016; unreferenced).

^b DPD [modified 2016]; Personal communication, e-mail from Therapeutic Products Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated April 28, 2016; unreferenced).

^c NHPID [modified 2017].

^d LNHPD [modified 2016].

^e Health Canada [modified 2015a].

^f Personal communication, e-mail from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated April 22, 2016; unreferenced.

^g Additionally, none of these substances are registered as active ingredients in pest control products in Canada (personal communication, e-mail from Pest Management Regulatory Agency, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated May 9, 2016; unreferenced).

- ^h Can be used as a formulant; however, it is currently not registered in any products (personal communication, e-mail from Pest Management Regulatory Agency, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated May 9, 2016; unreferenced).

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of the substances in the Fatty Acids and Derivatives Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure, with weighted 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., LC₅₀) for characterization. Since tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid, and ethylhexyl cocoate are UVCB substances and could not be suitably represented by single chemical structures, a manual judgement-based approach to classification was used. The following summarizes the approach, which is described in detail in ECCC (2016a).

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

Hazard profiles were established principally on the basis of metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles composed of multiple metrics, including potential emission rate, overall persistence and long-range transport potential, were also established. 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. However, in the case of the UVCBs, hazard and exposure could not be fully profiled because of the lack of a representative structure to estimate needed properties and the lack of empirical data for these properties. Therefore, manual classification of hazard and exposure based on examination of the UVCB constituents

and information obtained from section 71 surveys under CEPA was performed and decisions were based on consideration of similar substances and application of expert judgement.

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

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

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

The hazard and exposure classifications for the substances in the Fatty Acids and Derivatives Group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the substances in the Fatty Acids and Derivatives Group

Common name	ERC hazard classification	ERC exposure classification	ERC risk classification
Undecylenic acid	low	low	low

ALA	high	low	low
Tung Oil	low	high	low
Fats and glyceridic oils, margosa	high	low	low
Tall oil acid	high	low	moderate
Potassium tallate	high	low	moderate
Evening primrose oil	high	low	low
Ethylhexyl cocoate	low	low	low
Trimer acid	low	low	low
Dimer acid	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, undecylenic acid, ethylhexyl cocoate, trimer acid and dimer acid were classified as having a low potential for ecological risk. It is therefore unlikely that these substances will result in concerns for the environment in Canada.

Tung oil was classified as having a low hazard potential with a high exposure potential according to information considered under ERC due to moderate use quantities and a high margin of exposure. Accordingly, tung oil was classified as having a low potential for ecological risk. It is therefore unlikely that this substance will result in concerns for the environment in Canada.

Tall oil acid and potassium tallate were classified as having high hazard potential according to information considered under ERC due to reactive mode of action and increased potential to cause adverse effects in aquatic food webs given their bioaccumulation potential. Although the reported import/manufacture quantities of these substances were high and moderate, respectively, the exposure potential of these substances was classified as low according to information considered under ERC. Tall oil acid and potassium tallate were classified as having a moderate potential for ecological risk. The potential effects and how they may manifest in the environment were not further investigated due to the low exposure of these substances. Considering current use patterns, these substances are unlikely to result in concerns for the environment in Canada. As these substances are currently being used in high quantities in Canada, fluctuations in use patterns are unlikely to result in a significant increase in risk to the environment.

Fats and glyceridic oils, margosa, was classified as having a high hazard potential according to information considered under ERC on the basis of the agreement between reactive mode of action and elevated toxicity ratio, both of which suggest that this

chemical is likely of high potency. Fats and glyceridic oils, margosa, has an increased potential to cause adverse effects in aquatic food webs given the substance's bioaccumulation potential. Structural alerts from the OECD toolbox identified fats and glyceridic oils, margosa, as being a potential protein binder. Fats and glyceridic oils, margosa, was classified as having low ecological exposure potential and moderate potential for ecological risk. However, the risk classification was decreased to low potential for ecological risk following the adjustment of risk classification on the basis of current use quantities (see section 7.1.1. of the ERC approach document ECCC 2016a). The potential effects and how they may manifest in the environment were not further investigated due to the low exposure of these substances. Given the current use patterns, this substance is unlikely to result in concerns for the environment in Canada.

ALA and evening primrose oil were classified as having a high hazard potential according to information considered under ERC based on reactive mode of action and increased potential to cause adverse effects in aquatic food webs given their bioaccumulation potential. Structural alerts from OECD toolbox identified ALA and evening primrose oil as being potential DNA binders. ALA and evening primrose oil were classified as having a low ecological exposure potential and a moderate potential for ecological risk. However, the risk classification was decreased to low potential for ecological risk following the adjustment of risk classification on the basis of current use quantities (see section 7.1.1. of ECCC 2016a). The potential effects and how they may manifest in the environment were not further investigated given the low exposure of these substances. On the basis of current use patterns, these substances are unlikely to result in concerns for the environment in Canada.

6. Potential to cause harm to human health

6.1 Overview and approach

The available toxicity studies demonstrate the low acute toxicity of several of the fatty acids and their salts. The estimated LD₅₀s for 8 of the substances in this group are greater than 2000 mg/kg bw via oral route and greater than 3000 mg/kg bw via dermal route of exposure in laboratory animals (HERA 2002). Although the OECD toolbox prediction profiles identified ALA and evening primrose oil as being potential DNA binders based on structure, the (Q)SAR genotoxicity predictions from the Danish (Q)SAR database (2015) for ALA and for the major component of evening primrose oil were negative. In addition, ALA, an essential fatty acid for humans and the major component of evening primrose oil, along with 78 other fatty acids, was not identified by OECD (2014) as possessing properties indicating a hazard for human health for systemic health effects or for mutagenic or clastogenic activities. Given the apparently low toxicity of some of the fatty acids and derivatives in this assessment as identified in acute and repeated dose toxicity studies, ALA, tung oil, fats and glyceridic oils, margosa, evening primrose oil, tall oil acid, potassium tallate, dimer acid and trimer acid are addressed qualitatively in section 6.3. The remaining two substances, undecylenic

acid and ethylhexyl cocoate, are more complex and are described in more detail in section 6.4.

In the absence of data for UVCB substances, the information for the major constituents (as indicated in Table A-1 in Appendix A) and potential hydrolysis products was used to inform characterization of the potential health effects of the fatty acids and their derivatives.

6.2 General Information on fatty acids and derivatives

Environmental media

No empirical data on the presence of these substances in environmental media in Canada or elsewhere were identified. In general, considering their physical and chemical properties and current use patterns, the fatty acids in this group are not likely to be found in air, but may be found in water as a result of industrial releases or from the use of products available to consumers (down-the-drain releases). However, exposure of the general population to fatty acids and derivatives via environmental media is not expected to be of concern.

General toxicokinetic and metabolism information for fatty acids

There is no substance-specific toxicokinetic information identified for the fatty acids and their derivatives covered by this group, except for limited information on ALA. Fatty acid chain length and unsaturation number influence fat absorption. Shorter chain length fatty acids are more extensively absorbed than longer chain fatty acids because they can be solubilized in the aqueous phase of intestinal contents (Ramírez et al. 2001).

The dermal absorption of fatty acids demonstrated a decreased trend with increasing chain length (Howes 1975). An *in vitro* study in human skin confirmed the penetration of several fatty acid components (e.g., oleic, linoleic, lauric and capric acid) (Kezutyte et al. 2013). A 100% dermal absorption of alpha-linolenic acid (CAS 463-40-1) was predicted by an *in vitro* model (Buist et al. 2010; Kim et al. 2014). However, the predicted dermal absorption of ethylhexyl cocoate was very low, i.e., in the range of 1.26E-05 to 4.46E-05 mg/cm²/event (ECHA dossier c2007-2017d). Differences in physicochemical properties of fatty acids might determine their different affinity to skin lipids and mechanisms of action (Kezutyte et al. 2013).

6.3 ALA, tung oil, fats and glyceridic oils, margosa, evening primrose oil, tall oil acid, potassium tallate, dimer and trimer acids

There are no international classifications for carcinogenicity, genotoxicity, and developmental or reproductive toxicity for ALA, tung oil, fats and glyceridic oils, margosa, evening primrose oil, tall oil acid, potassium tallate, dimer acid, or trimer acid. The available oral and dermal repeated dose toxicity studies demonstrated the low toxicity of fatty acids and their salts (HERA 2002). OECD conducted a human health

assessment on a group of 78 naturally derived homologous straight-chain fatty acids together with a few fatty acid salts and esters, including ALA and 8 major components of the fatty acid UVCBs assessed here (as indicated in Appendix A). In addition, tall oil acid (CAS 61790-12-3) was included by the OECD (2014) as a supporting substance to inform the straight-chain fatty acids category assessment. Adverse effects from fatty acids and derivatives were only seen at high exposures (e.g., greater than 3000mg/kg bw/day). ALA, tung oil, fats and glyceridic oils, margosa, evening primrose oil, tall oil acid, potassium tallate, dimer acid, and trimer acid are therefore considered to have low hazard potential.

6.3.1 Alpha-linolenic acid (ALA)

The general population of Canada may be exposed to ALA from its natural presence in foods and from food packaging, cosmetics, natural and non-prescription health products, certain fungicides, fuels, lubricants and greases, and/or paints and coatings.

ALA is an essential *n*-3 or omega-3 polyunsaturated fatty acid (PUFA). It cannot be synthesized in humans (IOM 2005; FAO 2010).

A dietary reference intake (DRI) level, specifically, an adequate intake (AI), has been set for ALA by the Institute of Medicine (IOM) and has been adopted by Health Canada (Health Canada 2010). The AI for the various age groups ranges from 0.5 g/day for infants (0 to 12 months old) (based on intakes from human milk and complementary foods) to 1.1 and 1.6 g/day for females and males aged 14 years and older, respectively. These AIs were derived on the basis of an intake that supports normal growth and neural development and results in no nutrient deficiency. Currently, there is no tolerable upper intake level for ALA (IOM 2005).

There were no genotoxicity or repeated dose toxicity studies identified for ALA. However, there were numerous studies available investigating the beneficial effects of ALA in humans for the purpose of nutraceutical or pharmaceutical uses. The potential adverse human health effects of ALA, together with a group of 78 naturally derived homologous straight-chain fatty acids, were assessed by OECD (2014). ALA, a non-branched fatty acid with a carbon chain length of 18, was not identified by OECD as possessing properties indicating a hazard for human health for systemic health effects or for mutagenic or clastogenic activities based on the toxicity information of another C18 fatty acid, tung oil. Although structural alerts from the OECD QSAR Toolbox identified ALA and evening primrose oil as being potential DNA binders, the negative predictions from four main models in the Ames *Salmonella typhimurium* test for ALA obtained from the Danish (Q)SAR database (2015) indicate that its potential for mutagenicity is low.

Although the hazard database is limited, the available information indicates that ALA is considered to be of low hazard potential, and risk to human health is considered to be low.

6.3.2 Tung oil

The general population of Canada may be exposed to tung oil from its presence in food packaging, paints and coatings, and lubricants and greases.

The major constituent of tung oil, α -eleostearic acid (CAS RN 506-23-0), which makes up nearly 80% of the fatty acids in tung oil, was found to be converted to conjugated linoleic acid (CLA; 9Z, 11E-18:2) in the liver and the plasma in rats (Tsuzuki et al. 2004a). The conjugated linoleic acid (CLA)-rich oil was determined by EFSA (2010) as not indicating a risk for genotoxicity, reproductive toxicity or carcinogenicity based on animals studies. Moreover, α -eleostearic acid was shown to have antitumorigenic activity in cancer cells and in animal models. A recent *in vitro* study demonstrated that α -eleostearic acid inhibited growth and induced apoptosis in human breast cancer cells (Zhuo et al. 2014). In an *in vivo* study, a strong antitumorigenic effect of α -eleostearic acid was also reported by Tsuzuki et al. (2004b) in nude mice into which human colon cancer cells were transplanted.

Both sexes of weanling and adult rats were administered tung oil via gavage at 74 960 or 10 708 mg/kg bw/day, respectively, for 14 days. All weanling rats died by day 5 and 50% of the adult rats died at the end of the study. Immediate and significant suppression of diet intake occurred in weanling rats at the beginning of treatment. The same effect was reported in adult rats starting on day 3 of dosing. However, there were no gross lesions or pathological changes observed on autopsy of the dead rats. The lowest observed adverse effect level (LOAEL) for mortality in adult rats was 10 708 mg/kg bw/day (McPherson 1973). When rats were administered tung oil at 6 000 to 14 400 mg/kg bw/day in the diet for 28 days, an increase in serum cholesterol was reported. No other health effects were reported by the author (Hegsted 1957).

Although the hazard database is limited, the available information indicates that tung oil is considered to be of low hazard potential, and risk to human health is considered to be low.

6.3.3 Fats and glyceridic oils, margosa

The general population of Canada is exposed to fats and glyceridic oils, margosa, from its presence in cosmetics and natural health products.

Fats and glyceridic oils, margosa, was not mutagenic in Ames *S. typhimurium* tests in the presence or absence of metabolic activation (Polasa and Rukmini 1987; Vinod et al. 2011). In an *in vivo* test, it did not induce micronuclei in mice bone marrow cells at up to 500 mg/kg bw after intraperitoneal exposure (Vinod et al. 2011). The US EPA (2012) concluded that cold pressed neem oil (fats and glyceridic oils, margosa; CAS RN 8002-65-1) and its components are not structurally related to known mutagens, nor do they belong to any chemical class of compounds containing known mutagens.

In a 90-day oral repeated dose study, male albino mice were treated with cold pressed neem oil (fats and glyceridic oils, margosa; CAS RN 8002-65-1) in the diet at a dose of 5000 mg/kg bw/day (only dose tested). The treatment did not cause significant changes in body weight or in liver damage indicators in blood (NOAEL = 5000 mg/kg bw/day; Awad 2003, cited in US EPA 2009, 2012).

In a three-generation study in rats in which both sexes of NIN/Wistar rats were administered cold pressed neem oil (fats and glyceridic oils, margosa; CAS RN 8002-65-1) in the diet at 10% (equivalent to 4716 mg/kg bw/day), no mortalities, signs of clinical toxicity, or developmental health effects were observed. Reproductive performance and gross pathological and histopathological examinations of tissues, including testis and ovary, did not show any effects. The only significant finding was increased liver and testis weights in the first and third generation of treated rats compared to controls (LOAEL= 4716 mg/kg bw/day, Chinnasamy et al. 1993, cited in US EPA 2009, 2012).

US EPA conducted a biopesticides registration review on cold pressed neem oil (fats and glyceridic oils, margosa, CAS RN 8002-65-1) in 2012 and concluded that no unreasonable adverse effects to the US population will result from the use of cold pressed neem oil when label instructions are followed. Oleic acid, stearic acid, palmitic acid and linoleic acid, the major components of fats and glyceridic oils, margosa, were not identified by OECD (2014) as having properties indicating a hazard for human health for systemic health effects. Although the hazard database is limited, the available information indicates that fats and glyceridic oils, margosa, is considered to be of low hazard potential, and risk to human health is considered to be low.

The animal studies published after the US EPA (2012) assessment showed that exposure to neem seed preparations via the oral route may affect fetal developmental and induce reversible testicular damage. However, the identity of the test materials, such as the CAS RN or name, in these studies cannot be verified. When pregnant Sprague-Dawley (SD) rats were exposed to neem seed oil (pressed and filtered by filter paper) via gavage at 0 and 5789 mg/kg bw/day throughout pregnancy (20 days), an increase in the incidences of malformations and/or variations was seen in the fetuses of treated dams (11 fetuses with visceral or external malformations in treatment group versus 0 in control group; LOAEL= 5789 mg/kg bw/day, Dallaqua et al. 2013). Both sexes of Kunming mice were exposed to neem seed oil (carbon dioxide supercritical fluid extraction, an azadirachtin-enriched extraction method) via gavage at 0, 177, 533 or 1600 mg/kg bw/day for 30 days (Deng et al. 2013) or for 90 days with additional 30 days of recovery (Wang et al. 2013). Histopathological changes, such as central venous congestion in hepatocytes and vascular congestion in kidneys in both sexes, significant effects on sperm content, and destruction of seminiferous tubule in males were observed in high-dose groups after 28 days of exposure (NOAEL = 533 mg/kg bw/day, LOAEL = 1600 mg/kg bw/day). After 90 days, exposure to 177 and 533 mg/kg bw/day of neem oil induced mild effects in mice, including slight vascular congestions in liver, spleen, lung, and kidney in both sexes and slight congestion in testicles in males, while 1600 mg/kg bw/day had various degrees of effects on each organ, mainly granular and

vacuolar degeneration in cells and vascular congestion in both sexes. However, all effects on organs were lessened or restored after 30 days of recovery. A NOAEL of 177 mg/kg bw/day for organ damage was determined by the author of the 90-day study (Wang et al. 2013). However, it should be noted that it is unclear whether the observed effects were induced by azadirachtin or other unknown components, as the extractions used in these studies were prepared using azadirachtin-enriched methods, and the three-generation study by Chinnasamy et al. (1993) reviewed by the US EPA (2009) did not identify similar health effects.

As part of the neem seeds extract, azadirachtin (Azadirachtin technical extracts CAS RN 11141-17-6) had been proposed by BAuA (2014) to be classified as a Category 2 developmental toxicant (H361d, CLP criteria). The fats and glyceridic oils, margosa (CAS RN 8002-65-1) assessed here and the azadirachtin technical extracts (CAS RN 11141-17-6) may have some of the same constituents. However, the composition of neem seed preparation is largely unknown. Thus, the health effects associated with Azadirachtin technical extracts may not be relevant to fats and glyceridic oils, margosa (CAS RN 8002-65-1) evaluated in this assessment, and are therefore not used to inform the hazard characterization of fats and glyceridic oils, margosa.

6.3.4 Evening primrose oil (EPO)

The general population of Canada is exposed to evening primrose oil from its use in cosmetics and natural health products.

There were no genotoxicity studies identified for evening primrose oil. However, the major component of evening primrose oil, linoleic acid (CAS RN 60-33-3, 70-77% in evening primrose oil) was determined by OECD (2014) as not mutagenic based on an *in vitro* genotoxicity study.

In chronic studies in which both sexes of SD rats were administered Efamol, an evening primrose oil product containing 70 to 73% linoleic acid, via gavage at 0, 0.3, 1.0 or 2.5 mL/kg bw/day (equivalent to 0, 279, 928 or 2321 mg/kg bw/day of evening primrose oil) for 53 weeks, no significant adverse effects were found compared to the controls (Everett et al. 1988a, cited in NTP 2009; EMA 2011). In addition, Efamol did not induce significant differences in the nature or frequency of tumours between the treated and control animals when the same dosage regimen was used in SD rats for 104 weeks or in CD-1 mice for 78 weeks (NOAEL = 2321 mg/kg bw/day, Everett et al. 1988b, cited in NTP 2009; EMA 2011). When male F344/DuCrj rats were administered evening primrose oil at 5233 mg/kg bw/day in diet (only dose tested) for 15 weeks, the only effect observed was an increase in the cholesterol level (NOAEL = 5233 mg/kg bw/day, Fukushima et al. 2001).

Several animal studies showed that dietary supplementation of evening primrose oil had no effect on parturition, maternal or birth weight, postnatal growth rate, or fetal or placenta prostaglandin E2 levels (NTP 2009). When Wistar rats were exposed to evening primrose oil in diet at 0 or 1543 mg/kg bw/day for 5 weeks until mating, there

was no effect on parturition, birth weight, postnatal growth rate or maternal weight (NOAEL = 1543 mg/g bw/day, Leaver et al. 1986, cited in NTP 2009). Some studies showed that evening primrose oil exposure could benefit reproductive and developmental performance by enhancing male reproductive function and increasing neonate survival in animals (NTP 2009).

The major components of evening primrose oil—oleic acid (CAS RN112-80-1), palmitic acid (CAS RN 57-10-3) and linoleic acid (CAS RN 60-33-3)—were not identified by OECD (2014) as possessing properties indicating a hazard for human health for systemic health effects. Although the hazard database is limited, the available information indicates that evening primrose oil is considered to be of low hazard potential, and risk to human health is considered to be low.

6.3.5 Tall oil acid and potassium tallate

The general population of Canada may be exposed to tall oil acid from its use in food packaging, a few drug products, and cosmetics. It is also used by Canadian consumers in adhesives and sealants, building or construction materials, cleaning and furniture care products, automotive care products, lubricants and greases, and agricultural products.

Potassium tallate can be used in food packaging and in various commercial and industrial uses, and may be present as a component in an incidental additive (food contact surface cleaner with a potable water rinse).

No toxicity studies were identified for potassium tallate specifically. However, for fatty acids in general, their acid and alkali salt forms of the same fatty acid are expected to have many similar physicochemical and toxicological properties when they become bioavailable (HERA 2002). Thus, the potential health effect induced by potassium tallate is expected to be similar to that of tall oil acid. In addition, the contribution of the cation of fatty acid salt, in this case the potassium ion, is not expected to add excessively to the normal body load to induce health effects at current exposure levels. Therefore, the potential health effect induced by potassium ion released from potassium tallate will not be considered in this assessment.

Tall oil acid was not mutagenic in *S. typhimurium* strains (OECD 2014), and it was not clastogenic in either human lymphocytes or Chinese hamster ovary cells in the presence or absence of metabolic activation (ECHA c2007-2017e).

In a two-generation study, both sexes of rats (strain not specified) were administered 0, 5 or 10% of tall oil acid in the diet (equivalent to 0, 2500 or 5000 mg/kg bw/day). The F0 generation was exposed from age of 80 days to 100 days and through the weaning period of the first generation (F1). After weaning, 20 F1 males and 20 F1 females per group were maintained on the parental diet. At 100 days of age, these rats were mated and allowed to deliver pups (F2). Treatment did not affect the number of live born or stillborn F1 litters and pups, or F1 weaning weight. No treatment-related changes in

fertility, viability, lactation, or gestation indices were reported. Hematology, clinical chemistry and urinalysis parameters were unchanged, and gross and microscopic pathology revealed no treatment-related effects (NOAEL reproductive toxicity \geq 5000 mg/kg bw/day, OECD 2014).

In a 90-day study, both sexes of rats (strain not specified) were administered tall oil acid in the diet at 0, 5, 10 or 25% (equivalent to 0, 2 500, 5 000, or 12 500 mg/kg bw/day). No treatment-related effects were noted in any treated groups. A NOAEL of 2 500 mg/kg bw/day was determined by OECD (2014) based on slightly decreased food consumption in the mid- and high- dose groups. Male SD rats were administered tall oil distillate in the diet for 28 days at 0, 15, 30, or 60% (equivalent to 0, 7 500, 15 000 or 30 000 mg/kg bw/day). Significantly decreased growth rate accompanied by slightly decreased food consumption was reported in rats treated with 15 000 mg/kg bw/day of tall oil. All 10 animals in the high-dose group died in the first 4 days (Seppanen 1969). The major components of tall oil acid, oleic acid and linoleic acid were not identified by OECD (2014) as possessing properties indicating a hazard for human health for systemic health effects. Although the hazard database is limited, the available information indicates that tall oil and potassium tallate are considered to be of low hazard potential, and risk to human health is considered to be low.

6.3.6 Dimer and Trimer Acids

The general population of Canada may be exposed to dimer acid from its use in food packaging, as a component in an incidental additive (lubricant for non-food contact surface), in various industrial and commercial uses, and in certain personal care products, and in a specialized air filter oil that is available to consumers (SDS 2016).

No consumer uses were identified for trimer acid in Canada. However, it is used in various industrial and commercial applications.

Dimer acid contains two fatty acid molecules, dicarboxylic acids, and is produced by dimerizing unsaturated fatty acids. The chemical reaction can be taken further to form a trimer acid, where the product consists of three fatty acid molecules. Although the commercial products contain predominantly a dimer (C16-18), dimer acids also comprise various ratios of fatty acids trimer (ECHA dossier c2007-2017c) and vice versa. As there were no toxicity studies identified for trimer acid, the toxicity information for dimer acid is used to inform the hazard of trimer acid given the similarity of their physical-chemical properties.

In *in vitro* assays, in the presence or absence of metabolic activation, dimer acid tested negative in gene mutation assays with *S. typhimurium* strains or with mouse lymphoma cell lines. It also tested negative in chromosome aberration with human lymphocytes (US EPA 2005).

In a reproductive toxicity study, both sexes of SD rats were administered dimer acid in the diet at concentrations of 0, 200, 2 000, or 20 000 ppm (equivalent to 0, 15/17,

145/169, or 1 450/1 692 mg/kg bw/day, male/female). Males were dosed for at least 4 weeks, starting from 2 weeks prior to mating, while females were dosed from 2 weeks prior to mating until at least day 6 of lactation. A slight decrease in weight gain (statistically non-significant) and an increase in piloerection (lack of dose relationship) in parent rats were observed in high-dose groups. There were no effects on birth and live birth index, litter size, litter weight, pup weight, viability index or externally visible anomalies in any of the pups. There were no obvious maternal effects reported in this study (NOAEL maternal /developmental = 1 450/1 692 mg/kg bw/day, US EPA 2005).

In a 90-day study, SD rats were administered dimer acid in the diet at concentrations of 0, 0.1, 1 or 5% (equivalent to 0, 74/90, 740/854, or 3591/4085 mg/kg bw/day, male/female). At 3 591/4 085 mg/kg bw/day (male/female), histopathological changes, such as aggregations of macrophages in the mesenteric lymph nodes, statistically significant changes in multiple clinical chemistry parameters, and significant decreases in absolute and relative spleen and liver weights, were observed in both sexes of rats (NOAEL = 740/854 mg/kg bw/day, US EPA 2005).

In a multi-chemical Tier I human health risk assessment carried out by the Australian Government Department of Health (AGDH 2017), dimer acid was listed as one of the chemicals that were not considered to pose an unreasonable risk to the health of workers or the general public. In addition, as the predominant source of dimer and trimer acids, stearic acid (CAS RN 57-11-4), the monomer fatty acid, was not identified by OECD (2014) as possessing properties indicating a hazard for human health for systemic health effects. Although the hazard database is limited, the available information indicates that dimer and trimer acids are considered to be of low hazard potential, and risk to human health is considered to be low.

6.4 Undecylenic acid and ethylhexyl cocoate

6.4.1 Undecylenic acid

6.4.1.1 Exposure assessment

Environmental media and food

No empirical data on the presence of undecylenic acid in air, water, soil, sediment or dust were identified in Canada or elsewhere, and undecylenic acid did not have any reported uses above the section 71 reporting threshold of 100 kg (Environment Canada 2013). Therefore, exposures to undecylenic acid from environmental media are not expected (see section 6.2).

Undecylenic acid can be used as a flavouring agent in alcoholic beverages, baked goods, frozen dairy products, gelatins and puddings, gravies, meat products, non-alcoholic beverages, and soft candy (Burdock 2010). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated 42 flavouring substances including linear and branched-chain aliphatic unsaturated and unconjugated alcohols, aldehydes,

acids, and related esters (WHO 1999). As part of that evaluation, the Committee estimated the per capita intake of undecylenic acid from its use as a food flavouring agent to be 0.01 µg/kg bw/day for the US population and 0.5 µg/kg bw/day for the European population. In deriving these intakes which were estimated using a maximized survey-derived daily intake (MSDI) approach, it was assumed that the reported annual production amount of undecylenic acid in the United States and Europe was consumed by just 10% of the population (“eaters only”), and that only 60% of the annual production amount was reported in the poundage surveys (International Organization of the Flavor Industry 1995; US National Academy of Sciences 1989, both cited in WHO 1999).

Products available to consumers

Undecylenic acid is currently present as medicinal or non-medicinal ingredient in natural health products (LNHPD [modified 2016]). An oral product has been identified as containing undecylenic acid as non-medicinal ingredient, with an estimated daily exposure ranging from 0.42 to 0.63 mg/kg bw/day (see Appendix B). The topical products identified as containing undecylenic acid as a non-medicinal ingredient are considered to be covered by the cosmetic exposure estimates described below.

Undecylenic acid was identified in several cosmetics in Canada, including face and body moisturizers, shampoo, make-up, face and body cleansers, and nail conditioners (personal communication, e-mail from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 22, 2016; unreferenced). Table 6-1 summarizes the sentinel exposure scenarios for cosmetics containing undecylenic acid. ConsExpo Web was used to estimate cosmetic exposures (ConsExpo Web 2016) and details on the parameters used in the model are found in Appendix B. The dermal exposure estimates presented in Table 6-1 represent external exposure doses. Given that no information on the dermal absorption of undecylenic acid was identified and based on its physical and chemical properties (low molecular weight, moderate log K_{ow}), a dermal absorption of 100% is assumed.

Table 6-1. Estimated exposures to undecylenic acid from the use of cosmetics

Product scenario	Concentration range	Dermal exposure estimate for adults (mg/kg bw/day)	Dermal exposure estimate for infants (mg/kg bw/day)
Body lotion	0.0025	0.0017	0.0079
Specialized body lotion ^a	0.3 – 1%	0.093 – 0.31	
Face moisturizer	0 – 0.1%	0 – 0.03	N/A
Facial make-up	0.0011 – 0.3%	0.0001 – 0.028	N/A
Nail conditioner	3 – 10%	0.04 – 0.14 mg/kg bw per event	N/A

Abbreviations: N/A, not applicable

^a Specialized body lotions for soothing and warming, for adult use only (for feet and legs)

6.4.1.2 Health effects assessment

Undecylenic acid did not induce gene mutations in *in vitro* studies in the presence or absence of metabolic activation with *S. typhimurium* strains or mouse lymphoma cell lines, nor did it induce chromosome aberrations in human lymphocytes or cause DNA damage in rat hepatocytes (ECHA c2007-dossier 2017a). In an *in vivo* study, undecylenic acid did not induce micronucleus formation in bone marrow of mice administered doses of up to 4000 mg/kg via gavage (ECHA dossier c2007-2017a). There were no carcinogenicity studies identified for undecylenic acid.

In a prenatal developmental toxicity study, pregnant SD rats were administered undecylenic acid at 0, 150, 450 or 750 mg/kg bw/day via gavage from gestation day 6 to 20 (15 days). All rats in the 450 mg/kg bw/day group exhibited hypersalivation and significantly reduced body weight gain compared to controls. There was no embryonic toxicity or teratogenicity observed. The highest dose of 750 mg/kg bw/day was removed from the study due to the high maternal mortality (NOAEL teratogenicity = 450 mg/kg bw/day, NOAEL maternal toxicity = 150 mg/kg bw/day, LOAEL maternal toxicity = 450 mg/kg bw/day for hypersalivation and reduced body weight gain, ECHA dossier c2007-2017a). In a reproductive and developmental toxicity study, undecylenic acid was administered to both sexes of SD rats at 0, 50, 150 or 450 mg/kg bw/day via gavage. Males were dosed 2 weeks before mating, during the mating period (2 weeks), until sacrifice (at least 4 weeks in total); females were dosed 2 weeks before mating, during the mating period (2 weeks), during pregnancy and lactation period until day 4 of post-partum. No reproductive or developmental parameters investigated were affected. Two males in the high-dose group died on day 3 and two died on day 35 without ante-mortem clinical signs of toxicity. A LOAEL of 450 mg/kg bw/day was determined based on the mortality in high-dose male group (NOAEL parental effect = 150 mg/kg bw/day, NOAEL_{F1} = 450 mg/kg bw/day, NOAEL reproductive performance = 450 mg/kg bw/day; ECHA dossier c2007-2017a). When rats were administered orally with undecylenic acid at 0, 100, 200 or 400 mg/kg bw/day for 9 months via gavage, then mated, there were no abnormalities found in the litters and there was no sign of toxicity reported in parents rats (ECHA dossier c2007-2017a).

In a 90-day study, males and female SD rats were administered sodium salt of undecylenic acid (no CAS RN provided, presumably CAS RN 1002-62-6, ECHA dossier c2007-2017a) via gavage at 0, 20, 60 or 180 mg/kg bw/day for 50 days. The 180 mg/kg bw/day dose group was examined at 50 days then further administered a dose of 360 mg/kg bw/day for 40 days (as 180/360 mg/kg bw/day groups), with an additional 4 weeks of recovery. Dose-dependent clinical signs including ptialism, loud breathing, respiratory difficulties and poor clinical condition were reported. Reduced body weight gain in males accompanied by reduced food consumption in the 180 mg/kg bw/day dose groups and in the 180/360 mg/kg bw/day dose groups was reported. Reduced

glucose plasma levels (reversible) and reduced triglyceride-levels (not reversible) in females were observed in the 180 mg/kg bw/day dose groups as well as in the 180/360 mg/kg bw/day dose groups. Forestomach oedema and inflammatory cell infiltration were observed in the same dose groups. Cardiomyopathy, as reversible myocardial degeneration and monocellular aggregation, was reported in both sexes in the 180/360 mg/kg bw/day dose groups exclusively. A LOAEL of 180 mg/kg bw/day (NOAEL = 60 mg/kg bw/day) was derived for undecylenic acid sodium salt by ECHA dossier (c2007-2017a). The converted equivalent doses for undecylenic acid are 160 mg/kg bw/day (LOAEL) and 53 mg/kg bw/day (NOAEL), respectively. Given the paucity of relevant health effects studies for undecylenic acid, hazard data obtained from the ECHA dossier was utilized to inform critical health effects and subsequent risk characterization.

6.4.1.3 Characterization of risk to human health

The estimated per capita intake from the use of undecylenic acid as a possible flavouring agent in foods was derived by the JECFA to range from 0.01 µg/kg bw/day for the US population to 0.5 µg/kg bw/day for the European population. JECFA concluded that there is no safety concern for undecylenic acid used as a flavouring agent primarily on the basis of it being “expected to be oxidized to the corresponding aldehyde and carboxylic acid which is completely metabolized in the fatty acid and tricarboxylic acid pathways” (WHO 1999).

Undecylenic acid was not mutagenic *in vitro* or *in vivo*. It did not induce reproductive or developmental health effects at oral dose levels up to 450 mg/kg bw/day in rats. However, maternal health effects, such as hypersalivation, reduced body weight gain and death, occurred at this dose level. In addition, a 90-day oral study conducted with undecylenic acid sodium salt showed that the treatment related changes, such as altered multiple clinical chemistry parameters and reduced body weight gain, occurred at undecylenic acid equivalent dose level of 160 mg/kg bw/day (considered to be the LOAEL; NOAEL = 53 mg/kg bw/day). The use of critical effects levels derived from the 90-day oral toxicity study with undecylenic acid sodium salt is considered appropriate for characterization of the human health risk from exposure to undecylenic acid. This approach is considered to be conservative as the salts of the fatty acids tend to be more bioavailable given that they have greater water solubility than the free acids.

With respect to dermal toxicity, no studies were identified. The oral critical effect levels were therefore applied to the dermal external exposure scenarios presented in Table 6-1, assuming 100% dermal absorption.

Table 6-2 provides all relevant exposure and hazard values for undecylenic acid, as well as resultant margins of exposure, for determination of risk.

Table 6-2. Relevant exposure and hazard values for undecylenic acid, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure	Critical effect level oral	Critical health effect endpoint	MOE
-------------------	-------------------	----------------------------	---------------------------------	-----

Non-medicinal ingredient in natural health product - oral	0.42 – 0.63 mg/kg bw/day	53 mg/kg bw/day (NOAEL)	Changes in clinical parameter, body weight and clinical signs	84 – 126
Body moisturizer (adult)	0.0017 mg/kg bw/day	53 mg/kg bw/day (NOAEL)	Changes in clinical parameter, body weight and clinical signs	31 176
Body moisturizer (infant)	0.0079 mg/kg bw/day	53 mg/kg bw/day (NOAEL)	Changes in clinical parameter, body weight and clinical signs	6 709
Specialized body moisturizer (adult)	0.093 – 0.31 mg/kg bw/day	53 mg/kg bw/day (NOAEL)	Changes in clinical parameter, body weight and clinical signs	172 – 570
Face moisturizer	0 – 0.03 mg/kg bw/day	53 mg/kg bw/day (NOAEL)	Changes in clinical parameter, body weight and clinical signs	1 767
Facial make-up	0.0001 – 0.028 mg/kg bw/day	53 mg/kg bw/day (NOAEL)	Changes in clinical parameter, body weight and clinical signs	1 893 – 530 000
Nail conditioner (per event)	0.04 – 0.14 mg/kg bw/day	150 mg/kg bw/day (NOAEL)	Parental systemic effects	1 071 – 3 750

Abbreviations: NOAEL, no-observed adverse effect level

On the basis of the conservative parameters used in modelling exposure to products and their recommended conditions of use, as well as the use of conservative critical effect levels derived from undecylenic acid salt, which is considered to be absorbed to a much greater extent than undecylenic acid due to higher solubility, the calculated margins are considered adequate to address uncertainties in the health effects and exposure databases.

6.4.1.4 Uncertainties in evaluation of risk to human health

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

Table 6-3. Sources of uncertainty in the risk characterization for undecylenic acid

Key source of uncertainty	Impact
There is some uncertainty on the dermal absorption of undecylenic acid; however, it is assumed that 100% is considered reasonable given the molecular size and type of substance.	+
No chronic oral studies, inhalation studies or dermal studies were identified. No dermal absorption data were identified.	+/-
There is some uncertainty regarding the use of critical effective level of undecylenic acid salt to characterize the risk of undecylenic acid.	+/-

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

6.4.2 Ethylhexyl Cocoate

6.4.2.1 Exposure Assessment

Environmental media and food

No empirical data on the presence of ethylhexyl cocoate in air, water, soil, sediment, dust, or food were identified in Canada or elsewhere. Given the import quantities reported in Canada in 2011 (see Table 4-1), drinking water intakes were estimated using the Environmental Assessment Unit's Drinking Water Workbook (Health Canada 2015b), predicted wastewater treatment system removal rates (SimpleTreat 1997), and information on the quantities of the substance in Canada (Environment Canada 2013). The predicted drinking water intakes for ethylhexyl cocoate resulting from potential industrial and down-the-drain releases were less than 2.5 ng/kg bw/day and are therefore considered negligible.

Cosmetics

In Canada, ethylhexyl cocoate is used primarily as an emollient in cosmetics, including moisturizers, cleansers, conditioners, make-up, styling products, shaving products, bath products, and massage products (personal communication, e-mail from Consumer Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 22, 2016; unreferenced). Table 6-4 summarizes the sentinel exposure scenarios for cosmetics containing ethylhexyl cocoate. ConsExpo Web was used to estimate cosmetic exposures (ConsExpo Web 2016), and details on the parameters used in the model are found in Appendix B.

Table 6-4. Estimated exposures to ethylhexyl cocoate from the use of cosmetics

Product scenario	Concentration range	Dermal exposure estimate for adults (mg/kg bw/day) ^a	Systemic dermal exposure estimate for adults (mg/kg bw/day) ^b	Oral exposure estimate for toddlers (mg/kg bw per event) ^c
Body moisturizer	1 – 10%	0.68 – 6.8	0.041 – 0.41	N/A
Face moisturizer	0 – 30%	9.1	0.55	N/A
Facial make-up	0.025 – 100%	0.00024 – 9.4	1.4E-05 – 0.56	N/A
Hair oil	10 – 30%	2 – 6.1	0.12 – 0.37	N/A
Lipstick/lip gloss	0 – 0.1%	0.00034	N/A	0.00065
Massage oil (body) ^d	0.1 – 0.3%	0.045 – 0.14 mg/kg bw per event	0.0027 – 0.0084 mg/kg bw per event	N/A

Abbreviations: N/A, not applicable.

^a Dermal exposure scenarios except for lipstick, which is an oral exposure scenario.

^b Systemic exposures from the dermal route were derived using a dermal absorption value of 6%.

^c Lip gloss assumed to be used occasionally by toddlers (not every day).

^d Assume that use of massage oil does not occur daily, therefore exposure estimate is per event (not per day).

The dermal absorption rate of ethylhexyl cocoate was predicted to range between 1.26E-05 and 4.46E-05 mg/cm²/event (ECHA c2007-2017d). However, details on the method used to derive this prediction were not available. In an *in vivo* study in rats, the dermal absorption of 2-ethylhexanol, one of the hydrolysis products of ethylhexyl cocoate, was between 5% and 6% after 96 hours of dermal exposure (Deisinger et al. 1994, cited in EC, HC 2011). Given their physical and chemical properties, it is expected that the dermal absorption of ethylhexyl cocoate would be less than that of 2-ethylhexanol, which is a smaller molecule and more hydrophilic than ethylhexyl cocoate. In addition, ethylhexyl cocoate may be hydrolyzed in the stratum corneum (see section 6.4.2.2). As such, a dermal absorption of 6% from the *in vivo* rat study of 2-ethylhexanol was used to estimate systemic exposure of ethylhexyl cocoate from the dermal route (see Table 6-4).

6.4.2.2 Health effects assessment

No studies were identified for ethylhexyl cocoate. However, as a fatty acid ester, ethylhexyl cocoate can be rapidly hydrolyzed in digestive fluids and yield the corresponding alcohol and free fatty acid within the gastrointestinal tract after oral exposure (Bookstaff et al. 2003, cited in ECHA c2007-2017f). Thus, the available health effects information of the hydrolyzed products of ethylhexyl cocoate and the information of the major components of ethylhexyl cocoate were used in this assessment to inform the potential health effects of ethylhexyl cocoate.

Toxicity data of hydrolyzed products of ethylhexyl cocoate

Ethylhexyl cocoate could be hydrolyzed into fatty acids and 2-ethylhexanol (2-EH, CAS RN 104-76-7) post absorption in the gastrointestinal tract. Following dermal exposure, the absorption rate of 2-EH was only 5% to 6 % in rats within 96 hours (Deisinger et al. 1994, cited in EC, HC 2011). Given that the current use patterns indicate dermal exposure, it is important to consider how ethylhexyl cocoate may be metabolized on the skin by esterases. Although the majority of the esterase activity in human skin is located in the epidermis and hair follicles (Tokudome et al. 2015), such activity has also been found in the stratum corneum (Beisson et al. 2001). This suggests that ethylhexyl cocoate may be hydrolyzed by esterases in the stratum corneum to form 2-EH.

For 2-EH, a LOAEL of 150 mg/kg bw/day (NOAEL = 50 mg/kg bw/day) was derived from a chronic study based on reduced body weight gain and increased relative weights of brain, stomach, kidneys and liver in both sexes of rats after 2-EH was administered via gavage at 0, 50, 150 or 500 mg/kg bw/day for 24 months (EC, HC 2011).

For dermal route of exposure, there was no evidence of toxicity to the developing young at up to a maximum tested dose of 2520 mg/kg bw/day in a developmental toxicity study, in which rats were dermally exposed to 2-EH at doses of 0, 252, 420, 840, 1680, or 2520 mg/kg bw/day during gestation day 6 to 15 (NOAEL = 2520 mg/kg bw/day). However, decreased body weight gain in the dams was observed at 1680 mg/kg bw/day (EC, HC 2011). In addition, the lowest dermal LOAEL of 834 mg/kg bw/day for 2-EH was derived from a short-term study based on the health effects of lymphopenia, reduced spleen weights and histopathological effects on the skin in both sexes of rats exposed to 0, 0.5, or 1.0 mL of 2-EH (equivalent to 0, 417 or 834 mg/kg bw/day) 9 times within 12 days (EC, HC 2011).

2-EH was known to be rapidly and extensively metabolized into 2-ethylhexanoic acid (2-EHA, CAS RN 149-57-5) via oxidation *in vivo*. The risk to human health of 2-EHA was previously assessed by Health Canada (EC, HC 2011). Developmental toxicity was identified as a critical effect for 2-EHA by HC (EC, HC 2011). The lowest oral LOAEL of 100 mg/kg bw/day for 2-EHA was determined by Health Canada (EC, HC 2011) on the basis of dose-dependent increase in skeletal malformations in fetuses observed in an oral developmental toxicity study in which pregnant rats were dosed at 0, 100, 300 or 600 mg/kg bw/day of 2-EHA via drinking water from gestation day 6 to 19 of (EC, HC 2011). There is an uncertainty regarding the mode of action for developmental toxicity following 2-EHA oral exposure. 2-EHA has been shown to induce peroxisome proliferation in rodents (mediated by the peroxisome proliferator-activated receptor alpha or PPAR α) (EC, HC 2011). However, this is less likely to be relevant to humans and the role of PPAR α in developmental and reproductive toxicity remains to be established (EC, HC 2011).

The equivalent critical effect level for the oral route of exposure to ethylhexyl cocoate converted from that of 2-EH is approximately 120 mg/kg bw/day (NOAEL) for systemic effects following 24 months of exposure in rats. The equivalent critical effect levels for

dermal route of exposure to ethylhexyl cocoate converted from those of 2-EH are approximately 6045 mg/kg bw/day (NOAEL) for developmental effects and 2015 mg/kg bw/day (NOAEL) for maternal health effects following 9 days of exposure in rats. The lowest dermal NOAEL for ethylhexyl cocoate converted from the 12-day repeated dose study of 2-EH is 1000 kg/bw/day for increased incidences of lymphopenia, reduced spleen weights and histopathological effects on the skin at the next dose level.

There were no international health effect assessments identified for coconut fatty acids that may release from ethylhexyl cocoate upon esterase hydrolysis. However, the major components of coconut fatty acids—i.e., lauric acid (CAS RN 143-07-7), myristic acid (CAS RN 544-63-8), oleic acid (CAS RN 112-80-1) and palmitic acid (CAS RN 57-10-3)—were not identified by OECD (2014) as possessing properties indicating a hazard for human health for systemic health effects.

Toxicity data of the major component of ethylhexyl cocoate as UVCB

Ethylhexyl laurate (CAS RN 20292-08-4), a major component of ethylhexyl cocoate (45% to 52%), was negative in the Ames *S. typhimurium* test in the presence and absence of metabolic activation (Belsito et al. 2013). In an *in vivo* assay, it did not induce genotoxicity in mice at an oral dose of up to 5.0 mL/kg (Fiume et al. 2015). In a 28-day study, ethylhexyl laurate did not induce adverse effects in SD rats administered ethylhexyl laurate via gavage at doses of up to 1000 mg/kg bw/day (NOAEL = 1000 mg/kg bw/day, Fiume et al. 2015).

6.4.2.3 Characterization of risk to human health

The hydrolyzed product of ethylhexyl cocoate, 2-EH, did not impact the development of fetuses of rats after dermal exposure during gestation. However, it reduced maternal body weight gain in dams. Body and organ weights were also impacted by 2-EH after chronic oral exposure in rats. In addition, a dermal absorption of 6% derived from an *in vivo* rat study for 2-EH is used to estimate systemic exposures for ethylhexyl cocoate.

Exposure of the general population to ethylhexyl cocoate is expected to occur mainly from cosmetics. Table 6-5 provides all relevant exposure and hazard values from daily use of products containing ethylhexyl cocoate. Table 6-6 provides all relevant exposure and hazard values from intermittent use of products containing ethylhexyl cocoate.

In addition to the dermal scenarios presented in Table 6-5 and Table 6-6, a comparison of the oral exposures for adults and toddlers, using lipsticks/lip gloss containing ethylhexyl cocoate, with the critical oral effect level of 2-EH (converted NOAEL = 120 mg/kg bw/day) results in margins of exposures ranging from 184 615 to 352 941. The oral critical effect level of 2-EH is considered protective of the development effects induced by 2-EHA (converted LOAEL = 218 mg/kg bw/day) via the oral route of exposure.

Table 6-5. Relevant exposure and hazard values for ethylhexyl cocoate, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure (mg/kg bw/day)^a	Critical effect level (converted)^b	Critical health effect endpoint	MOE
Body moisturizer (adult)	0.041 – 0.41	NOAEL = 120 mg/kg bw/day	24-month oral study, derived from 2-EH for systemic effect	293 – 2 927
Face moisturizer	0.55	NOAEL = 120 mg/kg bw/day	24-month oral study, derived from 2-EH for systemic effect	200
Facial make-up	1.44E-05 – 0.56	NOAEL = 120 mg/kg bw/day	24-month oral study, derived from 2-EH for systemic effect	196 – >7 million
Hair oil	0.12 – 0.37	NOAEL = 120 mg/kg bw/day	24-month oral study, derived from 2-EH for systemic effect	297 – 917

^a Estimated exposures using a dermal absorption of 6%.

^b NOAEL of 50 mg/kg bw/day for 2-EH converted to 120 mg/kg bw/day for ethylhexyl cocoate using molecular weight of its major component ethylhexyl laurate.

Table 6-6. Determination of risk using relevant dermal exposures and 12-day dermal study for 2-EH

Exposure scenario	External exposure (mg/kg bw/day)	Critical effect level	Critical health effect endpoint	MOE
Massage oil for body (adult)	0.045 – 0.14 mg/kg per event	NOAEL = 1 000 kg/bw/day	12-day dermal, study, derived from 2-EH for systemic effect	7 143 – 22 222

The above-noted margins of exposure are considered adequate to address uncertainties in the health effects and exposure databases.

6.4.2.4 Uncertainties in Evaluation of Risk to Human Health

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

Table 6-7. Sources of uncertainty in the risk characterization for ethylhexyl cocoate

Key source of uncertainty	Impact
Maximum concentrations were used to estimate cosmetic exposures, which likely result in overestimates.	+
There is some uncertainty regarding the dermal absorption value used to estimate exposures from cosmetics; however, confidence is high that dermal absorption is likely low given the physical and chemical properties of the substance and existing dermal absorption data from breakdown products.	+
There is no genotoxicity study or repeated dose toxicity study identified for ethylhexyl cocoate. Toxicity studies of major components and potential hydrolyzed products of ethylhexyl cocoate were used to inform the health effects of ethylhexyl cocoate.	+/-
As the capacity of ethylhexyl cocoate to hydrolyze to 2-EH on the skin is unknown, the use of critical effect levels derived from the dermal and oral studies of 2-EH to characterize the risk from exposures to ethylhexyl cocoate, based on the assumption of 100% of hydrolysis, is likely an overestimate.	+

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

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid and ethylhexyl cocoate. It is proposed to conclude that undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid and ethylhexyl cocoate do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid and ethylhexyl cocoate do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that undecylenic acid, ALA, tung oil, fats and glyceridic oils, margosa, tall oil acid, potassium tallate, evening primrose oil, dimer acid, trimer acid and ethylhexyl cocoate do not meet any of the criteria set out in section 64 of CEPA.

References

- [AGDH] Australian Government Department of Health. 2017. Sydney (AU): Department of Health, National Industrial Chemicals Notification and Assessment Scheme. Tier I Human Health Assessments INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP) FRAMEWORK. [last updated 2017 May 3].
- Alternative Medicine Review. 2002. Undecylenic Acid, Monograph [PDF]. Alternative Medicine Review. 7(1):68-70. [accessed 2017 June 29].
- Awad OM. 2003. Operational use of neem oil as an alternative anopheline larvicide. Part B: Environmental impact and toxicological potential. East Mediterr Health J. 9(4):646-58.
- [BAuA] Federal Institute for Occupational Safety and Health, Federal Office for Chemicals Germany. 2014. CLH report, Proposal for Harmonised Classification and Labelling based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: dimethyl (2aR,3S,4S,4aR,5S,7aS,8S,10R,10aS,10bR)-10-acetoxy-3,5-dihydroxy-4-[(1aR,2S,3aS,6aS,7S,7aS)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-b]oxireno[e]oxepin-1a(2H)-yl]-4-methyl-8-[(2E)-2-methylbut-2-enoyl]oxy]octahydro-1H-naphtho[1,8a-c:4,5-b'c']difuran-5,10a(8H)-dicarboxylate; Azadirachtin; Neem seeds extract. CAS Number: 11141-17-6 [PDF]. [accessed 2017 June 29].
- Bayles B, Usatine R. 2009. Evening primrose oil. Am Fam Physician. 80(12):1405-8.
- Beisson F, Aoubala M, Marull S, Moustacas-Gardies A-M, Vouloury R, Verger R, Arondel V. 2001 Use of the tape stripping technique for directly quantifying esterase activities in human stratum corneum. Anal Biochem. 290:179-185.
- Belsito MD, Hill RA, Klaassen CD, Liebler DC, Marks Jr JG, Ronald C. 2013. Amended Safety Assessment of Alkyl Esters as Used in Cosmetics [PDF]. [accessed 2017 June 29].
- Bookstaff RC, PaiBir S, Bharaj SS, Kelm GR, Kulick RM, Balm TK, Murray JV. 2003. The safety of the use of ethyl oleate in food is supported by metabolism data in rats and clinical safety data in humans. Regul Toxicol Pharmacol. 37(1):133-48.
- Buist HE, van Burgsteden JA, Freidig AP, Maas WJ, van de Sandt JJ. 2010. New in vitro dermal absorption database and the prediction of dermal absorption under finite conditions for risk assessment purposes. Regul Toxicol Pharmacol. 57:200-209.
- Burdock GA, editor. 2010. Fenaroli's Handbook of Flavor Ingredients. 6th ed. 10-Undecenoic acid. Boca Raton (FL): CRC Press, Taylor & Francis Group.
- Canada. 1978. Food and Drug Regulations, C.R.C., c. 870.
- 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 [PDF].
- ChemIDplus [database]. 1993-. Bethesda (MD): US National Library of Medicine. [updated 2012 Nov 26; accessed 2017 June 29].

ChemCAN [level III fugacity model of 24 regions of Canada]. 2003. Version 6.00. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. [accessed 2016 Oct 19].

Chinnasamy N, Harishankar N, Kumar PU, Rukmini C. 1993. Toxicological studies on debitterized Neem oil (*Azadirachta indica*). *Food Chem Toxicol*. 31(4):297-301

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

Chow CK. 2007. Fatty acids in foods and their health implications. 3rd Edition. Boca Raton (FL): CRC Press.

Cunnane SC, Anderson MJ. 1997. The majority of dietary linoleate in growing rats is β -oxidized or stored in visceral fat. *J Nutr*. 127(1):146-52.

Dallaqua B, Saito FH, Rodrigues T, Calderon IM, Rudge MV, Volpato GT, Damasceno DC. 2013. *Azadirachta indica* treatment on the congenital malformations of fetuses from rats. *J Ethnopharmacol*. 150:1109-1113.

Danish (Q)SAR Database [database]. 2015. Division of Diet, Disease Prevention and Toxicology, National Food Institute, Technical University of Denmark. [accessed 2017 September 13].

Deisinger PJ, Boatman RJ, Guest D. 1994. Metabolism of 2-ethyhexanol administered orally and dermally to the female Fisher 344 rat. *Xenobiotica* 24:429–440 [cited in EC, HC 2011].

Deng Y, Cao M, Shi D, Yin Z, Jia R, Xu J, Wang C, Lv C, Liang X, He C. 2013. Toxicological evaluation of neem (*azadirachta indica*) oil: Acute and subacute toxicity. *Environ Toxicol Pharmacol* 35(2):240-6.

Dhar P, Ghosh S, Bhattacharyya DK. 1999. Dietary effects of conjugated octadecatrienoic fatty acid (9 cis, 11 trans, 13 trans) levels on blood lipids and nonenzymatic in vitro lipid peroxidation in rats. *Lipids*. 34(2):109-114.

Dietitians of Canada. 2017. Food Sources of Omega-3 Fats. [posted 2016 Oct 28; accessed 2017 May 15].

[DPD] Drug Product Database [database]. [modified 2015 Jul 17]. Ottawa (ON): Health Canada. [accessed 2016 April 22].

Dove D, Johnson P. 1999. Oral evening primrose oil: its effect on length of pregnancy and selected intrapartum outcomes in low-risk nulliparous women. *J Nurse Midwifery*. 44(3):320–324.

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

[ECCC] Environment and Climate Change Canada. 2016b. Gatineau (QC): Data used to create substance-specific hazard and exposure profiles and assign risk classifications in the Ecological Risk Classification of organic substances. Gatineau (QC). (disponible en anglais seulement) Accès : substances@ec.gc.ca.

[EC, HC] Environment Canada, Health Canada. 2011. Screening assessment for the Challenge: 2-Ethylhexanoic Acid: Chemical Abstracts Service Registry Number 149-57-5. Ottawa (ON): Government of Canada. [accessed 2017 May 20].

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2007 Apr 20]. Categorization. Ottawa (ON): Government of Canada. [accessed 2016].

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2017a. [Rapid screening of substances with limited general population exposure](#). Ottawa (ON): ECCC, HC.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2017b. [Draft screening assessment: 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](#). Ottawa (ON): ECCC, HC.

[ECHA] European Chemicals Agency. c2007-2017a. Registered substances database; search results for CAS RN 112-38-9. Helsinki (FI): ECHA. [accessed 2017 May 20].

[ECHA] European Chemicals Agency. c2007-2017b. Registered substances database; search results for CAS RN 61788-89-4. Helsinki (FI): ECHA. [accessed 2017 May 20].

[ECHA] European Chemicals Agency. c2007-2017c. Registered substances database; search results for CAS RN 68937-90-6. Helsinki (FI): ECHA. [accessed 2017 May 20].

[ECHA] European Chemicals Agency. c2007-2017d. Registered substances database; search results for CAS RN 92044-87-6. Helsinki (FI): ECHA. [accessed 2017 May 20].

[ECHA] European Chemicals Agency. c2007-2017e. Registered substances database; search results for CAS RN 68955-98-6. Submission from Pine Chemicals Association. Helsinki (FI): ECHA. [accessed 2017 May 20]

[ECHA] European Chemicals Agency. c2007-2017f. Registered substances database; search results for CAS RN 91051-05-7. Submission from Pine Chemicals Association. Helsinki (FI): ECHA. [updated yr mon date; accessed 2017 May 20].

Edwards VA, Kipping PJ, Jeffery PG. 1963. Composition of montan wax. Letters to Nature. Nature 199:171-172.

[EFSA] European Food Safety Authority. 2010. Scientific opinion on the safety of “conjugated linoleic acid (CLA)-rich oil” (Clarinol®) as a Novel Food ingredient [PDF]. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), European Food Safety Authority (EFSA), Parma, Italy. [accessed 2017 June 12].

[EMA] European Medicines Agency. 2011. Assessment report on *Oenothera biennis* L., *Oenothera lamarckiana* L., *oleum*. Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use). Committee on Herbal Medicinal Products (HMPC), European Medicines Agency. 16 December 2011, EMA/HMPC/277791/2009.

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.

Environment Canada, Health Canada. 2014. Approach for identification of chemicals and polymers as risk assessment priorities under Part 5 of the Canadian Environmental Protection Act, 1999 (CEPA 1999). Ottawa (ON): Environment Canada, Health Canada.

[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.

Everett DJ, Greenough RJ, Perry CJ, McDonald P, Bayliss P. 1988a. Chronic toxicity studies of Efamol evening primrose oil in rats and dogs. *Med Sci Res.* 16(16):863-864. [cited in NTP 2009].

Everett DJ, Perry CJ, Bayliss P. 1988b. Carcinogenicity studies of Efamol evening primrose oil in rats and mice. *Med Sci Res.* 16(16):865-866. [cited in NTP 2009].

[FAO] Food and Agriculture Organization of the United Nations. 2010. Fats and fatty acids in human nutrition: Report of an expert consultation 10 – 14 November 2008 [PDF]. Geneva. FAO Food and Nutrition Paper 91. Rome (Italy): Food and Agriculture Organization of the United Nations. [accessed 2017 June 12].

Ficheux AS, Morisset T, Chevillotte G, Postic C, Roudot AC. 2014. Probabilistic assessment of exposure to nail cosmetics in French consumers. *Food Chem Toxicol.* 66:36-43.

Ficheux AS, Chevillotte G, Wesolek N, Morisset T, Dornic N, Bernard A, Bertho A, Romanet A, Leroy L, Mercat AC, Creusot T, Simon E, Roudot AC. 2016. Consumption of cosmetic products by the French population second part: Amount data. *Food Chem Toxicol.* 90:130-141.

Fiume MM, Heldreth BA, Wilma FB. 2015. Safety assessment of alkyl esters as used in cosmetics. *Int J Toxicol.* 34(2 Suppl):5S-69S.

Fukushima M, Ohhashi T, Ohno S, Saitoh H, Sonoyama K, Shimada K, Sekikawa M, Nakano M. 2001. Effects of diets enriched in n-6 or n-3 fatty acids on cholesterol metabolism in older rats chronically fed a cholesterol-enriched diet. *Lipids* 36(3):261-6.

Gardner HA. 1926. A brief study of the physiological effects of tung oil products on rabbits and dogs with a note on percentages of accelerators for production of beta-elaeostearin from tung oil. Circular - Educational Bureau, Scientific Section, Paint Manufacturers' Association of the United States. No. 270. pp. 13-16.

Health Canada. 1995. Investigating human exposure to contaminants in the environment: A handbook for exposure calculations. Ottawa (ON): Health Canada, Great Lakes Health Effects Program.

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

Health Canada. 2005. Essential fatty acids discussion paper[PDF]. Report submitted to the Natural Health Products Directorate, Health Canada, March 2005.[accessed 2017 May 20].

Health Canada. 2008. Monograph: Evening Primrose Oil. [accessed 2017 May 20].

Health Canada. 2010. Dietary Reference Intakes Tables. [Internet]. [updated 2010 Nov 29; accessed 2017 May 20].

Health Canada. [modified 2015 Dec 14]a. Cosmetic Ingredient Hotlist: list of ingredients that are prohibited for use in cosmetic products. Ottawa (ON): Health Canada, Consumer Product Safety Directorate. [accessed 2016 April].

Health Canada. 2015b. Environmental Assessment Unit drinking water spreadsheets. [Excel format]. Ottawa (ON): Health Canada. [accessed 2017 June 29].

Health Canada. 2016. Science Approach Document: Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances. Gatineau (QC): ECCC. [accessed 2017 March 20].

Hegsted DM, Gotsis A, Stabe FJ. 1957. The effect of various fats upon experimental hypercholesteremia in the rat. *J Nutr*. 63(3):377-391.

[HERA] Human & Environmental Risk Assessment. 2002. Human & Environmental Risk Assessment on ingredients of European household cleaning products: Fatty Acid Salts, Human Health Risk Assessment, Draft for Public Comment. Brussels (Belgium): HERA. [cited accessed 2017 June 29].

Howes D. 1975. The percutaneous absorption of some anionic surfactants. *J Soc Cosmet Chem*. 26:47-63.

[IOM] Institute of Medicine. 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Chapter 8 and Summary Tables. Washington (DC): The National Academies Press. [accessed 2017 June 29].

Jahdi F, Kalati M, Kashanian M, Naseri M, Haghani H. 2016. Effect of oral evening primrose capsules on ripening of the cervix in nulliparous Iranian pregnant women (a randomized trial). *Acta Medica Mediterranea*. 32: 1273.

Kezutyte T, Desbenoit N, Brunelle A, Briedis V. 2013. Studying the penetration of fatty acids into human skin by ex vivo TOF-SIMS imaging. *Biointerphases*. 8(1): 3.

Kim K, Nam YA, Kim HS, Hayes AW, Lee BM. 2014. Alpha-linolenic acid: Nutraceutical, pharmacological and toxicological evaluation. *Food Chem Toxicol*. 70:163-78.

Kumar VS, Navaratnam V. 2013. Neem (*Azadirachta indica*): Prehistory to contemporary medicinal uses to humankind. *Asian Pac J Trop Biomed*. 3(7):505-514.

Leaver HA, Lytton FD, Dyson H, Watson ML, Mellor DJ. 1986. The effect of dietary $\omega 3$ and $\omega 6$ polyunsaturated fatty acids on gestation, parturition and prostaglandin E2 in intrauterine tissues and the kidney. *Prog Lipid Res*. 25:143-146. [cited in NTP 2009].

Leyton J, Drury PJ, Crawford MA. 1987. Differential oxidation of saturated and unsaturated fatty acids in vivo in the rat. *Br J Nutr* 57(3):383-93.

[LNHPD] Licensed Natural Health Products Database [database]. [modified 2016 Aug 10]. Ottawa (ON): Health Canada. [accessed 2017 June 29].

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.

Loretz L, Api AM, Barraj L, Burdick J, Davis DA, Dressler W, Gilberti E, Jarrett G, Mann S, Pan YHL, Re T, Renskers K, Scrafford C, Vater S. 2006. Exposure data for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. *Food Chem Toxicol.* 44: 2008-2018.

Loretz LG, Api AM, Babcock L, Barraj LM, Burdick J, Cater KC, Jarrett G, Mann S, Pan YHL, Re TA, Renskers KJ, Scrafford CG. 2008. Exposure data for cosmetic products: Facial cleanser, hair conditioner, and eye shadow. *Food Chem Toxicol.* 46: 1516-1524.

McGuire JM, Powis PJ. 1998. Gas chromatographic analysis of tall oil fractionation products after methylation with N,N-dimethylformamide dimethylacetal. *J Chromatogr Sci.* 36:104-108.

McPherson Jr JC. 1973. Suppression of food intake in the rat by tung oil. *Can J Physiol Pharmacol* 51(10):733-6.

Meehan E, Beauge F, Choquart D, Leonard BE. 1995. Influence of an n-6 polyunsaturated fatty acid-enriched diet on the development of tolerance during chronic ethanol administration in rats. *Alcohol Clin Exp Res.* 19(6):1441-6.

Mizushima Y, Tsuzuki T, Eitsuka T. 2004. Inhibitory action of conjugated C18-fatty acids on DNA polymerases and DNA topoisomerases. *Lipids.* 39(10):977-983.

[NCCIH] National Center for Complementary and Integrative Health. 2016. Evening primrose oil. [updated 2016 Nov 30; accessed 2017 Jun 19].

[NCI] National Chemical Inventories [database on a CD-ROM]. 2012. Issue 2. Columbus (OH): American Chemical Society, Chemical Abstracts Service. [accessed 2017 June 29].

Newell GW, Petretti AK, Reiner L. 1949. Studies of the acute and chronic toxicity of undecylenic acid. *J Invest Dermatol.* 13(3):145-9.

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2017 Oct 23]. Ottawa (ON): Health Canada. [accessed 2017 Dec 20].

[NTP] National Toxicology Program (US). 2009. Chemical Information Review Document for Evening Primrose Oil (*Oenothera biennis* L.) [CAS No. 90028-66-3][PDF]. Research Triangle Park (NC): US Department of Health and Human Services, National Toxicology Program. [accessed 2017 June 29].

[OECD] Organisation for Economic Co-operation and Development. 2010. SIDS Initial Assessment Profile (SIAP): 2-Ethylhexyl Acetate. SIAM 31, 20-22 October 2010 [accessed 2016 July 10].

[OECD] Organisation for Economic Co-operation and Development. 2014. SIDS Initial Assessment Profile (SIAP): Aliphatic Acids Category. CoCAM [Cooperative Chemicals Assessment Meeting] 6, 2014 September 30 – October 3. [accessed 2017 June 29].

Phillips II L, Steinberg M, Maibach HI, Akers WA. 1972. A comparison of rabbit and human skin response to certain irritants. *Toxicol Appl Pharmacol* 21(3):369-82.

Polasa K, Rukmini C. 1987. Mutagenicity tests of cashewnut shell liquid, rice-bran oil and other vegetable oils using the salmonella typhimurium/microsome system. *Food Chem Toxicol.* 25(10):763-766.

Ramírez M, Amate L, Gil A. 2001. Absorption and distribution of dietary fatty acids from different sources. Early Hum Dev. 65 Suppl. (2001) S95 – S101..

Riteks. 2008. Technical Bulletin: Dimer/Trimer Acid-RS Y 80. McKinney (TX): Riteks.

Robinson V, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, Alan Andersen F. 2009. Amended safety assessment of tall oil acid, sodium tallate, potassium tallate, and ammonium tallate. Int J Toxicol. 28(6 Suppl 2):252S-258S.

[SDS] Safety Data Sheet. 2016. No-Toil Biodegradable Foam Filter Oil. Gastonia (NC) [PDF]: Mann+Hummel Filtration Technology US LLC. [accessed 2017 June 29].

Seppanen 1969 as cited in: Anon. 1989. Final report on the safety assessment of tall oil acid. J. Amer. Coll. Toxicol. 8:769-776.

Shockey J, Rinehart T, Chen Y, Yangdong W, Zhiyong Z, Lisong H. 2016. Chapter 10: Tung (*Vernicia Fordii* and *Vernicia montana*). In: McKeon T, Hayes D, Hildebrand D, Weselake R, editors. Industrial Oil Crops. Amsterdam (the Netherlands): AOCS Press, Elsevier Inc.

SimpleTreat [sewage treatment plant removal model]. 1997. Ver. 3.0. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu (RIVM) [National Institute for Public Health and the Environment]. Laboratory for Ecological Risk Assessment.

Tokudome Y, Katayanagi M, Hashimoto F. 2015. Esterase activity and intracellular localization in reconstructed human epidermal cultured skin models. Ann Dermatol. 27(3):269-274.

Tsuzuki T, Tokuyama Y, Igarashi M, Miyazawa T. 2004a. Tumor growth suppression by alpha-eleostearic acid, a linolenic acid isomer with a conjugated triene system, via lipid peroxidation. Carcinogenesis. 25(8):1417-1425.

Tsuzuki T, Igarashi M, Miyazawa T. 2004b. Conjugated eicosapentaenoic acid (EPA) inhibits transplanted tumor growth via membrane lipid peroxidation in nude mice. J Nutr. 134:1162-1166.

[US EPA] US Environmental Protection Agency. 2005. Detail Query Results for Fatty Acid Dimers and Trimer Category. Posting dates of documents from HPV Challenge web site from which data have been entered into the HPVIS: February 2, 2005. [accessed 2017 07 02].

[US EPA] US Environmental Protection Agency. 2009. 40 CFR Part 180 [EPA–HQ–OPP–2007–1025; FRL–8434–5] Cold Pressed Neem Oil; Exemption from the Requirement of a Tolerance. Federal Register / Vol. 74, No. 207 / Wednesday, October 28, 2009 / Rules and Regulations.pg 55458-55462.

[US EPA] US Environmental Protection Agency. 2012. Biopesticides Registration Action Document: Cold Pressed Neem Oil PC Code 025006. [updated 2012 May 7; accessed 2016 May 20].

[US FDA] US Food and Drug Administration. 2016. Part 178: Indirect food additives: adjuvants, production aids, and sanitizers. [revised 2016 Apr 1; accessed 2017 May 20].

Versar, Inc. 1986. Standard scenarios for estimating exposure to chemical substances during use of consumer products. Vol. II. Consumer use of used motor oil. Springfield (VA): Versar, Inc. Prepared for US Environmental Protection Agency.

Vinod V, Tiwari PK, Meshram GP. 2011. Evaluation of mutagenic and antimutagenic activities of Neem (*Azadirachta indica*) seed oil in the in vitro Ames Salmonella/microsome assay and in vivo mouse bone marrow micronucleus test. *J Ethnopharmacol.* 134:931-937.

Wang C, Cao M, Shi DX, Yin ZQ, Jia RY, Wang KY, Geng Y, Wang Y, Yao XP, Yang ZR, Zhao J. 2013. A 90-day subchronic toxicity study of neem oil, a *Azadirachta indica* oil, in mice. *Hum Exp Toxicol.* 32(9):904-13.

[WHO] World Health Organization. 1999. Safety evaluation of certain food additives: fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additive Series, No. 42. Geneva (CH): World Health Organization. [accessed 2017 May 20].

Wormuth M, Scheringer M, Vollenweider M, Hungerbühler K. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Analysis.* 26(3):803-824.

Yasui Y, Hosokawa M, Sahara T, Suzuki R, Ohgiya S, Kohno H, Tanaka T, Miyashita K. 2005. Bitter gourd seed fatty acid rich in 9c, 11t, 13t-conjugated linolenic acid induces apoptosis and up-regulates the GADD45, p53 and PPAR γ in human colon cancer Caco-2 cells. *Prostaglandins Leukot Essent Fatty Acids.* 75:113-119.

Zhuo RJ, Wang F, Zhang XH, Zhang JJ, Xu J, Dong W, Zou ZQ. 2014. α -eleostearic acid inhibits growth and induces apoptosis in breast cancer cells via HER2/HER3 signaling. *Mol Med Rep.* 9(3):993-998.

Appendices

Appendix A. Substance identity information

Table A-1. Substance identity information for analogues used to inform the assessment

Major fatty acid constituents as single component				Single component fatty acid (%)		UVCB fatty acid major components (%)					
CAS RN	OECD 2014 assessed FAs (IUPAC or CAS Name)	Common name	Structure feature	α -linolenic acid (ALA) 463-40-1	Undecylenic acid 112-38-9	Tung oil 8001-20-5 ^a	Fats and glyceridic oils, margosa 8002-65-1 ^a	Tall-oil 61790-12-3 ^b	Potassium tallate 61790-44-1	evening primrose oil 90028-66-3 ^c	Ethylhexyl cocoate 92044-87-6
124-07-2	Octanoic acid	Caprylic acid	C8:0								5-10
334-48-5	Decanoic acid	Decanoic acid	C10:0								8
463-40-1	(9Z,12Z,15Z)-Octadeca-9,12,15-trienoic acid; 9,12,15-Octadecatrie	Alpha-linolenic acid	C18:3 ; cis-9,12,15	>99							
112-38-9	n/a	10- Undecylenic acid	C11:1 ; cis 10		>99						
143-07-7	Dodecanoic acid	Lauric acid	C12:0								45-52
544-63-8	Tetradecanoic acid	Myristic	C14:0								16-21
57-10-3	Hexadecanoic acid	Palmitic acid	C16:0			~4	13.6-16.2	~6.3	~6.3	5.8-7	7-10
57-11-4	Octadecanoic acid	Stearic acid	C18:0				14.4-20.4			1.5-2.5	
112-80-1	(Z)-Octadec-9-enoic acid; 9-Octadecenoic acid, (Z)-	Oleic acid	C18:1; cis 9			~8	49-62	39-48.2	39-48.2	5-11	5-8
60-33-3	(9Z,12Z)-Octadeca-9,12-dienoic acid; 9,12-Octadecadienoic acid	Linoleic acid	C18 :2; cis 9, cis 1			~4	2.3-15.8	34-35.9	34-35.9	70-77	
26764-25-0	n/a	Octadecadienoic acid	C18:2; trans 7, cis 9					2.3-10	2.3-10		
506-23-0	n/a	Alpha eleostearic acid	C18:3; cis 9, trans 11, trans 13			~80					
506-26-3	n/a	Gamma-linolenic acid	C18:3; cis-6,9,12							9-10.9	

^a <https://www.chempro.in/fattyacid.htm>

^b McGuire and Powis 1998

^c www.essentialoils.co.za/evening-primrose-analysis.htm

^d Chemical Associates: <http://www.chemicalassociates.com/products/dimer-acids.html>

Appendix B. Parameters used to estimate exposures.

Cosmetic exposures were primarily estimated using ConsExpo Web (2016). Exposure estimates were calculated on the basis of default body weights of 70.9 kg, 15.5 kg, and 7.5 kg for adults (20 years and older), toddlers (6 months to 4 years old), and infants (0 to 6 months old), respectively (Health Canada 1998). The estimated dermal and oral exposure parameters for cosmetics are described in Table B-1 and Table B-2, respectively. Details on the dermal absorption rate used to derive systemic exposures can be found in section 6.4.1 for undecylenic acid and 6.4.2 for ethylhexyl cocoate.

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

Product (substance)	Assumptions ^a
Body moisturizer (Undecylenic acid and ethylhexyl cocoate)	Adults: Product amount (g/use): 4.4 (Loretz et al. 2005) Frequency (use/day): 1.1 (Loretz et al. 2005) Surface area: whole body – head = 16 925 cm ² (Health Canada 1995) Infants (for undecylenic acid only): Product amount (g/use): 1.4 (Wormuth et al. 2006) Frequency (use/day): 1.7 (Wormuth et al. 2006) Surface area: whole body – head = 3 020 cm ² (Health Canada 1995)
Specialized body moisturizer	Adults: Product amount (g/use): 2.2 (assume use half the amount of body lotion) Frequency (use/day): 1 Surface area: Assume used on legs and feet only (based on personal communication, e-mail from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 22, 2016; unreferenced)
Face moisturizer (Undecylenic acid and ethylhexyl cocoate)	Adults: Product amount (g/use): 1.2 (Loretz et al. 2005) Frequency (use/day): 1.8 (Loretz et al. 2005) Surface area: Half area of head = 637.5 cm ² (Health Canada 1995)
Facial make-up (Undecylenic acid and ethylhexyl cocoate)	Adults: Product amount (g/use): 0.54 (Loretz et al. 2006) Frequency (use/day): 1.24 (Loretz et al. 2006) Surface area: Half area of head = 637.5 cm ² (Health Canada 1995)

Hair oil (Ethylhexyl cocoate)	Adults: Product amount (g/use): 13.1 (Loretz et al. 2008) Frequency (use/day): 1.24 (Loretz et al. 2006) Retention (or transfer) factor: 0.1 (amount on the scalp available for absorption) Surface area: Half area of head = 637.5 cm ² (Health Canada 1995)
Nail conditioner (Undecylenic acid)	In the absence of specific data for this exposure scenario, adjusted product amount for hand cream using a surface area adjustment factor (hands to fingertips). Adults: Product amount (g/use): 0.1 g (adjusted product amount for hand cream 1.7 g by 0.058 (surface area adjustment) Frequency is less than once a day, exposure estimates are per event Surface area: Hands = 910 cm ² (Health Canada 1995), surface area of fingernails ~ 50 cm ² (Ficheux et al. 2014)
Massage oil (body) (Ethylhexyl cocoate)	Adults: Product amount (g/use): 3.2 (Ficheux et al. 2016) Frequency is less than once a day, exposure estimates are per event Surface area: Total body surface area - half area of head – half area of trunk = 14 380 cm ² (Health Canada 1995)

^a Unless specified, a retention factor of 1 was used

Table B-2. Oral exposure parameter assumptions for oral natural health product and cosmetics

Product (substance)	Assumptions
Non-medicinal ingredient in natural health product ^a (Undecylenic acid)	2-3 capsules once a day. 15 mg of undecylenic acid per capsule. Adults: Estimated dose = $\frac{15 \text{ mg/capsule} \times 2 \text{ or } 3 \text{ capsules/day}}{70.9 \text{ kg}}$ Estimated dose = 0.42 to 0.63 mg/kg bw/day
Lipstick/lip gloss ^b (Ethylhexyl cocoate)	Adults: Product amount (g/use): 0.01 (Loretz et al. 2005) Frequency (use/day): 2.4 (Loretz et al. 2005)

	Toddler: Product amount (g/use): 0.01 (assumed to be the same as adults from) Frequency is less than once a day, exposure estimates are per event
--	--

^a Product is associated with the recommended use or purpose “Garlic is traditionally used in Herbal Medicine to help relieve the symptoms associated with upper respiratory tract infections and catarrhal conditions,” The duration of use statement “Consult a health care practitioner for use beyond 6 weeks,” and other recommended conditions of use, such as cautions and warnings, contra-indications, and known adverse reactions (LNHPD [modified 2016]; personal communication, e-mail from the Natural and Non-prescription Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated April 28, 2016; unreferenced).

^b Assume amount applied is completely ingested, no dermal exposure